Executive Function in Multiple Sclerosis

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Abstract

Executive function in Multiple Sclerosis

Executive function refers to mechanisms which optimise performance in situations requiring multiple cognitive processes and is associated with the frontal lobes of the brain. There are various competing theories of executive function but current thinking in this area has moved towards identifying separable executive processes.

It is well established that executive skills are compromised in patients with Multiple Sclerosis. This is thought to arise as a result of the effects of the disease process on the frontal regions of the brain, in the context of a disseminated pathology. An executive process that appears to have received relatively little attention in the MS research literature is the ability to initiate and suppress undesired verbal responses, despite clinical reports of disinhibition in some patients with MS. There is also evidence for impairment in the ability to switch between task demands and to manipulate information in working memory in this patient group. This thesis sets out to examine these executive processes in a group of people with MS.

22 participants with clinically definite or clinically probable MS, and 22 matched healthy controls, were assessed on a range of cognitive measures including tests of executive function. Participants also performed two new experimental tasks that were designed to examine the ability to switch demands and to inhibit verbal responses, particularly when the inhibitory demand was varied.

The MS participants showed evidence of verbal disinhibition compared to the healthy controls, particularly when inhibitory demands were higher. There was further evidence of impairment in other executive functions in the MS group including working memory, in the context of poor performance on tasks of information processing speed. The MS group's ability to switch between task demands, however, appeared to be relatively preserved.

The results partly confirm previous findings of cognitive dysfunction in MS but add to the knowledge about verbal disinhibition, set switching and working memory. There are important clinical implications that arise from these findings which are associated with improving the quality of life of people with MS.

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CHAPTER 1

INTRODUCTION

The presence of cognitive deficits in Multiple Sclerosis (MS) has long been recognised and impairment has been noted even at the early stages of the disease (Amato, Ponziani, Pracucci, Bracco, Giamfranco & Amaducci, 1995). Studies have highlighted the presence of cognitive deficits in a number of areas of brain functioning including memory, attention, and information processing.

Impairment in executive functions such as self- monitoring, planning, sequencing & problem solving (Brassington & Marsh, 1998), has been established in patients with MS (e.g. Arnett, Rao, Bernardin, Grafman, Yetkin & Lobeck, 1994; Swirsky-Sacchetti et al., 1992) and these deficits can impact significantly on peoples' everyday lives, causing distress and reducing quality of life. One executive process that appears to have received little attention within the MS literature is the ability to initiate and suppress verbal responses. Should an impairment in this ability be established in people with MS, then clinical approaches may be developed to help manage disinhibition in a rehabilitation setting.

It is apparent from clinical reports (Langdon, 1998) that patients with MS can also lack flexibility in their cognitive style. Research studies have highlighted impairment in the executive ability of MS patients to switch from one task demand to another, a process that requires a degree of cognitive flexibility (Arnett et al., 1994; Comi, Rovaris, Falautano, Santuccio, Martinelli, Rocca et al., 1999). The ability to hold and manipulate information in very short term (working memory) has further been shown to be compromised in this patient group (Ruchkin, Grafman, Krauss, Johnson, Canoune & Ritter, 1994). Since these impairments are known to have an adverse effects on health and quality of life of people with MS (Langdon, 1998), task switching and working memory will also be examined.

The review will begin by describing the nature of Multiple Sclerosis and cognitive function in this patient group, before moving onto describing executive functioning in MS and how impaired executive functions affect thinking and behaviour in daily life, drawing on clinically relevant studies (Chapter 1). An overview of theoretical models of executive function will be provided in the second part of the review, reviewing studies addressing theoretical issues (Chapter 2). In particular, the discussion will focus on response initiation and suppression, task switching and working memory. Finally, the aims and hypotheses of the study will be considered (Chapter 4). Some of the methodological issues in undertaking research into executive functioning and in MS that are relevant to the present study will be outlined in Chapter 3.

1. 1. MULTIPLE SCLEROSIS

1.1.1. The nature of Multiple Sclerosis

Multiple Sclerosis (MS) has been described as 'potentially the most common cause of neurological disability in young adults' (p. 1221, Compston & Coles, 2002). It is an autoimmune disorder of the Central Nervous System in which parts of the nervous system known as nerve axons become inflamed. This leads to the loss of axons and the demyelination of sheaths that serve to insulate the axons (Kalkers, Vrenken, Uitdehaag, Polman & Bbarkhof, 2002). Where demyelination of fibres has occurred, sclerotic plaques or scar-like lesions within the brain white matter and spinal chord form (Brassington & Marsh, 1998). The transmission of nerve impulses is prevented which results in the neurodegeneration of the central nervous system and the development of a variety of clinical symptoms which contribute to an unpredictable disease course (Compston & Coles, 2002).

1.1.2 Prevalence

It has been estimated that approximately 2.5 million individuals suffer from Multiple Sclerosis worldwide. It is possible that the variability in the prevalence rates of MS may be reflective of better case recognition in some areas of the world than others. Twice as many women as men are diagnosed with the disorder (Compston & Coles, 2002).

1.1.3. Cause

Although the exact nature of the cause of MS remains unknown, research has suggested that an interaction between genes and the environment contributes to the onset of the disease (Brassington & Marsh, 1998). In terms of hereditability, the recurrence rate of MS in families has been estimated to be about 15% and in monozygotic twins it is approximately 35% (Compston & Coles, 2002). Speculations as to possible environmental factors causing onset of MS include a viral infection (Compston & Coles, 2002).

1.1.4 Symptoms

Symptoms of MS vary from individual to individual because lesions may develop anywhere in the Central Nervous System (Brassington & Marsh, 1998). Symptoms include sensory, visual and motor difficulties and range from a blurring or loss of vision due to inflammation of the optic nerve (optic neuritis), dysarthria (impaired speech), pain, spasms or numbness in the limbs, impaired balance, coordination or gait (ataxia), and bladder dysfunction (Compston & Coles, 2002). Fatigue following physical activity or cognitive tasks is a common symptom (Compston & Coles, 2002).

1.1.5. Subtypes

Within MS different subtypes of disease course have been defined (Brassington & Marsh, 1998). Three subtypes are commonly recognised (Compston & Coles, 2000):

- Relapse-remitting type- involves episodes of relapse at random intervals with full recovery following a relapse. This type of MS is most common in young women and occurs in approximately 80% of presenting MS cases.

- Primary-progressive type- progression of the disability occurs from onset. There are no (or possibly a few minor) relapses.

- Secondary-progressive type- this follows an initial relapse-remitting phase (remitting type, see above) in which relapses become more frequent and increasingly prolonged with incomplete recovery following a relapse. Following this initial phase there begins a continued phase of disease progression (Rice, 2002; Wolinsky, 2002). The greatest amount of axonal loss is observed to occur in this type of MS (Compston & Coles, 2002).

1.1.6. Diagnosis

A diagnosis of clinically definite MS is made following at least two episodes or attacks of neurological symptoms. There should be a minimum period of a month between both episodes with each episode lasting for at least 24 hours. Neurological symptoms associated with the attacks should arise from two separate areas of the CNS (Poser et al., 1983). Patients may be classified according to different diagnoses subtypes (clinically definite, clinically probable or clinically possible MS). However it has been suggested that only patients with clinically definite or clinically probable diagnoses of MS be included in research studies (Poser, 1994).

1.1.7. Prognosis

Prognosis has been considered to be better where there are less motor difficulties and where sensory or visual problems dominate (Compston & Coles, 2002). The disease tends to progress at a faster rate in people who have been diagnosed after the age of 40 (late onset MS).

1.1.8 Impact of MS on daily living

It has been reported that MS affects activities of daily living in about 75% of patients. MS sufferers experience a range of degrees of disability reflecting their varying symptomology.

1.1.9. Treatment

Treatment has been focused on reducing the relapse rate and associated disability and in preventing further progression of the disease (Compston & Coles, 2002). Use of Bete-Interferon is one of the immunomodulatory drugs used in the treatment of remitting-remitting type. Corticosteroids have been used to reduce inflammation during relapses (Brassington & Marsh, 1998) and other symptomatic treatments are available.

1.2. COGNITIVE FUNCTION IN MS

1.2.1 Overview

Cognitive impairments in MS were initially identified more than a century ago (Charcot, 1877). Since the 1980s, however, cognitive functioning in MS has been a rapidly growing area of research as impairments are known to have widespread effects on daily functioning (Barak & Achiron, 2002).

Prevalence rates of cognitive impairment have been reported to vary between 40% and 60% (Hohol et al., 1997; Rao, Hammeke, McQuillan, Kahtri & Lloyd, 1984). The variation in rates have been attributed to factors such as type and number of neuropsychological tests used, the influence of clinical variables such as disease duration and degree of disability, and criteria for patient selection (Nocentini et al., 2001).

Cognitive changes have been found to vary with disability status, disease progression and disease duration (Brassington & Marsh, 1998). There are mixed findings as to the extent of the relationship between degree of cognitive impairment and these factors. Some studies suggest that cognitive impairment may become more widespread as the disease progresses due to an increased involvement of the sub cortical white matter and greater extent of lesion sites (Beatty, 1999; Brassington & Marsh, 1998; Heaton, Nelson, Thompson, Burks & Franklin, 1985). Other studies have found little relationship between degree of cognitive impairment and these factors (Amato et al., 1995; Penman, 1991).

Similarly, there are contradictory findings in relation to an association between disease subtype and degree of cognitive impairment, yet there appears to be some degree of association in patients with the progressive type MS (Camp et al., 1999; Comi, Filippi, Martinelli, Campi, Rodegher & Alberoni, 1995; Heaton et al., 1985). Other studies, however, have provided little or no support for this relationship (Amato et al., 1995; Beatty, Goodkin, Beatty & Monson,1989; Rao, Grafman, DiGiulio, Mittenberg, Bernardin & Leo, 1993). Impaired cognitive function has been observed in patients who are at the early stage of onset (Amato, Ponziani, Siracusa & Sorbi et al., 2001), and even where there are as yet few noticeable physical symptoms (Hotopf, Pollock & Lishman, 1994). Similarly cognitive deficits have been established in people at the later or more advanced stages of MS (Ryan, Clark, Klonoff, Li & Paty, 1996).

1.2.2 MS and subcortical dementia

The issue of whether or not MS is a subcortical dementia remains a continuing debate (Brassington & Marsh, 1998). Certainly there appear to be aspects of MS that are consistent with that of a sub cortical dementia. These include cognitive slowing, reduced insight, forgetfulness, emotional difficulties such as depression, and executive impairment characterised by apathy, reduced initiative and changes in premorbid personality (Peterson & Kokmen, 1989). Further support for this debate comes from studies reporting subcortical and frontal involvement in patients with MS where there are lesions to these areas (Brassington & Marsh, 1998).

Studies examining cognitive function in MS have highlighted the relative preservation of language functions in the context of impaired memory and learning, attention, speed of information processing and executive abilities (Rao et al., 1991a; Ron, Callanan & Warrington, 1991). Each of these areas of cognitive function will be addressed in turn before focusing more specifically on executive function in this patient group.

1.2.3 Intellectual Functioning

Intellectual functioning is relatively well-preserved in MS although there may be a small decline over time (Rao, 1986). Impaired sensory and motor skills as a result of the disease process may interfere with performance on intellectual tasks such that performance IQ scores are frequently found to be significantly lower than verbal scores (Penman, 1991). Various versions of the Wechsler Adult Intelligence test (WAIS) have been used in MS research studies to obtain a current level of intellectual functioning. However, the Verbal and Spatial Reasoning Test (VESPAR) (Langdon & Warrington, 1995) has been employed in a growing number of studies (Camp et al., 1999; Langdon & Thompson, 1999) to ascertain inductive reasoning ability in people with MS.

Premorbid intellectual level is commonly estimated in the UK in MS patients using the National Adult Reading Test (NART) (Brassington & Marsh, 1998; Camp et al., 1999; Foong, Rozewicz, Quaghebeur, Thompson, Miller & Ron, 1998; Langdon & Thompson, 1999).

1.2.4 Memory

Between 40% -60% of people with MS are reported to suffer from memory difficulties (Rao et al., 1993). Memory is one of the most significant areas of cognitive function to be affected in this disorder (Brassington & Marsh, 1998). Minden, Moes, Orav, Kaplan & Reich (1990) reported up to 60% of their sample of MS patients to experience moderate or severe memory difficulties.

Studies have highlighted a variability in the type of memory affected in MS. Recognition memory, implicit learning and the storage and encoding of information into long term or secondary memory appears to remain relatively intact. In contrast to this, impairment in working or immediate memory, recent and remote memory, and recall of information from long term memory that requires effort and the development of strategies to aid retrieval have been highlighted (Grafman, Rao, Bernardin & Leo, 1991; Rao et al., 1993).

There have been mixed findings in terms of the degree of awareness that patients with MS have of their cognitive difficulties. Kujala, Portin & Ruutiainen (1996) found subjective reports of memory deficits to be accurate in MS patients with early cognitive decline although subjective reports in another sample of MS patients were found to be inaccurate (Beatty & Monson, 1991). Further research is needed to ascertain the nature of these subjective reports and the degree of awareness that MS patients have of their cognitive difficulties in order to help clarify the likely impact of such difficulties on everyday functioning.

1.2.5. Speed of information processing

Studies have supported a slowing in cognitive processing speed in this group (Beatty, Goodkin, Monson, Beatty & Hertsgaard, 1988; De Sonneville, Boringa, Reuling, Lazeron, Ader & Polman, 2002), and it is particularly salient for patients who have mild cognitive deterioration (Kujala, Portin, Revonsuo & Ruutiainen, 1995). Longer disease duration and greater plaque involvement have been associated with a slowing of processing speed (Rao, Leo, Haughton, St. Aubin-Faubert & Bernardin, 1989).

The Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) (see section 5.4.2.2.) has been commonly employed to examine the efficiency and speed of cognitive processing, sustained attention and working memory in MS patients (Archibald & Fisk, 2000; Brassington & Marsh, 1998; Hohol et al., 1997; Rao et al., 1991a). It was originally developed for assessing information processing in brain injured patients for the purpose of rehabilitation (Gronwall, 1977).

Rao et al. (1991a) demonstrated the PASAT to be one of the four most sensitive tests for detecting cognitive impairment in MS. DeLuca, Johnson & Natelson (1993) found patients with MS to be more impaired on all rates of information presentation of the PASAT than control participants, particularly when information was presented at faster rates and was thus more demanding (Litvan, Grafman, Vendrell, Martiner, Junque & Venrell, 1988). An association between verbal memory impairment and poor information processing efficiency has been established (Beatty, Goodkin, Beatty & Monson, 1989; Litvan et al., 1988; Rao et al., 1989). Slowed information processing is believed to contribute to impaired encoding of verbal material (Faglioni, Bertolani, Botti & Merelli, 2000) and to the failure of working memory (more specifically the central executive (D'Esposito, Onishi, Thompson, Robinson, Armstrong & Grossman, 1996) or articulatory loop (Litvan et al., 1988)). The PASAT has, however, been criticised for lacking in ability to vary the operational or structural capacities of working memory and for focusing solely on speed of information processing (Archibald & Fisk, 2000).

1.2.6. Executive function in MS

Executive functions in MS have shown to be compromised in patients with Multiple Sclerosis. In recent years there has been a growing number of neuropsychological studies that have highlighted difficulties patients with MS can have with abstract concept formation and set shifting (Heaton et al., 1985), abstract reasoning (Amato et al., 2001; Nocentini et al., 2001), sequencing tasks (Beatty & Monson, 1994), and verbal abstracting ability (Beatty, Hames, Blanco, Paul & Wilbanks, 1995). This section will discuss clinically-relevant articles addressing executive functions.

It would be important to uncover the nature of the cognitive processes that underlie the executive deficits highlighted in this neurological condition. However it appears that few studies have focused specifically on the precise cognitive processes or particular mechanisms that are impaired in patients with MS, particularly the ability to shift set or task demand, the ability to inhibit prepotent responses, or working memory ability. These executive processes in MS will now be discussed as they are considered to be relevant to the current research study.

1.2.6.1. Response initiation/generation

Studies have highlighted impaired verbal fluency in MS patients (e.g. Beatty et al., 1988; Comi et al., 1999; Foong., Rozewicz, Quaghebeur, Davie, Kartsounis, Thompson, Miller

& Ron, 1997; Heaton et al., 1985; Pozzilli et al., 1991; Swirsky-Sacchetti et al.,1992), which indicates that there is an impairment in the ability to initiate or retrieve items from semantic memory (see section 2.3.4.1). The Controlled Oral Word Association Test (COWAT) (see section 5.4.3.1) has been frequently used in MS studies. Beatty (2002) compared the usefulness of three verbal fluency measures (letters beginning with F, A or S or were examples of the categories of animals or parts of the body) in patients with MS. The study highlighted that all three measures were similar in sensitivity and specificity in discriminating MS patients from controls. The COWAT was found by Rao et al. (1991a) to be one of the four most sensitive tests of cognitive impairment in MS.

1.2.6.2. Response inhibition

There has been relatively little investigation of the ability of patients with MS to inhibit distracting stimuli and selectively attend to target stimuli. Previous studies using the Stroop colour/word task (see section 2.3.4.2), have highlighted how MS patients are often impaired on this task of selective attention (Comi et al., 1999; Foong et al., 1997). This has been represented by greater interference effects on performance in the MS group in comparison to controls when there was conflict between the colour of the ink that names of colours are written in. Response times were found to be longer in this condition (e.g. Kujala et al., 1995; Rao et al., 1991a). Vitkovitch, Bishop, Dancey & Richards (2002) employed the Stroop colour-word interference task to establish the exact nature of impaired performance on the Stroop task: whether this represented impaired excitatory processes /excitation of the target; an impairment in inhibitory processes /suppression of the distracting item; or inability to maintain the goal of the task. Performance on four experimental conditions was compared across two groups of 20 participants: one group of MS patients and a group of healthy control participants matched for age, sex and education. The findings suggest that the MS patients were able to inhibit distracter items but that a partial breakdown in inhibitory processes may be a plausible explanation for findings which included increased Stroop interference. The authors suggest that a greater sample size may be one factor to ensure that findings are robust. They also consider the potential effects of depression on performance, as negative effects have previously been found (Arnett et al., 1999; Filippi et al., 2000). Although the increased interference effects on the Stroop task did not appear to relate to depression scores in the MS group, it is possible that fatigue may have affected performance in some patients more than others which contributed to the tentative findings. It may therefore have been worthwhile to have included a measure of fatigue in the study in order to explore the relationship between fatigue and Stroop interference.

To date there appear to be few studies that have explored the ability of patients with multiple sclerosis to inhibit over learned responses whilst generating new words to replace them. This suggests that executive functioning in Multiple Sclerosis remains a relatively under researched area.

1.2.6.3 Set-shifting

A study by Rao, Hammeke & Speech (1987) employed the Wisconsin Card Sorting Test (WCST; Heaton, 1981) to examine executive function in two types of MS, relapse-remitting and chronic progressive. The WCST is a popular neuropsychological test of conceptual reasoning and shifting of rules or task demands (see section 2.3.6). The test involves sorting cards into four piles according to rules that the individual must learn via feedback that is given when each card is placed down. When the category changes positive feedback is given every time the card is placed in the correct pile according to the new rule. The ability to change or shift category and the number of perseverations made are observed. A difficulty in utilising feedback may underlie the inability to shift to a new category (Kimberg & Farah, 1993).

The ability of each MS group to shift set and to form concepts was compared to a control group of back pain patients matched for age and education. A patient control group was used to control for factors such as effects of medication and emotional distress as a result of chronic illness, on cognitive performance. The chronic progressive group, unlike the relapse-remitting group, exhibited impaired performance on the WCST, making significantly more perseverative errors and hence achieving fewer categories. Differences between groups are unlikely to have been the effect of illness-related factors such as duration and severity, or medication. However subtype of course of MS, more specifically chronic progressive type, appears to relate to level of performance. This has been supported by Mahler (1992) and suggests that future research should focus on conducting research using homogenous groups of patients (for example, only patients with secondary progressive MS). This methodology would perhaps allow for a more accurate understanding of the nature of cognitive impairment in MS to be gained.

Further studies highlight similar findings in which MS patients have made perseverative errors on the WCST, despite feedback (Arnett et al., 1994; Beatty et al., 1989; Comi et al., 1999; Heaton et al., 1985; Swirsky-Sacchetti et al., 1992). Impaired performance appeared to relate to difficulties in set shifting abilities rather than an ability to sustain attention (maintaining set) or to learn efficiently (Rao et al., 1987).

1.2.6.4 Working Memory

Studies have highlighted an impairment in immediate memory for verbal material (verbal working memory) (Rao et al., 1993; Ruchkin et al., 1994). Impaired performance on the Digit Span Backwards test of the Wechsler Memory Scale-Revised (WMS-R) (see section 5.4.2.1.) has been highlighted in various studies (Ruchkin et al., 1994; Rao et al., 1993). This immediate memory deficit for verbal information has been linked to an impairment in the articulatory loop in terms of Baddeley's (1986) model of working memory (Litvan, 1988; Rao et al., 1993; Ruchkin et al., 1994) (see section 2.3.1.3). On the contrary, visuospatial working memory remains relatively preserved (Brassington & Marsh, 1998). There is support for an impaired Central Executive System (CES) of Baddeley's working memory in patients with MS as reflected by poorer performance on a dual paradigm task than a healthy control group (D' Esposito et al., 1996).

Matotek, Saling, Gates & Sedal (2001) examined the relationship between verbal fluency, working memory and subjective complaints of memory difficulties by patients with mild MS. A Speaking Span Test was used to assess working memory and the MS group were found to show poorer performance on the verbal fluency and working memory tasks than a control group. A correlation was established between working memory and both verbal fluency and subjective difficulties in the MS group. The authors suggest that a reduced working memory capacity is likely to have contributed to these difficulties, explaining that the MS group made more errors when planning or generating their verbal output than was normally expected. They speculate that an effect of disease process rather than mood was more likely to underlie these difficulties.

1.2.6.5. Attention

Impaired attention and poor short term capacity span are frequently observed in patients with MS even in mild stages of the disease (Kujala et al., 1995). Impairment in both visual and verbal attention has been highlighted (Litvan et al., 1988; Ron et al., 1991). Kujala et al. (1995) suggest that tests of attention should be used systematically when examining cognitive functioning in this patient group. Commonly employed measures of attention in studies of MS include the Digit Span task (Amato et al., 2001; Beatty, Wilbanks, Blanco, Hames, Tivis & Paul, 1996; Pozzilli et al., 1991) as well as the PASAT (Litvan et al., 1988). Beatty et al. (1996) suggest that attentional impairment may underlie the memory difficulties observed in their MS group.

However, performance on the forward digit span task by MS patients has frequently been found to remain intact (De Luca et al., 1993; Klonoff, Clark, Oger & Paty, 1991; Litvan et al., 1988; Pozzilli et al., 1991; Rao et al., 1984). Similarly, Archibald and Fisk (2000) failed to find a significant difference between MS patients with mild to moderate MS and cognitive complaints, and a neurologically intact group, in terms of immediate memory span.

1.2.7. Further factors affecting cognition in MS

1.2.7.1 Affective and Psychiatric disturbances

It is known that individuals with MS may suffer from emotional difficulties or psychiatric disturbances such as affective disorders, personality change and psychosis (Peterson & Kokmen, 1989). It has been hypothesised that the onset of emotional or mental health difficulties may be the result of the disease process itself, or is associated with the process of adjustment to living with MS. It is speculated that in people with a vulnerability to developing emotional difficulties, MS may serve as a contributing factor or stressor (Brassington & Marsh, 1998).

Depression is commonly experienced by people with MS (Brassington & Marsh, 1998). Studies have reported lifetime prevalence rates of depression of approximately 50% (Kroencke, Denney & Lynch, 2001). Studies have provided support for the lack of a significant relationship between depression and impaired cognitive function (Camp et al., 1999; Krupp, Sliwinski, Masur, Friedberg & Coyle, 1994; Moller, Wiedemann, Rohde, Backmund & Sonntag, 1994; Rao et al., 1991a). Depression has not been associated with degree of disability, disease duration or clinical course / disease subtype (Moller et al., 1994). Nevertheless, other studies have provided support for a significant relationship between depression and information processing speed, working memory and executive skills (Arnett et al., 1999).

Measures commonly used to assess affect in MS include the Beck Depression Inventory (BDI; Beck & Steer, 1987) and the Zung Self-Rating Depression Scale (Zung, 1995). However items in measures such as the BDI may be rated according to physical symptomology rather than in terms of mood *per se*. The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) overcomes this limitation by including items that are more likely to be rated according to mood. Crawford, Henry, Crombie & Taylor (2001) provide normative data for the HADS from a large non-clinical sample considered to be relatively representative of the general adult population of the UK in terms of age, gender and occupational status. The HADS has been employed as a measure of anxiety and depression in several MS studies (Camp, Thompson & Langdon, 2001; Foong et al., 1998; Foong, Rozewicz, Davie, Thompson & Ron, 1999).

1.2.7.2 Fatigue

Fatigue is one of the most serious complaints by people with MS and can affect up to 90% of individuals (Brassington & Marsh, 1998), particularly patients with progressive type MS (Iriarte & Carreno, 1996). Different types of fatigue have been delineated. Motor fatigue is described as a decline in strength during muscle contractions. Cognitive fatigue is a decline in mental or cognitive performance during tasks that demand sustained attention. Lassitude is the subjective sense of reduced energy (Schwid, Covington, Segal & Goodman, 2002).

There are variable findings to support a relationship between fatigue and cognitive impairment. Several studies have failed to find fatigue to affect cognitive function (Geisler, Sliwinski, Coyle, Mauser, Doscher & Krupp, 1996; Parmenter, Denney & Lynch, 2003) which contrasts with Sandroni, Walker & Starr (1992) who found an effect of fatigue on memory task performance, more specifically in slowing down reaction times. People with MS also report that their cognitive abilities are affected by fatigue (Schwartz, Coulthard-Morris & Zeng, 1996).

Various measures have been employed to measure different aspects of fatigue in MS (Flachenecker, Kumpfel, Kallmann, Gottschalk, Grauer, Rieckman et al., 2002). These include the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) which focuses on physical fatigue, and the Visual Analogue Scale which measures lassitude (VAS; Krupp et al., 1989). The VAS provides a global description of fatigue by asking the patient to indicate the degree of fatigue on a scale. In a recent study Archibald and Fisk (2000) included a visual analogue rating scale of fatigue severity where patients rated their current level of fatigue at the beginning and end of each test session from a scale of 0 (no fatigue) to 10 (extreme fatigue). The scale highlighted a significant difference between the patient and control group with patients reporting greater fatigue.

1.2.7.3 Disability

Various measures have been employed within research studies in order to examine the degree of disability experienced by individuals which can allow for comparison with the degree of cognitive impairment. The most widely used measure of disability in MS is the Kurtze Expanded Disability Scale (Kurtze, 1983). However this tool has been criticised for its poor reliability and its focus on mobility as the primary indication of degree of disability. It is considered to lack sensitivity to clinical changes that occur in other areas of physical functioning (Amato et al., 2001; Brassington & Marsh, 1998). Various other measures have since been developed such as the Neurological Rating Scale (Sipe, Knobler, Braheny, Rice, Panitch & Oldstone, 1984) and the Ambulation Index (Hauser, Dawson, Lehrich & Cohen, 1983). The latter tool has been employed in a more recent study to measure degree of disability (Aupperle, Beatty, Shelton & Grontkovsky, 2002).

1.2.7.4. Medication

There is a concern that medication used in the care of patients with MS may affect cognitive function. However, several studies have failed to find a significant association between cognitive impairment and prescribed medication usage (Heaton et al., 1985; Rao et al.,1991a). Use of corticosteroids have been found to affect psychological function in MS (Brassington & Marsh, 1998) and thus the potential effects of such medication should be taken into consideration when carrying out research into cognitive function in this patient group. Turning to the immunomodulatory drugs, Interferon-beta 1a has been shown to slow cognitive deterioration (Barak & Achiron, 2002).

1.3. The relationship between executive function and frontal lobe pathology in MS

In the light of the research findings in the literature which have highlighted impairment in executive processes in patients with MS (see section 1.2.6), the question has been raised as to the role of focal pathology, or presence of lesions in the frontal lobe, in contributing to executive deficits in the context of evidence of widespread brain abnormalities in MS (Foong et al., 1997; Foong et al., 1999). Clinical and imaging studies have provided support for a relationship between frontal pathology and executive dysfunction in this patient group.

Arnett et al. (1994) demonstrated that patients with a preponderance of lesions in the frontal lobe were impaired on the WCST. The authors found that patients made significantly more errors on the test and achieved fewer categories overall than did patients with lesions that were not predominantly located in the frontal lobe.

Foong et al. (1997) further investigated the role of frontal lobe lesion load in contributing to executive deficits in 42 patients with multiple sclerosis. Techniques in MRI considered by the authors as sensitive to detecting lesion load were employed. Performance of the patient group was compared with a control group matched for age and estimated premorbid IQ on a neuropsychological battery comprising of a series of tests focusing on executive skills. The findings showed evidence of impairment in some executive functions, more specifically in working memory, verbal fluency, planning and use of strategy, cognitive estimation and performance on the Stroop test, independent of intellectual decline, psychiatric symptomology or other physical health factors such as impaired vision that ordinarily may have affected performance (Foong et al., 1997). Significant correlations between frontal lesion load and scores on executive tests were established.

Swirsky-Sacchetti et al. (1992) found evidence for a relationship between left frontal lobe pathology and reduced performance on executive tasks of abstract problem solving and verbal fluency in 40 patients with either relapse-remitting or chronic progressive MS. However total lesion load as a result of widespread demyelination was not controlled for in this study.

A more recent study by Benedict, Bakshi, Simon, Priore, Miller & Munschauer (2002) examined the ability of a group of 35 MS patients of progressive and relapse-remitting subtypes on tests of executive function which formed part of a general neuropsychological battery of memory and learning tests and a measure of information processing (PASAT, see section 5.4.2.2.). The WCST was also incorporated and the results highlighted impairment in conceptual reasoning, attention, verbal- and spatial-learning. When controlling for total lesion load in this study, amongst other factors, a strong relationship between the executive process of conceptual reasoning and the superior frontal area of the cortex was nevertheless established using MRI. Although caution has been suggested when generalizing these findings to the rest of the MS population because of the potential selection bias of patients towards those with a greater severity of brain pathology (Benedict et al., 2002), there have been further studies supporting a specific relationship between frontal lobe pathology and executive performance (Comi et al., 1999; Pozzilli et al., 1991).

Turning to the natural history of executive dysfunction in MS, Amato et al. (2001) measured the progress of the disease in patients over a ten year period and found memory and abstract reasoning (an executive ability) to be the first cognitive functions to be affected. Linguistic processes appear to become compromised later in the disease process although linguistic functions are generally considered to remain relatively intact in MS. Linguistic processes can be characterized as less distributed in the cerebral cortex and are therefore less vulnerable at any given cerebral lesion load. Conversely, executive processes rely on more distributed networks (see section 2.2) and are therefore more likely to be affected at any given lesion load.

Although the exact nature of the damage to the frontal lobe as a result of the disease process and the subsequent deficits on executive task performance do not appear to have been fully clarified in MS research, it is likely that frontal cortico-subcortical circuits that link areas of the frontal cortex with other brain regions such as the thalamus, basal ganglia and striatum (Alexander, DeLong, & Strick, 1986; Tekin and Cummings, 2002) are particularly affected by the demyelinating process. These subcortical areas are predominantly white matter and especially vulnerable to the pathological processes in MS.

Thus it is possible that areas outside of the frontal cortex may contribute to executive impairment in MS patients. In MS, lesions to subcortical pathways have been linked to specific cognitive deficits including executive deficits, for example, impaired auditory selective attention (Brassington & Marsh, 1998). Similarly, Comi et al. (1999) consider the 'selective involvement of frontal lobe executive functions' as resulting from the 'disruption of neural connections among cortical associative areas, as well as between cortical and subcortical structures' as a consequence of lesions to the white matter (p. 135). Further studies have reported subcortical and frontal involvement in patients with MS with lesions present in these areas (Brassington & Marsh, 1998).

Nevertheless, there appears to be evidence to support the hypothesis that specific frontal lobe pathology contributes to executive impairment in patients with MS in the context of a widespread disease process, and that anterior brain areas may be one of the initial areas to be affected by the disease (Rao et al., 1991a). In particular, an impairment of response initiation and inhibition processes, and in the ability to switch between task demands, as has been highlighted in the MS literature (Arnett et al., 1994; Comi et al., 1999), is possibly associated with underlying frontal lobe pathology in MS. Given that there is evidence for an impairment of executive processes in this patient group, it is likely that these deficits will impact on the everyday lives of people with MS. This issue will be now be considered in relation to the present study.

1.4. The impact of impaired abilities in the everyday functioning of people with MS

Severe impairment in executive function in any patient group can lead to significant difficulties with planning, dealing with novelty, implementing strategies to successfully perform complex activities, poor attention and poor self-awareness in every day life (Ahola, Vilkki & Servo, 1996; Van den Broek,1999). This is known as 'dysexecutive syndrome'. Changes in personality may be observed, for example increased apathy, a lack of initiation or concern, and increased irritability in an individual who was previously active, enthusiastic and even-tempered (Ahola et al., 1996). Dysexecutive syndrome is associated with focal anterior lesions (Bryan & Luszcz, 2000; Crawford, 1998a; Fuster, 1989; Weinberger, 1993). The precise role of the frontal lobes is discussed in section 2.2.

The inability to inhibit inappropriate verbal responses or behaviour is observed in dysexecutive syndrome. Verbal disinhibition may take the form of 'slips of the tongue', strong habit intrusions, or tactless or inappropriate sexual comments that cause social embarrassment but which are difficult to stop from saying (Reason, 1979). Verbal disinhibition may reveal an underlying dysexecutive syndrome or impairment in inhibitory control mechanisms, particularly when the supervisory attentional system becomes overloaded (Roberts, Hager & Heron, 1994). Patients with frontal lobe pathology or damage, following a head injury for example, have been noted to have difficulties with social disinhibition which cause major difficulties in every day life, particularly in the work place and in social settings (Deb, Lyons & Koutzoukis, 1999). Emotional and cognitive deficits such as these are considered to be the most important factors in determining an individual's ability to return to work and social activities (Van den Broek, 1999). In clinical settings, rehabilitation often targets these difficulties.

Changes in personality and behaviour that are characteristic of frontal lobe syndrome have been reported in some patients who suffer from Multiple Sclerosis (Beatty, 1999; Diaz-Olavarrieta, Cummings, Velazquez & Garcia de al Cadena, 1999). Impairment of various cognitive processes as a result of the disease process can impact on daily life causing significant distress to the individual (Langdon, 1998). More recently, verbal disinhibition and disinhibited behaviour have been reported in MS patients (Diaz-

Olavarrieta et al., 1999; Chiaravalloti & Luca, 2003). Disinhibition has taken the form of sexual disinhibition (Frohman, Frohman & Moreault, 2002), uninhibited talking, the blurting out inappropriate comments and a failure to respond to normal social cues (Lou et al., 2002). It is possible that underlying this evidence of disinhibition is an impairment in inhibitory control processes which may be associated with frontal lobe pathology.

Further impairments such as a lack of flexibility in the cognitive style of patients with MS that can lead to ineffective everyday problem solving and a difficulty in stopping actions which are no longer appropriate to current task demands. A reduced working memory ability can lead to difficulties with tasks that demand planning, organizing and multi-tasking (Langdon, 1998). These executive difficulties can impact on the individual's family and work life. Consequently, a move towards understanding such processes at a cognitive level is likely to provide a more sound basis on which to base rehabilitation techniques that will help people with MS to better manage their cognitive difficulties and will contribute to an improvement in their quality of life (Langdon, 1997).

The second chapter of this thesis will therefore further discuss the nature of executive function and associated theoretical models, particularly the cognitive processes of response inhibition and suppression, task switching and working memory, and the role of the frontal lobes in executive functioning. An overview of how people understand proverbs and metaphors will also be provided since this material is considered relevant to the experimental design of the present study.

CHAPTER 2

THE NATURE OF EXECUTIVE FUNCTION

2.1 Overview

Theoretical models of executive function posit mechanisms which optimize performance in situations requiring the control of multiple cognitive processes (Bryan & Luszcz, 2000). The model includes mechanisms involved in providing appropriate responses to novel situations and mechanisms involved in problem-solving (Christ, White, Brunstrom & Adams, 2003). Also included are abilities to plan, organise, sequence, monitor and correct behaviour, to attend selectively to information and to suppress unwanted or strong habitual responses. Processes associated with working memory also involved (Petrides, 2000b).

Various studies have been conducted to examine how aspects of the theoretical model of executive processes underlie our everyday behaviour. The three executive processes that are considered to be most commonly referred to in the literature include the inhibition of inappropriate responses, shifting of mental set and the monitoring and updating processes involved in working memory (Miyake, Freidman, Emerson, Witzki & Howerter, 2000). These specific processes will be described in more detail later in this chapter (section 2.3.4. to 2.3.6) as they are considered pertinent to the present study. Prior to this issue, however, the specific role played by the frontal lobes in executive functioning will be considered before an overview of the theoretical models of executive function is presented.

2.2. Do the frontal lobes play an exclusive role in executive functioning?

The current literature continues to reflect the debate on whether the frontal lobes play an exclusive role in executive functioning, or whether there is involvement of other brain regions (Andres & Van Der Linden, 1998; Garavan, Ross, Li, & Stein, 2000).

Frontal subcortical circuits that link the frontal cortex of the brain to other brain areas are believed to play an important role in mediating behaviour. These circuits originate from frontal cortical areas including the dorsolateral and orbital frontal regions and the cingulate gyrus (Tekin & Cummings, 2002). Executive problems are believed to arise from lesions to the *dorsolateral prefrontal* cortex and include difficulties with shifting set, mental flexibility, generating or initiating motor programmes and strategies, attending to information, organizing behaviour, monitoring in working memory, and ordering events within the correct time sequence. Lesions to the *orbitofrontal* cortex are thought to result in changes of personality, for example increased disinhibition. Apathy and reduced motivation are associated with damage to the *anterior cingulate gyrus* (Tekin & Cummings, 2002).

Several studies, including functional imaging studies, have provided support for a link between executive process and the frontal lobes (Burgess & Shallice, 1996a; Burgess & Shallice, 1996b; Miller, 1984; Regard, 1981). Duncan and Owen (2000) employed functional imaging methods to highlight the involvement of three regions of the prefrontal cortex of the frontal lobes, the mid-dorsolateral, mid ventrolateral and dorsal anterior cingulate cortex and executive functions such as problem solving, suppression/inhibition of prepotent responses and response selection, working memory, and initial learning of novel tasks. The mid-dorsolateral prefrontal cortex has been found to play a role in the monitoring of information in visual working and spatial memory (Alexander et al., 1986, Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Petrides, 2000a). The mid-ventrolateral prefrontal cortex is involved with executive processes associated with memory processes such as comparing and judging stimuli (Petrides, 2000b) and active retrieval of visual information (Cadoret, Pike & Petrides, 2001).

The anterior cingulate gyrus is located on the medial surface of the frontal lobes (Carter, Botvinick & Cohen, 1999) and is considered to play an important role in the allocation of attention, for example when there is the need to inhibit a prepotent responses or to detect conflicts, motivated attention and error detection (Carter et al., 1999). It is believed that the mid-dorsolateral, mid ventrolateral and dorsal anterior cingulate cortical regions of the frontal lobe collaborate in dealing with complex cognitive demands, lending support to the theory of specialization of function within a particular brain region (Duncan & Owen, 2000). The ACC is also thought to play a role in verbal fluency tasks where several responses are cued or initiated and there is competition in the production of responses. Duncan and Owen describe electrophysical studies in which neurones spread across the dorsal and ventral regions of the frontal cortex are found to adapt the type of information they carry to the demands of the executive task.

A relationship between the frontal lobe and processes of response initiation and suppression has been supported by further functional imaging studies (e.g. Nathaniel-James et al., 1997) and clinical studies using the verbal fluency and Stroop tasks (Frith, Friston, Liddle & Frackowiak, 1991; Pardo, Pardo, Janer & Raichle, 1990; Perret, 1974) (see sections 2.3.4.1 & 2.3.4.2, respectively). Both the anterior cingulate and left dorsolateral prefrontal cortex have been implicated (Barch, Braver, Sabb & Noll, 2000; Frith et al., 1991; Warburton et al., 1996).

Further experimental and clinical evidence suggests that the frontal lobes play a central role in set shifting ability (Metzler & Parkin, 2000; Monsell, 2003), more specifically, the dorsolateral region of the prefrontal cortex (Milner, 1963; Milner, 1964; Monsell, 2003; Sandson & Albert, 1984; Stuss et al., 2000). Patients with frontal lobe lesions have often been observed to have difficulty switching from use of a previous strategy to use of a novel strategy when sorting a series of cards on the WCST (Kimberg & Farah, 1993). 'Stuck-in-set' perseveration is considered to be related more specifically with the left frontal cortex (Monsell, 2003; Sandson & Albert, 1984).

Contrary to the above findings, however, executive function has also been associated with a 'distributed set of neural networks' (Andres & Van Der Linden, 2001). It has been considered that 'supervisory attentional functions, including inhibition (Norman & Shallice, 1986), are sustained by a cortical-subcortical network, and not by a localised region such as the frontal lobes' (p. 39, Andres & Van der Linden, 1998).

Several studies have provided little evidence to support the exclusive involvement of the frontal lobes in response inhibition (Anderson, Damasio, Jones & Tranel, 1991). A review of the literature by Andres and Van Der Linden (1998) in which studies employed 'classical tests' of inhibition, provide contradictory evidence to this exclusive frontal involvement. Andres and Van Der Linden invited a group of patients with lesions exclusively located in the frontal lobes to complete tests of inhibition. The authors found that although the patients were slower than the control group on these tasks, they were not less accurate.

Andres and Van Der Linden (2001) examined the performance of patients with focal lesions located exclusively in the frontal lobes on executive tests such as planning, rule detection and inhibition previously employed by Shallice and others (Shallice, 1982; Burgess & Shallice, 1996a; Burgess & Shallice, 1996b). The findings showed that although this patient group was slower than the control group on two of the executive measures, the groups did *not* differ in terms of accuracy of performance on all three executive tasks as might be expected in patients with lesions exclusive to the frontal lobe. Shallice and Burgess found that significantly more errors and slower responses latencies were produced by the patient group who had lesions that were not exclusively located in the frontal cortex when compared to the control group (Burgess & Shallice, 1996b). This suggests that there is not necessarily an exclusive relationship between the frontal cortex and executive processes and that there may be relative sparing of some executive processes in patients with damage to the frontal lobe (Andres & Van Der Linden, 2001). Andres & Van der Linden (2002) suggest that the frontal cortex 'cannot serve, on its own, as the CE (Central Executive) of the brain' (p. 843). Neuroimaging studies by Garavan, Ross, Li and Stein (2000) have provided further evidence for activation of cortical areas outside of the frontal lobes during performance on executive tests. Involvement of the parietal lobe has also been implicated (Miyake et al., 2000).

Brain regions outside of the frontal cortex have also been implicated in the process of set switching through brain imaging studies. These areas include the parietal lobes, cerebellum, basal ganglia and other subcortical brain structures (Gotham et al., 1988; Monsell, 2003).

There have been several competing theories of executive function that have been proposed by those working in the field of cognitive and neuropsychology. This section will provide an overview of models of executive function to date.

2.3. Theoretical Models of Executive Function

2.3.1. Overview of earlier models

Examples of important models that have shaped our understanding of the role of the frontal lobes in our ability to plan, implement and monitor complex thoughts and actions have been proposed by Luria (1966; 1973) and Norman and Shallice (1980).

2.3.1.1. Luria (1966, 1973)

Luria's work provided early indications that the frontal cortex was associated with executive functioning. Luria suggested that the frontal lobes were involved in the planning, programming, sequencing and control of non-routine actions, overseen by a unitary mechanism, the central executive. He proposed that actions and behaviour are guided by the knowledge gained from errors made by an individual. Subsequently the ability to use such feedback by patients with frontal lobe lesions would be impaired leading to a disruption in their behaviour (e.g. Luria, Primbram, & Homskaya, 1964). The theory, however, has been criticised on the basis that patients with frontal lobe lesions can still perform poorly on executive tasks that rely minimally on feedback from errors (Kimberg & Farah, 1993). Despite these criticisms Luria's work has provided a basis from which much of today's research on executive functioning has stemmed.

Among Luria's many important proposals to the area of neuropsychology, he made a further valuable contribution to the understanding of the frontal lobes in speech and language functions, focusing on the disturbances in language that result from damage to the frontal lobes (Stuss & Benson, 1990).

2.3.1.2. Norman and Shallice (1986)

Supervisory Attentional System (SAS)/Contention Scheduling

Since Luria's earlier account of frontal lobe functioning was proposed, the model that dominated our understanding of executive functions until more recently is one that has been developed by Norman and Shallice (1986). The model attempts 'to characterise the cognitive operations of the frontal lobes and their architecture' (p. 2, Godfrey et al., 1999). Norman and Shallice have proposed a single, or unitary, mechanism that underlies the control of attention and behaviour and provides an understanding of how people might perform in routine and novel, non-routine tasks that involve planning and decision-making. The model comprises of two parts, the Contention Scheduling System (CSS) and Supervisory Attentional System (SAS).

The Contention Scheduling System (CSS) is associated with performance in routine tasks. It is proposed that stored schemata, or collections of actions for routine tasks, are triggered by a stimulus above its threshold level of usual activity. This allows for the actions to continue running until the goal is reached or until competing well learned schema inhibit the present schemata. Input of 'higher level' attentional control is minimal, and actions may run at varying levels of consciousness and complexity, with several schema sometimes operating simultaneously.

When an individual enters a non-routine, novel situation, or one where schemata are conflicting, the SAS (the 'higher level' system) becomes involved in directing attention so that automatic responses of the CSS (the 'lower level' system) are prevented or inhibited from influencing non-routine actions. The SAS, which is believed to be of limited capacity, is hence thought to be involved in situations where there is a strong habitual response to be overcome or where temptation is to be resisted. It is also thought to allow for the planning, organisation and direction of actions towards goals in non-routine, novel situations, and where intervening with difficulties associated with automatic processes is required. Further roles of the SAS include involvement in situations thought to be dangerous, and in allowing for one schemata to be favoured over another. It is also believed to be involved in monitoring of errors. Impairment in these functions of the SAS is thought to result in disorganised behaviour and problems in executing every day tasks such as making a cup of coffee or brushing one's teeth (Forde & Humphreys, 2000).

The SAS is believed to be associated with the frontal lobes since studies of patients with frontal lobe damage have frequently highlighted impairment in their ability to inhibit over-learned or prepotent responses in tasks where novel responses are expected (Forde & Humphreys, 2000) (see section 2.2, chapter 2). The SAS appears to have difficulty 'switching off' a dominant schema which leads to perseverative behaviour.

2.3.1.3. Baddeley's model of Working Memory and the Central Executive

Baddeley (1986) proposed a model of working memory allowing for the very temporary storage, maintenance and manipulation of visual and verbal material. Working memory is theorised to be composed of component parts; two slave systems (the phonological loop and visual-spatial scratchpad), and the central executive. The phonological loop is believed to hold and manipulate verbal or speech based information, and the visuospatial scratch pad is involved in the manipulation of visual information and images. The central executive is proposed to act as an attentional control system whose remit is to control the two slave systems. The central executive is thought to be brought into play when coordinating two simultaneous tasks. Norman and Shallice's (1986) SAS was brought into the model by Baddeley (1986) as a mechanism involved in controlling and diverting attention where required (Barnard, Scott & May, 2001).

Baddeley (1996) has suggested that the central executive may be used as a structure or component through which executive processes may be further studied and analysed. The central executive has been associated with the frontal lobes (Baddeley, Della Sala, Papagno & Spinnler, 1997b), more specifically the prefrontal cortex, as supported by brain scanning studies (Braver, Cohen, Nystom, Jonides, Smith & Noll, 1997).

2.3.2. A new understanding of Executive Function- the fractionation of executive processes

While both Norman and Shallice's (1986) and Baddeley's (1986) models of cognitive function have been able to explain the reason for impaired performance of patients with frontal lobe lesions on some executive-type tasks, both models fail to account for why these patients can show variability of performance on executive tests, often attaining scores within the normal range on some but not all executive tasks (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999; Shallice, 1988).

One explanation for this phenomenon that has been proposed is the existence of clearly separable processes or fractionated subprocesses that may underlie the control of cognitive functions. This has been provided as an alternative approach to understanding executive function and has been central to a current debate within the field (Miyake, Freidman, Emerson, Witzki, & Howerter, 2000). These authors have cited various studies that have provided evidence in support of this argument including studies employing tests of executive function that tap specific executive processes, and functional neuroimaging and lesion studies (Duncan, Johnson, Swales, & Freer, 1997; Duncan & Owen, 2000; Petrides, 2000a).

Godefroy et al. (1999) suggest that such uncertainty about executive function still persists because of an 'underspecification of the control operations themselves' which results in 'a severe limitation of any theoretical account ' (p. 2). Further research is thus required to continue to work towards a better understanding of this area and, in particular, to identify or specify the key cognitive processes involved in the control of complex thoughts and behaviour. This has been supported by other theorists such as Smith and Jonides (1999) who state that the 'highest priority is to turn now further attention to executive processes and their implementation in the frontal cortex' (p.1660).

2.3.3. Executive Theory: the way forward

More recently, there has been increasing emphasis on the importance of inhibition as an executive function. Miyake et al. (2000) quote that this process 'deserves further investigation' (p. 89). Since the purpose of the present study is to examine specific executive functions in MS, which includes the processes of response inhibition and initiation, the review will now focus on the these particular processes. The review will then turn to examine the ability to shift from one task demand to another which is a further focus of the present study.

2.3.4. Executive function and Inhibitory Control

2.3.4.1. Response Initiation

A process that is associated with inhibitory control is the ability to initiate appropriate responses (response initiation) (Burgess & Shallice, 1996a). Studies examining this ability have highlighted how patients with frontal lobe lesions have shown poorer performance on tests of verbal fluency that examine response initiation when compared to patients with lesions to other areas of the brain (Burgess & Shallice, 1996a; Miller, 1984). The Verbal Fluency task is considered to be a classic test of executive functioning because of its reliability and good discriminatory power (Phillips, 1997) (see section 5.4.3.1.). It is thought to involve processes of selecting, generating or initiating stimuli from a larger set (animal names or words beginning with a particular letter). Both the maintenance and monitoring of word production, and the generation and control of strategies in retrieving items from longer term memory, are also thought to be involved (Fletcher & Henson, 2001).

2.3.4.2. Response Inhibition

Various studies have focused on inhibitory control, a process involving the purposeful and controlled inhibition or suppression of over learned, dominant, automatic or prepotent (previous) responses that allows for more goal directed behaviour (Miyake et al., 2000). Inhibition has been defined by Simpson and Schmitter-Edgecombe (2000) as 'the process by which the irrelevant stimulus is ignored' (p. 310).

There are several neuropsychological tests commonly used in neuropsychological studies to examine the ability to both initiate and suppress responses. Traditionally Go/No-Go tasks (Drewe, 1975) have been employed to examine inhibitory control and response selection. Smith and Jonides (1999) have described use of the Stroop task (Stroop, 1935) to consider the relationship between inhibition and attention. This task consists of names of colours which are presented in different coloured print in relation to two conditions. In the first condition colour names are presented in the same colour print. The second condition involves colour names presented in different colour print. Performance in the latter condition is usually poorer due to competition arising between two conflicting executive processes. Attention is automatically focused on naming the word that is in conflict with the process of naming the colour of the print (the weaker process of the two). Attention and inhibition processes are subsequently brought into play and attention is diverted to processes relevant to the task (that is, naming the print colour and to deliberately inhibiting the irrelevant but automatic and more dominant process of naming the colour word) to ensure that the task performance is successful (Smith & Jonides, 1999). See section 2.2 for discussion of the relationship between response inhibition and the frontal lobes.

There appears to be speculation as to the relationship between response suppression and initiation (Perret, 1974). One well-established neuropsychological measure, the Hayling test, developed by Burgess and Shallice (1996a; 1996c), has been used in clinical and research capacities to examine the ability to both initiate and to inhibit verbal material (see section 5.4.3.2.). The advantage of this test, unlike those employed in earlier studies, has been the possibility of examining both of these executive processes within the same task and under the same demands and conditions, thus reducing the potential effect of background factors that may interfere with the findings.

2.3.4.3. The Hayling Test

The Hayling test involves two sections, both of which involve the presentation of 15 sentences in which the last word is missing. The individual is required to complete each sentence with a missing word; the missing word is expected to be strongly cued by the sentence itself with a 'high probability of a particular response occurring' (p. 264). Section A involves completing the sentence as quickly as possible with a word that best completes the sentence, thus examining the ability to initiate automatic responses. Section B, however, requires the individual to complete the sentence with a word that does not make sense in the context of the sentence, for example, by using a nonsensical word. This condition examines the ability of the individual to initially suppress an automatic, strongly cued, well-learned response prior to generating a novel word that makes no sense in the context of the sentence. Responses in section B are categorised according to whether they were unrelated to the sentence (as required by the instructions), were connected to the sentence (a sensible completion) thus breaking the test instructions, or were semantically related to the sentence in some way. Response latencies are also examined to provide a measure of response initiation speed (sum of the response latencies) for each section. In particular, the difference between section B latencies minus section A latencies is calculated. This is thought to represent the thinking time required to generate an inappropriate, novel response compared to a word that best fits the context of the sentence as in section A.

Burgess and Shallice (1996a) examined the relationship of semantic or verbal inhibitory processes with the frontal cortex in an attempt to evaluate the functioning of the SAS (see section 2.3.1.2.). In comparing patients with damage to the frontal lobe (the 'anterior' group) with the patient control group (posterior group with no frontal involvement) that were matched for age and IQ, the anterior group were more impaired in their ability to initiate verbal responses and to suppress habitual responses as expected (see section 2.2). The anterior group appeared to have used their 'thinking time' less effectively by taking significantly longer in both sections than the patient control group. The importance of considering both errors rates and response latencies in understanding the nature of spared abilities in tasks of inhibition has been supported by Christ et al. (2003).

To date there appears to be only one (unpublished) study that has applied the Hayling test to an MS group (Nathaniel-James, 2000). The study found MS participants to perform significantly worse on Part B of the Hayling test in term of response suppression (number of errors) and efficiency in suppressing inappropriate responses (time latency). No differences were observed between the groups in terms of response initiation (part A).

Two perspectives will now be outlined in providing a theoretical underpinning to an understanding of response initiation and suppression.

2.3.5. A Cognitive Perspective to the understanding of initiation and inhibitory mechanisms

There is as yet little understanding of the nature of these executive processes at a cognitive level (Metzler & Parkin, 2000). Metzler and Parkin (2000) state that ‘demonstrations of frontal disinhibition are not linked to any formal specified account of inhibitory processing’ (p. 364). Consequently relevant theoretical accounts of inhibitory processing that take a cognitive perspective will now be reviewed.

2.3.5.1. Information Processing Model (Posner & Snyder , 1975)

According to this model, two processes of ’spreading activation’ and strategic conscious attention can be both called into play when single word items are retrieved from long term memory. Nathaniel-James et al. (1997) have applied this theory to better understanding the role of response initiation and suppression processes during completion of the Hayling test as follows.

‘Spreading activation’ involves an association process that is automatically initiated by presentation of a stimuli. Nathaniel-James et al. have hypothesised that when sentences are presented in the first part of the Hayling task, related or connected words that best complete the sentence are retrieved from long termed memory via this automatic, non-attention demanding cognitive process where strategic processes play little role. The second process, involving conscious attention, is thought to be called upon in the second part of the Hayling task. It is suggested that this second condition requires the employment of attention demanding strategies to allow for the suppression of automatic prepotent responses and the generation of an unrelated, inappropriate word.

2.3.5.2. Working memory and inhibition

Working memory in MS is a further focus of the present study, yet there remains relatively little understanding about the relationship between working memory (Baddeley, 1986) and inhibition (Roberts et al., 1994). It has been suggested that these two processes are 'intimately' related such that a reduction in the efficiency in one of these processes (for example, working memory) can reduce the ability to inhibit prepotent responses (Roberts et al., 1994). Similarly, greater activation of working memory may be required when inhibition of stronger prepotent responses is required (Cohen & Servan-Schreiber, 1992). Roberts et al. (1994) suggest that there are two minimum requirements to successfully prevent disinhibition; to keep in mind information that is required in making an appropriate response and then to use that information in order to guide actions appropriately.

2.3.5.3. Production-system model and inhibition

According to this connectionist model by Kimberg and Farah (1993), the likelihood of prepotent responding increases as working memory associations weaken and there is difficulty in coping with competition between responses. Consequently, success in inhibiting responses efficiently is considered to be 'a function of the strength of the prepotency, the current functioning of working memory processes, and the working-memory demand of the task' (p.376, Roberts et al., 1994).

2.3.5.4. Neural Network Model (Houghton and Tipper, 1996) and inhibition

A model that has been developed in recent years to allow for a better understanding of the procedure involved in the selection of appropriate responses is that by Houghton and Tipper (1994; 1996). Metzler and Parkin (2000) have outlined how the model incorporates the role of inhibitory mechanisms and proposes that there are at least two processes that work together. The inhibitory mechanism enables the processing of distracter information to be suppressed while an excitatory mechanism allows for the processing of the target. Distracter items are hence in competition to gain control in determining the response.

Systems or 'fields' are believed to be involved in the selection of an appropriate target which are associated with different areas of the cortex. Critical features of the target are internally represented as selection or 'target' templates and stored in 'target fields'. The prefrontal cortex is thought to be associated with the generation of goals, plans and selection templates that are involved with carrying out the task. When a target and distracter item are physically presented to the individual, internal representations of these items or objects are believed to be activated. These internal representations are known as 'object fields' and are associated with the posterior cortex.

During selection of a target, the internal representation of the object is compared with the selection/target template. Both of these internal representations are believed to be represented at the neural level as particular patterns of activation over nodal connections composed of 'property nodes'. The degree of activation of the object representation is determined by whether there is a match between the object and target patterns of activation. A match involves inhibitory feedback loops to the nodes being removed resulting in a greater degree of activation of the object representation. Excitatory feedback loops are removed when there is a mismatch, resulting in a reduction or suppression of the activation of the object representation. It is proposed that the matching of the representations occurs in the basal ganglia. In terms of the distraction representation, the distracter pattern will continue to be activated above the baseline level in the physical presence of the distracter resulting in the continued excitation of the representation. However, the level of activation will drop below the baseline when the distracter is removed and excitatory input is no longer present. The activation level is reduced as a result of the suppressing function of an inhibitory mechanism.

2.3.6. Executive Function and Set-Shifting

Various cognitive models have now been summarised to better understand the processes of response initiation and suppression. However, since a further important focus of this study is the ability to shift concept or task demand in patients with MS (see section 1.4), the review will now turn to consider the literature concerning this executive process.

The term 'set-shifting' refers to the ability to shift between multiple tasks, concepts or mental set involving cognitive, attentional, or executive control (Monsell, 1996). The ability to sequence complex cognitive tasks relies on the ability to switch between information or task set. An impairment in the ability to shift set, for example on the WCST (see section 1.2.6.3) can lead to perseveration, in which a particular response or strategy that has been triggered by internal or external stimuli is repeated continually when it is no longer appropriate, or required for the given event (Stuss & Benson, 1986). There is likely to be a dissociation between actions and goals and the individual becomes 'stuck' on an old task, response or motor programme (Sandson & Albert, 1984).

A difficulty in changing set may indicate impaired inhibitory mechanisms that fail to inhibit the prepotent (and possibly previously correct) response strategies. This failure does not allow for a shift in application of a new rule. A difficulty in utilizing feedback may underlie the ability to shift to a new category (Kimberg & Farah, 1993).

There appears to be a variety of ways in which task sets may be evoked. The tendency to perform particular task sets may be triggered by external stimuli that are habitually associated with such sets. This may occur in the presence or absence of the intention to select and implement a task set (intentional control, Monsell, 2003). Intentional control enables planned goals to be achieved through the active selection and execution of appropriate task-sets whilst allowing for irrelevant goals to be ignored (Duncan, 1990). More practiced tasks may be held in memory, thus allowing for their more efficient retrieval. It is thought that under intentional control, a change in task-set can also occur in advance of the triggering effect of an external stimulus (Monsell, 2003). Hence the ability to shift-set and perform complex cognitive tasks 'results from a complex interplay of deliberate intentions that are governed by goals and the availability, frequency, and recency of the alternative tasks afforded by the stimulus and its context' (p. 134; Monsell, 2003). A fine balance between the degree of intentional control that ensures the task is performed effectively, and the degree of flexibility needed to enable a change in set to occur as demanded by the environment, is considered to be essential to the effective execution of cognitive processes and switching of task-set (Monsell, 2003).

When designing experimental tasks to examine the phenomenon of task-switching, particular issues should be considered (Monsell, 2003). Set shifting experiments commonly involve training participants to undertake simple tasks or trials at the initial stage of the experiment that do not involve switching set ('non-switch' trials). On subsequent trials of the experiment the requirement to shift set may be introduced ('switch' trials). Cognitive processes involved in set shifting, and / or associated brain areas, are examined when there is a change in task demands.

Monsell (2003) has outlined four important concepts should be considered when undertaking experimental tasks of set shifting. These are reviewed below:

- **Switch cost (task repetition benefit):**

Longer response initiation times and a higher error rate are usually apparent after a task switch (a trial involving task switching) than when a trial does not involve task switching or when it only involves the repetition of tasks within the trial.

- **Preparation effect:**

There is usually a reduction in the switch cost (see above) when knowledge of an upcoming task is given in advance allowing the participant to prepare for this process. However this effect is not necessarily eliminated (Meiran, Chorev, & Sapir, 2000b). An alternative view, however, considers the reduction in switching cost to result from the passive dissipation of the previous task set rather than from time to prepare (Meiran et al., 2000b).

- **Residual cost:**

This is the remaining cost when the switch cost is not completely eliminated by preparation (Meiran, 1996).

- **Mixing cost**

As well as a short term cost of switching, there is a longer term cost of switching. The latter occurs because resources must be allocated to prepare for, or manage, the possibility that a shift could be required. The no-shift condition cannot be assumed. Thus there is a slowing of responses that occurs following a switch trial compared to when a task-repetition trial is performed.

Switching set is thus considered to involve a variety of cognitive processes or a 'mental gear changing' or 'task set reconfiguration' (TSR) (p.135; Monsell, 2003). Processes include: shifting attention between concepts or stimuli; retrieving information about goals and methods or rules for achieving these; reevaluating the response criteria; and inhibition of previous or irrelevant sets and initiation of the new set.

Various reasons for the occurrence of switch cost have been suggested and there has been a move towards considering more than one reason for this phenomenon rather than focusing on a single explanation (Monsell, 2003). One explanation for the switch cost effect is the time involved in undertaking TSR (Monsell, 2003). It has been suggested that the process of 'task set reconfiguration' occurs in an 'all-or-nothing' fashion (De Jong, 2000). That is, prior to the onset of the stimulus, the TSR will be attempted and participants are likely to be as fully prepared for the shift of set as for a trial that does not require a change in set (a task repetition trial). However they will only be successful on some of the switching trials, possibly because these are trials for which the participant was able to retrieve information concerning goals and methods of their achievement successfully. When participants are unable to mentally 'shift gear' prior to the onset of the stimulus, they are believed to do so after stimulus onset. Speed of processing is known to be reduced in MS (Beatty et al., 1988), therefore it is hypothesised that MS patients may make more errors after a task switch.

Secondly it is suggested that switch cost occurs when a participant is required to overcome a stronger or more familiar task-set so that a weaker or less familiar task set may be performed (Allport et al., 1994). The participant is required to apply a greater amount of inhibition to the stronger set and the effect of this inhibition continues in the subsequent trial leading to residual cost. Thus performance is affected because initiation or selection of the new response is likely to take more time whilst the residual inhibition is being overcome. The stronger the task-set the greater the switch cost (Allport et al., 1994; Allport & Wylie, 1999). Since disinhibition is a feature of MS, switching task set may demonstrate a deficit (Diaz-Olavarrieta et al., 1999; Lou et al., 2002).

Thirdly it is suggested that when the current stimulus primes the retrieval of task sets with which it is associated (associative retrieval), a mixing cost may occur; that is, there is a greater slowing of responses following the trial (Allport & Wylie, 2000; Monsell, 2003). This is known as long term priming and tends to be greater on a switch trial than a repetition trial. Hence a switch cost may result (Allport & Wylie, 1999). Efficiency of processing in MS is poor, and thus reduced speed and disinhibition are likely to compound, resulting in a large effect on mixing cost.

The above accounts of the switch cost phenomenon have not escaped criticism. There has been a lack of consideration of other cognitive processes that may also been involved in switch cost (Monsell, 2003). For example, when the participant is able to predict the task switching pattern (predictable switching), information concerning the next task is likely to be retrieved from memory. When the switching task is unpredictable (unpredictable switching), the process of recognising or interpreting the stimulus or cue to the next switch is involved. These processes may also contribute to the preparation effect (Monsell, 2003). A greater involvement of working memory is likely in switching tasks since participants are required to hold two tasks simultaneously in memory whilst monitoring the task sequence (Monsell, 2003).

Baddeley, Chincotta, & Adlam (2001) carried out a series of experiments to investigate the relationship between working memory and task switching. They concluded that when participants were required to perform blocked or alternating (switching) tasks of arithmetic, either alone or with a concurrent condition (a verbalising task placing demands on the phonological loop of Baddeley's working memory model), the switch cost effect increased with concurrent task demands. The authors suggest that under switching conditions the central executive plays a consistent role, where as the articulatory loop plays a greater role when the switching programme is to be maintained. Working memory in MS has found to be reduced (Litvan et al., 1988; Rao et al., 1993).

Various experimental tasks have been employed to investigate set-switching. Earlier designs include comparison of the time taken to complete blocks of alternating tasks versus blocks of a single repeating task (Jersild's method, Monsell, 2003). An alternative paradigm involves alternating the task after a predictable number of trials. This allows for the comparison of task switching versus repetition tasks *within* a block (alternative-running paradigm). This paradigm is considered to overcome problems of additional inconsistencies that may occur between blocks found with Jersild's method. For example, a greater load is likely to be placed on working memory with alternative blocks than with repetition task blocks, possibly leading to greater arousal on the alternating blocks (Rogers & Monsell, 1995).

A further paradigm is the task-cueing paradigm (Meiran, 1996; Sudevan & Taylor, 1987). Here the task that is to be performed is cued either prior to or with the stimulus. Thus the random nature of the condition makes the task far less predictable. The amount of time between the cue and the presentation of the stimulus may also be manipulated to allow the participant to actively prepare for the task (Monsell, 2003). It is likely that experimental procedures involving switching will be particularly challenging to people with dysexecutive difficulties. The relationship between set shifting and the frontal lobes has been described earlier in section 2.2).

In the light of the present study which is investigating executive processes including the inhibition of verbal responses and ability to switch task demands in patients with MS, two experimental tasks have been designed specifically for this purpose. The final section of this chapter provides an overview of salient concepts associated with these tasks, in particular, the use of proverbs which compose one of these tasks.

2.4. Proverbs and Metaphors

Clinically, it has long been acknowledged that people with frontal lobe dysfunction cannot explain proverbs but offer literal, concrete meanings ('literal-mindedness', Lezak, 1995). In healthy people, it has been shown through experimental tasks (Blasko & Connine, 1993; Keysar, 1989) that metaphors can be understood 'as quickly and automatically as we understand literal meanings' (p. 92; Glucksberg, 2003). Thus, understanding literal meanings is not necessarily more efficient than the comprehension of non-literal metaphors. The process of understanding metaphor (for example, 'he kicked the bucket') is thought to involve three stages (Glucksberg & Keysar, 1993): first, deriving the literal meaning of the metaphor and then evaluating the metaphor in the context in which it has been said. Finally, since the literal metaphor does not make sense, it is rejected and a non-literal meaning that does not make sense is found. Thus, comprehending metaphors is often difficult to inhibit or ignore and this process of understanding occurs with little intentional effort (Glucksberg, 2003). It is believed that metaphors with meanings that have greater salience or are of greater familiarity will be more quickly understood than those which are less familiar or have less salience (for example, 'he kicked the bucket' versus 'dead cat bounce') (Glucksberg, 2003).

However, these factors alone do not increase the metaphor's comprehensibility, and a novel or non-literal metaphor will be as quickly comprehended as a literal phrase. It appears, therefore, that metaphor may offer an experimental model for the investigation of dysexecutive syndrome and the ability to inhibit or suppress verbal material.

CHAPTER 3

METHODOLOGICAL ISSUES IN RESEARCH

3.1 Executive Function Research

Several methodological issues have been raised in relation to research into executive function. Those issues that are more pertinent to the present study are outlined below.

There has been debate as to whether use of groups or single case studies are adequate methodologies for research into this area. There has been a tendency to employ group studies. However, single cases have been considered to be more suited for the development of theory, particularly at the cognitive model level. The use of single case designs and double dissociation type methodology, nevertheless, has its limitations. For example there is rarely a direct correspondence between observed behaviour and underlying executive processes that subserved these behaviours, which results in a low process- behaviour correspondence (Burgess, 1997). Consequently, the use of group studies in conjunction with single case designs has been advocated to ensure that the methodology employed for the purpose of research in executive function is sufficient and adequate. Group studies are considered particularly useful in examining more global issues concerning the executive function system (Burgess, 1997).

A fundamental problem in executive research is the relative impurity of executive tasks employed. Executive measures are considered to be more impure than non-executive tasks because executive tasks are unlikely to exclusively tap the process in question. Rather, they tap a range of processes that are *not* intended to be measured. This measurement error leads to uncertainty about the purity of results and validity of executive tests: do they really measure what they are meant to measure? (Burgess, 1997; Phillips, 1997). Executive tests have also been criticised for their 'failure to capture the core difficulties faced by the client with executive dysfunction' because of their high structure and lack of clearly specified criteria for successful completion of the task (p. 209, Crawford, 1998a).

Task demands such as 'inhibition', 'planning' and 'monitoring' may lack construct validity because they may all arise from the same underlying system but are simply given different names or labels (Rabbitt, 1997). The exact definition of this system is unclear and may be defined at various levels (at the neuronal level or cognitive level, for example). Executive tasks are also considered to have low test- retest reliability which can lead to measurement error. This is because such tests can only be novel once and novelty is thought to be a key factor in highlighting executive deficits (Rabbitt, 1997).

The idea that executive tasks commonly share underlying processes leads to problems in investigating the separability of executive processes (Burgess, 1997). It is observed that performance by individuals without brain damage on one cognitive task is likely to correlate positively with performance on other cognitive tasks (known as cognitive congruence). In order to overcome this problem the use of a task where there is consistency in the background demands of the test has been suggested. The Hayling test (Burgess & Shallice, 1996c) is considered to be one such task that allows for exploration of a possible dissociation of executive processes (Burgess, 1997) (see section 2.3.4.3).

Use of large samples in group study design has been advocated in overcoming problems such as task impurity and cognitive congruence which can hide subtle deficits in executive function. Furthermore, the generalisability of findings to the wider patient population in terms of executive processes may be difficult when single case methodology is employed because results from an individual may be atypical of the group (Baddeley et al., 1997a).

The use of a correlational, factor-analytic approach to examining hypotheses in research on executive function is considered to be limited. Correlation does not imply causation and thus testing of hypotheses about executive mechanisms or cognitive models may be inadequate (Baddeley et al., 1997a). An approach that is considered to be better suited to the testing of hypotheses is use of an experimental design that allows for the manipulation of variables (Baddeley et al., 1997a).

More recently, Miyake et al., (2000) have promoted the use of another approach to examining the organization of executive functions and the degree to which they are unitary or separable. They consider latent variable analysis, which involves examining what is *shared* among multiple task examples for each executive function, to be an approach that overcomes problems that have been previously encountered using factor analysis at the level of *manifest* variables (i.e. individual tasks). This particular approach is considered to reduce the problem of task impurity and poor construct validity.

3.1.2. Ecological Validity of neuropsychological measures

There is a growing emphasis and awareness of the need to ensure that measures employed in assessing disability, functional and cognitive capabilities have ecological validity; that is, 'the degree to which clinical tests of cognitive functioning predict functional impairment' (p.185, Higginson, Arnett & Voss, 2000). Such measures should increasingly focus on how impairments meaningfully impact on patients' lives (Brassington & Marsh, 1998) and this idea is particularly important for the purpose of rehabilitation where strategies and interventions are offered so that identified impairment may be better managed by the patient in improving quality of life. This concept should apply to research in MS in the light of the everyday difficulties that are reported by these patients as a result of cognitive impairment (Amato et al., 2001; Langdon, 1998). Higginson et al. (2000), nevertheless, found that the best predictors of functional impairment in patients with MS were standardised tests and questionnaires of memory and attention that were analogous to everyday tasks. Experimental tasks, however, often target very circumscribed cognitive skills, whereas tasks in everyday life require a wide range of cognitive competence.

Finally there is an issue as to how accurately formal psychometric test scores reflect a patient's own experience (Langdon, 1997). Thompson (2002) has suggested that gaining an understanding of the patient's perspective into cognitive function is 'undoubtedly an increasingly important consideration' (p. 358) and there is now an impetus to include measures in future research studies, including those with MS patients, that will provide an insight into the patient's perspective of their difficulties. A self-rating questionnaire, the DEX (Wilson, Alderman, Burgess, Emslie & Evans, 1996), which samples many of the symptoms associated with impairment of executive function (e.g. motivation, behavioural, cognitive changes) has been used to gain participants' views of their difficulties, including those of patients with MS (Nathanial-James, 2000).

3.2. Issues Pertinent to Research in Multiple Sclerosis

There are several potential confounding factors to studying cognitive function. These should be taken into consideration when undertaking research in MS. Physical impairments that include visual problems may affect performance on tasks requiring sensori-motor response such as pressing keys and completing the performance subtests of intellectual test batteries. Physical slowing may confound the results of tasks measuring cognitive information processing speed. Fatigue and mood may also affect performance on tests and fluctuations in these variables from one occasion to another may confound test results. Use of suitable measures with people who have MS that do not, for example, rely on strong sensory-motor abilities may be advised.

Further important factors to be considered when undertaking research in MS include the nature of the participants who may vary in the degree of their disability, disease subtype, level of fatigue, affect, and type of medication they are taking. MS studies may be potentially criticised for failing to control for the effect of these factors on performance. To ensure that participants perform at their optimum level it is important to identify when the best time of day is when the patient is least fatigued, and to test patients in their own home. Frequent rest breaks are advised (Beatty, 1999).

The sensitivity of executive tests to frontal lobe pathology in neurological conditions in which there is widespread damage may be questioned because poor executive performance may arise from abnormalities outside of the frontal lobes which hence influences findings (Anderson et al., 1991). Subsequently it is suggested that caution should be taken when interpreting poor performance on executive tests as indicating frontal lobe pathology in MS (Anderson et al., 1991; Foong et al., 1997).

CHAPTER 4

RATIONALE, AIMS & HYPOTHESES OF THE THESIS

4.1. Rationale & Aims

Since it is now well established in the literature that executive skills are compromised in patients with Multiple Sclerosis, and given that there is evidence for some degree of frontal lobe pathology in this patient group, including verbal and behavioural disinhibition (Diaz-Olavarrieta et al., 1999; Frohman et al., 2002; Lou et al., 2002), in the context of a disseminated pathology (e.g. Arnett et al., 1994; Swirsky-Sacchetti et al., 1992), one could speculate that the ability to initiate and suppress verbal responses may be compromised in patients with MS. Consequently, one aim of this study is to examine whether the ability to initiate and suppress verbal responses, and to generate novel responses following response suppression, is significantly impaired in individuals with MS when compared to a normal healthy control group.

To enhance our understanding of the nature of executive function, it is important to examine different executive processes. The ability to switch from one instruction or task demand to another was therefore also examined. This executive process has been found to be compromised in MS patients with significant frontal lesions and it appears to have received limited attention within the MS research literature. Working memory will also be considered because of the significant impairment in this cognitive function that has been highlighted in patients with MS. The potential value for examining these questions for the clinical setting have been outlined in section 1.4.

The relationship between mood, disability, fatigue and patients' own perspective of their difficulties, and their actual performance on cognitive tests, will also be examined as these factors may affect performance and should be taken into consideration when explaining the findings.

4.2. Research hypotheses

1. Participants with MS will perform significantly worse than normal healthy controls on the Hayling test and experimental tasks in conditions that require initiation and suppression /inhibition of verbal responses, and in conditions requiring the generation of novel responses to replace responses that have been suppressed. It was predicted that MS participants will be less able to suppress obvious choices to complete a series of sentences, and particularly when required to suppress over learned habitual verbal responses when completing a series of familiar proverbs of the experimental task.

2. Participants with MS will perform significantly worse than normal controls in conditions that require the ability to switch from one task demand or instruction to another of the experimental task.

3. Participants with MS will perform significantly worse than normal controls on tests of working memory.

CHAPTER 5

METHOD

5.1. Participants

Ethical approval for the recruitment of MS participants for the study was obtained from the Harrow Research Ethics Committee. Further amendments that were made to the research protocol (increasing the age of the participants from 65 to 70 years and including participants with all subtypes of MS) were approved at a later date by Chairman's action.

Ethical approval was obtained from the research ethics committee at Royal Holloway and Bedford College, University of London, for the recruitment of control participants.

All participants gave written informed consent before taking part in the study (see Appendices 1 & 2, p.s 191 - 196 for copies of ethics approval letters, information sheets and consent forms).

5.1.1. MS participants

A total of 22 participants who had been diagnosed with clinically definite or clinically probable MS (Poser et al., 1983) were recruited for the study. All patient participants were under the care of two Consultant neurologists at a regional hospital. Participants were recruited on the basis of MS diagnoses recorded in medical notes, providing that they met other inclusion criteria for the study.

5.1.2. Exclusion criteria

MS Participants were excluded if they did not have a diagnosis of clinically definite or clinically probable MS recorded in the medical notes. Participants were excluded if they were not between the ages of 18 and 70 or if they had previously suffered a neurological condition such as meningitis or epilepsy or a head injury leading to unconsciousness. Participants with a past history of severe mental illness were excluded. Any participant who met criteria for alcohol or drug dependence were excluded.

Any participants with significant sensory or motor difficulties, for example visual problems, hearing impairment or language difficulties including severe dysarthria were excluded because it was thought that these factors might significantly interfere with their neuropsychological and experimental test performance. Any participant deemed too cognitively impaired to give informed consent would not be recruited. Because the tests were predominantly language-based, participants were also required to be educated in England. The exclusion criteria were ascertained using a brief questionnaire composed and administered by the author at the time of meeting the participants, with follow up questions as appropriate (see Appendix 3.1, p. 197 for a copy of the questionnaire), and by consulting the medical notes.

Twenty-two participants with MS were recruited. Four participants had a diagnosis of primary progressive MS, 12 had secondary progressive MS, 1 was described as having progressive type MS, and 5 had relapsing remitting type. Sixteen were female, six were male. The mean age was 53.3 years (range 25-70 years). The mean number of years of education was 13.8 (range 9-19 years). The mean duration of disease was 15.9 years (range 4-38 years). All participants were educated in England and fluent in English. None were excluded because of severe cognitive impairment or current severe distress. All participants lived in their own home.

Two participants who were approached for the study declined to take part due to time constraints and family commitments. A further participant was excluded after having participated in the study when it was discovered that she had not been educated in England.

5.1.3. Healthy control participants

Twenty-two healthy control participants were recruited for the study from the general population through a local company and through friends of the author. The control participants were matched with the MS participants according to age, gender, years of education, and premorbid and current IQ (see sections 6.3 & 6.4). Sixteen were female, six were male. The mean age of the control participants was 46.2 (range 21- 70 years). The mean number of years of education was 13.8 (range 9-19 years). All participants were educated in England and were fluent in English. There were no control participants who declined to take part in the study after having been approached. The same exclusion criteria for the MS participants (see above) were applied to the control sample. Control participants met the inclusion criteria on the basis of a questionnaire composed by the author (see Appendix 3.1, p. 197) that was administered at the time of meeting the participant.

5.2. Effect of disability on performance

The measures that were chosen for the study, and their mode of presentation, were not considered to place heavy demands on the motor abilities of participants. Motor abilities may be compromised in people with MS, and therefore the majority of the measures relied on spoken responses rather than speeded manual responses to ensure that participants would perform at their optimal level. The following measures were used:

5.3. Background measures

5.3.1. Disability

Disability rating scales were included to establish the degree of disability experienced by MS participants and the relationship of disability with other factors such as cognitive abilities.

5.3.1.1. The Hauser Ambulation Index (AI) (Hauser et al., 1983)

This index is an ordinal scale that provides an assessment of timed walking and ability to transfer. The scale ranges from 0 (normal gait) to 9 (unable to walk or transfer independently) and may be administered by a family member or nurse. Although there has been no formal validation of the scale the index is considered to have face validity. It has further been suggested that the AI may be a more sensitive method of detecting a change of neurological impairment that the EDSS (Kurtze Expanded Disability Scale (Kurtze, 1983). It appears to be well correlated with the EDSS (Beatty & Goodkin, 1990) and has the advantage of being quickly and easily administered. The AI has been employed in a more recent study to measure degree of disability in MS (Aupperle et al., 2002).

5.3.1.2. The Troiano Scale (TS) (Herndon, 1997)

This descriptive scale assesses gait, activities of daily living (ADL) and the ability to perform a transfer to provide a measure of impairment and disability. It is an ordinal scale where gait is measured on a 5-point scale, ADL on a four-point scale, and transfers on a 3-point scale. Although this scale has not been formally validated, it has the advantage of being quickly administered by a nurse or technician.

The two disability measures were only given to the MS participants. Both measures were recommended by Herndon (1997).

5.3.2. Fatigue

Visual Analogue Scale (VAS)

The VAS provides a global description of fatigue by asking the patients to indicate their degree of fatigue on a scale. The VAS used in the present study asked participants to rate their level of fatigue on a Likert-type scale with choices ranging from 'not at all tired', 'a little tired', 'quite tired', 'very tired', or 'the most tired I have ever felt.' When scoring the rating of fatigue, a number will be ascribed to each label such that the measure is a 5 point ordinal scale (see Appendix 3.2, p. 199).

In a recent study Archibald and Fisk (2000) used a visual analogue rating scale of fatigue severity that highlighted a significant difference between the MS and control group.

5.3.3. Mood

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983).

The aim of this questionnaire is to detect anxiety and depression. The scale consists of seven anxiety items and seven depression items that are rated by the participant. Their immediate reaction to the items is encouraged and items are rated according to the participant's mood state over the past week. Each item is rated on a four-point scale ranging from absence of a symptom (0) to maximum symptomology (3). A total score of 8 and above for each subscale (anxiety or depression) is considered significant.

The HADS scale has the advantage over other mood measures such as the BDI (Beck & Steer, 1987) of reducing the confounding effects of physical symptoms on the measurement of mood. This was considered a particularly important issue when assessing mood in an MS population where there is a high incidence of physical symptoms. This would allow for the identification of participants who were more severely depressed or anxious and to help establish whether or not mood might have affected performance on tasks.

Crawford et al. (2001) provide normative data for the HADS from a large non-clinical sample considered to be relatively representative of the general adult population of the UK in terms of age, gender and occupational status. The HADS has been employed as a measure of anxiety and depression in several MS studies (Camp et al., 2001; Foong et al., 1998; Foong et al., 1999).

5.3.4. Subjective rating of difficulties

The Dysexecutive Questionnaire (DEX) (Wilson et al., 1996)

This is a 20 item questionnaire that samples four broad areas that are usually associated with Dysexecutive syndrome: emotional or personality changes, motivational changes, behavioural changes, and cognitive changes. The DEX is part of the Behavioural Assessment of the Dysexecutive Syndrome (Wilson et al., 1996) that predicts everyday problems arising out of Dysexecutive Syndrome. One of the items of the DEX measures disinhibition ('I do or say embarrassing things when in the company of others'). Another item measures the inability to inhibit responses ('I find it difficult to stop myself from doing something even if I know I shouldn't). Participants rate items on a five point Likert scale from 0-4 (from 'Never' to 'Very often'). There are two versions of the questionnaire. One version is completed by the participant, and the other version is completed by someone who knows the participant well such as a relative or carer. For the purpose of the present study, however, only the version to be completed by the participant was included in the protocol. This would provide an insight into the MS participant's own experience of their difficulties and the impact of these on their everyday life. Although this idea is not part of a formal hypothesis of the study, gaining an understanding of the patient's own perspective is becoming increasingly important in research in MS (Thompson, 2002).

5.4. Baseline Cognitive measures

5.4.1. General Intellectual Functioning

The NART and VESPAR measures were included to provide an estimate of premorbid and current level of intellectual functioning.

5.4.1.1. The National Adult Reading Test (NART) (Nelson, 1991)

The NART provides a premorbid estimate of intellectual or cognitive functioning. This test assesses single word-reading ability, which is thought to be relatively well-maintained in the presence of a widespread impairment of cognitive processes. The test is composed of a list of 50 single words presented in order of increasing difficulty. All of the words are irregular according to the common rules of word pronunciation. The words were presented in large enough print to ensure the visual problems associated with MS would be unlikely to interfere with reading. The error score is the total number of errors made on the complete NART (50 minus the total number of errors made).

The test has been standardised on neurological patients. It is considered reliable (a split-half technique was used) and the test has been validated on patients with dementia (Nelson & McKenna, 1975; Nelson & O'Connell, 1978). Paque and Warrington (1995) compared the performance of a group of patients with dementia on the NART with performance on a shortened form of the WAIS-R (a formal test of IQ) in a longitudinal study. They found that the decline in performance on the WAIS-R was more severe and occurred more rapidly than the decline in performance on the NART. They conclude that, when given that the verbal IQ is greater than performance IQ, 'the NART can be used as a predictor if the premorbid intellectual functioning of a patient with dementia' (p.517). The NART is shown to have been validated in MS research (Ron et al., 1991; Camp et al., 1999).

5.4.1.2. The Visual Spatial Reasoning Test (VESPAR)

(Langdon and Warrington, *1995)*

The test was specially designed for use in assessing cognitive test performance and intellectual level in patients with organic brain disease because it attempts to reduce the confounding effects of sensori-motor impairments on performance. Langdon and Warrington (1995) provide normative data for the VESPAR from a large non-clinical sample that is considered to be broadly representative of the general adult population of the UK in terms of age, gender and occupational status.

The VESPAR was used in the present study to provide an estimate of current level of intellectual or cognitive functioning. Reasoning is assessed in terms of three styles of inductive reasoning ability: categorising, analogy and series completion. Only the verbal and spatial analogies were used in the present study. These subtests are each composed of 25 items and the participants must decide how words or shapes go together. The VESPAR has been employed in more recent MS studies (Camp et al., 1999).

5.4.2. Attention/Concentration & Working Memory

5.4.2.1. Digit Span test (Forward & Backward span) (WMS-III) (Wechsler, 1997)

This test provides a measure of immediate memory span, attention and working memory (particularly digit span backwards). Participants are read a string of digits at the rate of one digit per second and asked to repeat back the digits either in the same order (forward) or in reverse sequence (backwards) as instructed. Digit strings range from 2 to 9 digits. The test is stopped when the participant fails on two sequences of the same length. The total score is the sum of the scores for each digit sequence.

The forward span test was included because previous MS studies have shown that performance of both MS and controls generally do not appear to differ significantly on this test of immediate memory span and attention (Archibald & Fisk, 1999; De Luca et al., 1993; D' Esposito et al., 1996; Litvan et al., 1988; Klonoff et al., 1991; Pozzilli et al., 1991; Rao et al., 1984). The inclusion of a measure on which both groups would not differ in performance was to exclude the possibility of generally poorer task performance in the MS group.

5.4.2.2. Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977)

The PASAT is a complex measure that is sensitive to assessing the speed of information processing, sustained attention and working memory in patient groups. It has reasonable convergent validity as a measure of attention /concentration (Crawford et al., 1998b). This was established using principal component analysis of the PASAT and 11 subtests of the Wechsler Adult Intelligence Scale- Revised (Wechsler, 1981). These authors provide additional normative data for this measure based on a sample that was considered reasonably representative of the general adult population in the UK.

The PASAT involves the presentation of a pseudorandom series of single digit numbers at the rate of 1 every 3 seconds. The digits are presented on a cassette tape and the participants is required to listen for the first two digits, add them up, and give the answer before the next digit is presented. When the next number is presented on the tape the participant is required to add it to the digit they heard just before. Thus, the participant is not being asked to give a cumulative total of all of the numbers but rather to give the sum of the last two numbers they have heard. The second part of the test is identical to the first except that the digits are being presented at a faster rate (1 digit every 2 seconds). The score is the number of correct responses per trial.

The PASAT is able to assess more accurately cognitive processing speed in MS, because the test is not heavily reliant on visuomotor abilities (Demaree et al., 1999). The test therefore allows for some differentiation between cognitive and physical slowing.

5.4.3. Executive Functioning

5.4.3.1 The Controlled Oral Word Association Test (COWAT)

(Spreen & Strauss, *1991)*

This measure of executive function (and fluency of speech) consists of three word-naming trials. Three letters are commonly used (F, A & S). The participant is asked to say as many words as he or she can that begin with the given letter in one minute. However, proper nouns, repetitions of words, or use of the same word but with a different ending, are not allowed. The score is the sum of all acceptable words produced in the three one-minute trials. This measure was included in the study to examine the process of response initiation (similar to the process involved in condition A of the Hayling Test-described below).

5.4.3.2. Hayling Test (Burgess & Shallice, 1996c)

This test of basic task initiation speed and performance in suppressing verbal responses is considered sensitive to dysexecutive function and it has been considered to show adequate reliability. It was standardised on three lesion groups and one control group (see section 2.3.4.3 for further details of the Hayling test). As yet there appear to be no published studies that have employed the Hayling test in patients with MS.

5.5. Experimental tasks

The experimental designs were be based on the Hayling test to enable both processes of response suppression and initiation to be examined within the same task.

5.5.1. Experimental Task 1- Switching Test

This task was based on the format of the Hayling Test (Burgess & Shallice, 1996c) but with an additional condition that required participants to switch task demand. Details of experimental switching tasks and associated theoretical concepts concerning set switching have been outlined in section 2.3.6.

The following steps were taken in developing the task:

1. A list of 54 simple sentences (similar to the Hayling sentences) with the last word missing from each was generated by the author and a senior lecturer in psychology (see Appendix 3.3.2, p. 202 for an example of sentences used in the switching task).

2. The sentences were arranged into 9 blocks of 6 sentences. Sentences within each block were composed of an equal number of words. Blocks of six sentences were presented so that participants could become used to the expectations of the task and the different task demands involved.

3. The 9 blocks of sentences were composed of three blocks with different task demands. One task demand required participants to complete sentences with a word that

would best complete the sentence (a sensible word, S). A second task demand required participants to complete sentences with a word that does not make sense in the context of the sentence (an unconnected word, U). Both of these task demands were consistent with requirements of the Hayling Test. A third task demand required participants to complete sentences with either a sensible word or an unconnected word (mixed block, M) as instructed before each sentence was presented. This latter task demand brought in the element of switching task demands.

For each item, participants were instructed before each sentence was presented, whether they should complete the sentence with a sensible or an unconnected word (see Appendix 3.3.1., p. 200 for instructions for switching test). This provided participants with some knowledge of the upcoming task to allow them some amount of time to prepare for this process.

For the blocks with only one repeated task demand, participants could likely predict the task demand for some items. For the mixed blocks, it is unlikely that the participants could predict the requirement for the next item until the instruction was given since the order of presentation of the sentences within the switching / mixed block (M) was randomised using random number tables (Coolican, 1990). Within each mixed block there was an equal number of sentences requiring sensible versus unconnected completions (3 of each). This randomisation prevented participants from learning to anticipate the next task demand in the sequence, that might occur if the sequences were simply alternated rather than randomised. Thus participants would be forced to adopt the appropriate performance criteria only at the point of the instruction being given. However, participants had some knowledge that task demands would vary during the experiment because before they began the task they were instructed that some blocks of sentences would require completion with only sensible words, some blocks with only unconnected words, and some blocks would require switching between completion with sensible versus unconnected words.

4. The order of presentation of the blocks across the three different task demands (S, U, & M) was also randomised using random number tables to allow for further examination of the shifting set and switch costs.

5. Participants' responses on this switching task were scored in a similar way to that of the Hayling Test. Both response latencies (time taken to generate a response) and accuracy of response (number of errors made) were recorded. Errors were categorised according to criteria used by Burgess and Shallice (1996a) in scoring responses on the Hayling Test (see Appendix 3.3.3., p. 203 for scoring criteria for the switching test). Since one cause of the errors made and longer time taken when shifting task demands is thought to result from the time involved in 'changing mental gear' to adjust to this process, MS participants are predicted to make more errors and spend more time at the point of shifting from one task demand to another given evidence of a slowing of information processing speed in this group (Litvan et al, 1988), and difficulties with set-switching (Arnett et al., 1994), as compared to healthy normal controls.

5.5.2. Experimental Task 2-Proverbs task

The degree of demand on inhibitory processes was varied by including both well-known and less well-known proverbs. The test included well-known proverbs which aimed to increase the demand on inhibitory processes involved in suppressing responses to incomplete, well-known phrases.

Less well-known proverbs (Romanian, in English translation) were included as a control for aphorism. It is not immediately apparent whether the quality of aphorism in likely unknown proverbs will have any effect on disinhibition in MS. One model, in which the quality of metaphor involves abstraction and the sentences become more obscure to the MS participants, predicts the MS participants will find them more difficult to complete nonsensically. Another model suggests the concreteness of the sentences will lead the MS participants to produce literal nonsensical completions with the same efficiency as to the standard Hayling items. These concepts have been outlined in section 2.4.

The following steps were taken in developing the test:

1. A total of 18 common English proverbs were selected from a Dictionary of Proverbs (Fergusson, 1983).

2. A total of 18 likely unknown English and Romanian proverbs were generated. Romanian proverbs were taken from an Internet website of Romanian- English proverbs (Flonta, 1995). Less well known English proverbs that had been identified by the author and a senior lecturer in psychology as being less familiar were taken from the Dictionary of Proverbs (Fergusson, 1983). Romanian proverbs were included in the study because it was thought they would be unfamiliar to the majority of participants.

This condition was considered to be a control condition for aphorism to the well-known English proverbs. Each Romanian or less well-known English proverb was matched by meaning to each of the well-known English proverbs, to make the completion task as similar as possible, apart from familiarity. The proverbs were matched for meaning by inspection (see Appendix 3.4.1, p. 204 for list of matched proverbs).

3. English proverbs were categorised as being either well-known and less-well known by the author and a senior lecturer in psychology on the basis of their own knowledge and familiarity with the proverbs. This categorisation was confirmed by undertaking a small study for test development in which ten people who were unrelated to the study were invited to rate all of the proverbs used in the test, according to whether (a) each proverb was well-known, (b) whether they may have heard of the proverb before or were unsure about this, or (c) whether they had definitely never heard of the proverb. The participants were administrative staff and health professionals of various disciplines employed at the author's current place of work. The results confirmed the distinctions that had been originally made. The proverbs which had been considered by the author and senior lecturer to be well-known proverbs were also thought to be 'well-known' by a minimum of 90% of the respondents. Eighty percent of respondents also agreed with the author and senior lecturer in rating proverbs as being less well- known (that is, either that they might have heard of the proverb before but were not sure, or had definitely never heard of the proverb before).

4. Proverbs were completed with the correct word (an ideal word), or a word that best completed the proverb (a sensible word), or with a word that made no sense in the context of the proverb (an unconnected word). This requirement was consistent with instructions of the Hayling test.

Each proverb was presented twice, with a completion request for either a sensible (or the ideal word) or an unconnected word. A total of 72 proverbs were therefore presented to each participant.

5. Proverbs were arranged into 12 blocks of proverbs (6 proverbs per block). Six blocks contained proverbs that were to be completed with correct (or sensible) responses and 6 blocks were to be completed with unconnected words. Blocks of six proverbs were presented at a time so that participants could get used to the expectations of the different task demands involved. The order of the presentation of blocks (sensible versus unconnected blocks) was randomised using random number tables (Coolican, 1990).

6. Each block of 6 proverbs was composed of 3 well-known proverbs and 3 rare proverbs. The order of presentation of rare versus well-known proverbs within a block was randomised using random number tables. No two proverbs were the same within a block (see Appendix 3.4.2., p. 205 for example of recording sheet for proverbs task).

7. The first response uttered was taken as the participant's answer. Responses were scored according to criteria used by Burgess and Shallice (1996a) in scoring their responses on the Hayling Test. Both response latencies (time taken to generate a response) and accuracy of response (number of errors made) were recorded.

5.5.3. Consistencies between both experimental tasks

Consistent with the Hayling test, practice items were given to participants before each of the experimental tasks (four practice items per experimental task) to enable participants to become practised at what was required of them. This included the requirement of participants to switch task demands (completing sentences with sensible or unconnected words). Instructions for both experimental tasks were also based on the Hayling test to maintain consistency in task demands (see Appendix 3.3.3, p. 203 for example of test instructions).

Sentences and proverbs of both experimental tasks were presented on a tape recorder to ensure consistency in method of presentation of the material. The material was recorded by the author. Before each sentence or proverb was stated, the participant was cued as to whether to complete the sentence with a connected or an unconnected word. It was also ensured that the penultimate word of each sentence or proverb was presented very clearly in order to cue a response (particularly with the well-known proverbs).

The order of presentation of the Hayling test and both experimental tasks 1 & 2 were kept the same for each participant in order to maintain consistency of the format of presentation across participants. The Hayling task was always presented first so that participants would be well-versed in inhibiting responses and understanding task demands before attempting the experimental tasks.

5.6. Piloting study

Both experimental tasks were piloted on a small normal sample of acquaintances of the author to establish whether there should be any changes to the test design. The sample included one person with diabetes who experienced similar type of symptoms to MS, such as fatigue and pain, that might influence performance. This enabled the author to decide upon the order of testing and appropriate methods of presenting the material, and to consider ways of minimising fatigue.

No substantial changes were made except that a few sentences of the switching task were altered as they were more difficult to complete with an unconnected word as compared to other sentences within the same block. This was to ensure that there was consistency in the level of difficulty in completing responses within each block.

5.7. Procedure

Suitable participants with MS (see section 5.1.2) who had been identified for the study were invited to take part via a letter or a telephone call. The testing was arranged at a time of day when participants would usually be least fatigued. MS participants were seen in their own homes and the cognitive assessment took in the region of 2- 2 1/2 hours.

Seventeen suitable healthy control participants were recruited via a local company. The company was initially approached via a letter and the testing of staff members was arranged through the Personnel department. The testing was carried out over a period of a week at the participants' place of work. The remaining five control participants were friends of the author. They were approached via a 'phone call inviting them to participate in the study. These participants were tested in their own home. The testing of control participants took in the region of 1 1/2 hours per person.

All participants completed the testing in one session apart from two MS participants who completed the tests over two sessions. One participant reported fatigue and wished to stop, and a second participant received a distressing phone call during the session. The session was stopped and, with the participant's permission, was completed on a second occasion. Participants, particularly those with MS, were encouraged to take breaks as and when they needed in order to minimise the effect of fatigue on test performance.

Tests and questionnaires were presented to all participants in the same order to ensure that the order of presentation was standardised across participants. The Hayling test and the two experimental tasks were presented relatively early on in the session to further minimise any effects of fatigue on test performance. The Hospital Anxiety and Depression Scale was presented at the beginning of the session to ensure that any high scores on the depression or anxiety subscales could be addressed before testing continued. The PASAT test can be uncongenial for people with MS due to the cognitively demanding nature of this task. Consequently the PASAT was presented as the final test.

All published tests were administered according to administration guidelines and scored according to the test manual guidelines. Scoring of responses was undertaken in the following manner. For the Hayling test (section B) and the two experimental tasks, two raters who had no involvement with the study and were blind to the purpose of the study, rated each of the participant responses, classifying the responses according to the appropriate scoring criteria. This was to discover whether the groups differed in their ability to produce words unrelated to the sentence (in the 'unconnected' condition) and words related to the sentence (in the 'sensible' condition). A third rater was employed to decide which of the original two markers' was correct according to the scoring criteria when a discrepancy in the responses between both original raters existed. Written copies of the scoring criteria were given to all three markers. This method of scoring responses of the Hayling test was previously used by Burgess and Shallice (1996a) and was extended to the scoring of responses of the two experimental tasks.

5.8. Rationale for testing

Hypothesis 1 was tested using the Hayling test and both experimental tasks (Switching and Proverbs tasks).

Hypothesis 2 was tested using experimental task 1 (Switching task).

Hypothesis 3 was tested using the digit span and PASAT tests.

CHAPTER 6

RESULTS

6.1. Overview

The chapter consists of seven sections. The first section describes the data preparation. The second section will describe and compare the demographics of the MS and healthy control group to ensure that both groups are well-matched. A description of the disease characteristics of the MS group, and ratings of both groups on measures of mood, fatigue and subjective ratings of executive difficulties in everyday life, will also be presented. The third section will describe and compare the performance of both groups on the baseline cognitive measures to allow for the testing of hypothesis 3. The fourth section will examine the performance of both groups on the two experimental tasks to allow for the testing of hypotheses 1 and 2. The fifth section will examine the relationship between mood, fatigue, disability ratings and performance on cognitive measures.

6.2. Data Preparation

The data were first examined to ensure that assumptions that underlie parametric tests were not violated. This involved inspecting the data for missing data, normality, skewness, and the distribution of outliers.

6.2.1. Missing data

There were six cases with missing data. These data were three of the MS participants' raw scores on the two conditions of the PASAT. These scores were not obtained because these participants did not wish to complete the PASAT test due to fatigue at the end of the session. Their wishes were abided by according to the ethical requirements of the research.

The missing values were replaced by a number that the statistical package (SPSS for Windows version 10.1, SPSS Inc., 2000) recognized to be a missing value (100, as it is not possible to score 100 on the PASAT since the maximum score for each part is 60).

6.2.2. Normality of Distribution

The normality of the distribution for all variables was examined. All variables that did not meet the assumption of normality were transformed. Non parametric analyses were carried out on the variables that failed to meet the assumption of normality following transformation.

Premorbid IQ scores (WAIS-III equivalent) were obtained by converting total error scores of the NART of each participant to the WAIS-R IQ equivalent. Similarly, raw scores on the VESPAR test were converted to WAIS-R IQ equivalents for verbal and spatial abilities (Langdon & Warrington, 1995). WAIS-R equivalent scores were then converted to the WAIS-III equivalent IQ scores (The Psychological Corporation, 1999).

6.2.3. Statistical analysis

The majority of the analyses were carried out using parametric tests. The tests used were independent sample t-tests in order to examine differences in variables between the MS and control groups, paired sample t-tests to examine differences in performance between conditions within each group, and Pearson's correlations to examine associations between variables. Repeated measures analysis of variance tests were used to establish whether there were any main effects of group, condition, or interactions between both.

Non parametric analyses employed were the Mann Whitney U test to examine differences in variables between the MS and control group, and the related samples Friedman test that allowed for examination of performance on conditions within each group. Spearman's rho correlation analyses were employed to examine relationships between variables.

All analyses were carried out using SPSS for Windows version 10.1 (SPSS Inc., 2000).

6.3. Background demographics

This section will allow for the examination of the background demographics of the two groups to ensure that they are well-matched.

6.3.1 Demographics of MS and control group

There was no significant difference in mean age between the groups ($t(42) = 1.8$, $p = 0.07$) as shown in table 1. However, the MS group were, on average, 7 years older than the control group. The groups did not differ significantly in terms of mean years of education ($t(42) = 0.05$, $p = 0.96$).

Table 1

Descriptive demographic variables for MS and control group

(means and standard deviations)

Variable	MS group	Control group	t-value	p-value
Sample size	22	22	------	----
Gender	6 M, 16 F	6 M, 16 F	------	-----
Age (years)	53. 3 (12.7) *(25 – 70)*	46.2 (12.9) *(21 – 70)*	1.8	0.07 (NS)
Years of education	13.8 (3.1) *(9 – 19)*	13.8 (2.8) *(9 – 19)*	0.05	0.96 (NS)

Numbers in brackets represent the standard deviation of scores, and those in italics represent the range of scores. (NS) represents non-significance.

6.3.2. Disease variables of MS group

Within the MS group there were five participants with relapse-remitting MS, four with primary progressive MS, one with 'general progressive' MS and twelve participants had secondary progressive MS (Poser et al., 1983). The mean duration of the disease was 15.9 years and ranged between 4 and 38 years. The median disability rating on the Hauser Ambulation scale was 5 (ranging between 0 and 9) (Hauser et al., 1983). The median disability rating on the Troiano functional scale was 5 with ratings ranging between 1 and 12 (Herndon, 1997).

6.3.3 Mood

There was no significant difference between the groups in terms of their mean anxiety score ($t(42) = 0.29$, $p = 0.77$, Table 2). Twenty seven percent of the MS group scored within the 'clinically anxious' range. Just over thirty percent of the control group scored within the 'clinically anxious' range.

However the MS group had a significantly higher depression rating than the control group ($t(42) = 3.40$, $p = 0.01$). Fourteen percent of the MS group scored within the 'clinically depressed' range. No members of the healthy control group score within this range.

6.3.4 Fatigue

Groups did not differ in terms of their ratings of fatigue level pre- and post assessments shown in table 2. However the change in fatigue score between pre and post assessment was found to be greater in the MS group (ranging from 'not at all tired' to 'very tired') than the control group ('not at all tired' to 'quite tired') ($U = 137$, $p < 0.01$).

Table 2

Mood (HADS scale, Zigmond & Snaith, 1983) (means and standard deviations) and fatigue ratings (medians and ranges)

Variable	MS group	Control group	t value	U value	p- value
anxiety (HADS)	5.95 (4.18)	6.27 (2.91)	0.29		0.77 (NS)
depression (HADS)	4.36 (3.81)	1.82 (1.65)	3.40		**0.01 (S)**
Pre test fatigue	1 (0 - 2)	1 (0 - 3)		192.50	0.20 (NS)
Post test fatigue	2 (0 - 3)	1.5 (0- 3)		196.50	0.26 (NS)
Change in fatigue	1 (0-3)	0 (0 - 2)		137.00	**0.01 (S)**

Fatigue rating from 0 (not at all tired) to 4 (most tired I have ever felt).

HADS of 8 – 10 represents borderline cut-off range for clinically anxiety or depression.

(NS) = non-significance, (S) = significance at the 5% level ($p < 0.05$).

6.3.5. Subjective rating of executive difficulties in every day life

The groups did not differ significantly in their self-ratings of executive-type difficulties that might be encountered in everyday life ($t(42) = 1.05$, $p = 0.30$), highlighted in table 3.

Table 3

Self-ratings of executive type difficulties encountered in every day life (DEX, Wilson et al., 1996) (means and standard deviations of raw scores).

	MS group	Control group	t value	p value
DEX rating	17.14	18.59	1.05	0.30 (NS)
	(15.2)	(7.75)		

See section 5.3.4 for explanation of the DEX scale ratings

6.4. Baseline cognitive measures

This section will allow for the further comparison of both groups and for the testing of hypotheses 3 (see chapter 5, section 5.8).

6.4.1 General Intelligence

The MS and control group did not differ significantly in terms of their estimated premorbid level of intellectual functioning (NART, Nelson, 1991) ($t(42) = 0.42$, $p = 0.68$) as shown in table 4. The VESPAR scores were converted to IQ equivalent scores (VESPAR, Langdon & Warrington, 1995). There was no significant difference between the groups in terms of their current reasoning ability in both verbal and non-verbal domains ($t(42) = 1.82$, $p = 0.08$; $t(42) = 1.64$, $p = 0.11$ for verbal and spatial VESPAR analogies, respectively). All mean IQ scores fell within the average range.

Table 4

Raw scores of tests of premorbid (NART, Nelson, 1991) and current intelligence (Langdon & Warrington, 1995) (means and standard deviations).

Tests	MS group	Control group	T value	p-value
Premorbid IQ*	104.24 (12.13)	102.64 (12.89)	0.42	0.68 (NS)
VESPAR (IQ equivalent)*				
Verbal analogy	100.64 (7.33)	104.95 (8.38)	1.82	0.08 (NS)
Spatial analogy	103.50 (10.13)	107.86 (7.31)	1.64	0.11 (NS)

*Premorbid IQ and VESPAR IQ equivalent represent WAIS-III IQ equivalent score across groups (see section 6.3.2. for details of the method of conversion). (NS) = non significance at the 5% level.

The groups appear to be relatively well matched with no significant difference between them in terms of their premorbid and current level of intellectual functioning, or mean age and years of education (see table 1). Thus statistical comparisons of the two groups showed good comparability on demographic and cognitive variables. The only significant differences are in rating of depression, and change in fatigue during testing.

6.4.2 Further baseline cognitive measures

The MS group's performance was significantly lower than the control group on most baseline cognitive measures as shown in table 5. These included verbal fluency ($t(42) = 2.76$, $p = 0.01$), digit span total score (attention) ($t(42) = 2.18$, $p = 0.04$), and the PASAT (working memory) (at three seconds, $t(39) = 4.69$, $p < 0.01$, and at 2 seconds, $t(39) = 3.88$, $p < 0.01$)).

Table 5

Raw scores for baseline cognitive measures (means and standard deviations) (Digit Span, Wechsler, 1997; PASAT, Gronwall, 1977; Verbal Fluency (COWAT), Spreen & Strauss, 1991).

Variable	MS group	Control group	t value	p-value
Digit Span				
total score	15.09 (3.15)	17.59 (4.37)	2.18	**0.04 (S)**
forwards	9.09 (1.93)	10.59 (2.26)	2.37	**0.02 (S)**
backwards	6.00 (1.75)	7.00 (2.55)	1.52	0.14 (NS)
PASAT				
3 secs	31.45 (15.13)	49.89 (9.70)	4.69	**0.00 (S)**
2 secs	22.00 (11.33)	36.26 (12.21)	3.88	**0.00 (S)**
Verbal Fluency (COWAT)	35.64 (12.33)	44.91 (9.80)	2.76	**0.01 (S)**

(NS) = non significance, (S) = significance at the 5% level ($p< 0.05$).

6.5. Hayling Test

The findings for both groups are presented in table 6. The MS group had a significantly lower scaled score on the timed activity of section A of the Hayling test compared to the control group (U = 124, $p = 0.01$), reflecting longer response times by the MS group. However, there was no significant difference between groups in timed scale score (U = 172.5, $p = 0.06$) and error scaled score ($t(42) = 1.83$, $p = 0.07$) on part B of the Hayling test.

Table 6

Raw scores of Hayling test performance (Burgess & Shallice, 1996c)

for sections A & B variables (medians and ranges for t-tests; median scores and ranges for U-test).

Variable	MS group	Control group	t value	U value	p-value
Section A					
Time	13.5	3.5			
(raw score)	(3 – 106)	(<1 – 30)			
Time	5	6		124.00	**0.01** (S)
(scaled score)	(1 – 6)	(3 – 7)			
Section B					
Time	61.5 (59.8)	23.0 (20.5)			
(raw score)					
Time	6	6		172.50	0.06 (NS)
(scaled score)	(1 - 8)	(4 – 7)			
Category A	3.0 (2.9)	1.9 (1.7)			
Errors*					
Category B	1.9 (1.6)	1.0 (1.3)			
Errors*					
Total errors*	4.9 (3.9)	2.9 (2.1)			
Errors	5.0 (2.3)	6.2 (1.9)	1.83		0.07 (NS)
(scaled score)					

* denotes total number of errors (raw score). All times in seconds.

Higher scaled scores represent less time taken or fewer errors made and thus better performance. (NS) = non significance, (S) = significance at the 5% level ($p < 0.05$).

6.6. EXPERIMENTAL TASKS

6.6.1. Experimental Switching Task

This task examines the set switching ability in a group of people with MS as compared to a healthy control group. Conditions vary in their task demands: some conditions require participants to switch task, whereas other conditions do not. The task demand involves completing sentences with either a sensible word or a word that is unconnected to the context of the sentence.

This task also allows for the examination of differences in performance between completion of sentences with either a sensible word or an unconnected word irrespective of type of block format (switch or non switch format). This will highlight any differences between groups in ability to initiate and suppress verbal responses on novel sentences, which can be directly compared with switching performance.

6.6.1.1. Switching Experimental Task Part A: sensible- unconnected completion task demand

The following analyses examine the performance of both groups in completing sentences with either a sensible word or with an unconnected word in this task. The findings are presented in tables 7 and 8. The 'Sensible' score for each participant was calculated by adding up the time taken by the participant (or error scores made) for each sentence requiring completion with a sensible word across all block formats of the task (whether switch or non switch blocks). This method was repeated in order to calculate 'unconnected' timing and error scores. There were 27 sentences of each type (requiring sensible or unconnected completions).

Table 7

Switching Experimental task: sensible versus unconnected completions (Time)

Comparison of raw time scores (seconds) on sensible and unconnected completions (means and standard deviations for time taken to provide a response to complete the sentence).

Completion	MS group	Control group
Sensible	22.3 (20.3)	9.7 (8.5)
Unconnected	66.8 (76.1)	24.1 (24.9)

A 2 x 2 repeated measures analysis of variance showed that there was a significant main effect of group (MS versus control) ($F (1, 42) = 7.43$, $p < 0.01$) and of type of completion (sensible versus unconnected) ($F (1, 42) = 16.24$, $p<0.001$). There was a significant interaction effect between group and type of completion ($F (1,42) = 4.24$, $p=0.04$).

Further analysis of the significant main effects found was undertaken. A post-hoc independent t – test found revealed a significant difference between both groups in completion of sentences with sensible or unconnected words. The MS group took significantly longer to complete both types of sentences than the control group (sensible: $t (28) = 2.70$, $p = 0.01$; unconnected: $t (42) = 2.50$, $p = 0.02$). A post hoc paired samples t-test showed that within the MS group, participants took significantly longer to complete sentences with unconnected words (t (21) = 3.24, p< 0.01). Similarly, control participants took a significantly longer time when completing sentences with unconnected words than with sensible words (t (21) = 2.91, p<0.01).

Table 8

Switching Experimental Task: sensible versus unconnected completions (Error)

Comparison of raw error scores on sensible and unconnected completions (medians and ranges for error scores in providing responses to complete the sentence).

Completion	MS group	Control group
Sensible	0 (0 - 1)	0 (0 - 1)
Unconnected	13 (0 - 43)	7.5 (1 - 15)

A Mann Whitney U test showed that the groups did not differ in error score when completing sentences with a sensible word (U = 220, p = 0.30). However the MS group's error score was significantly greater than the control group's when sentences were to be completed with an unconnected word (U = 145.50, p = 0.02).

6.6.1.2. Experimental Switching Task Part B: switch / non-switch task demand

All data of the switching task were based on composite scores of the relevant individual raw scores of the task. The individual scores were calculated as follows:

1. Non switch S-S:

An item requiring a sensible completion, following an item requiring a sensible completion, within a block where no switching was required.

(15 items)

2. Switch S-S:

An item requiring sensible completion, following an item requiring sensible completion, in a block where switching was intermittently required but not on this particular item.

(3 items)

3. Switch U-S:

An item requiring sensible completion, following an item requiring unconnected completion, in a block where switching was intermittently required and also on this particular item.

(6 items)

4. Non switch U-U:

An item requiring unconnected completion, following an item requiring unconnected completion, in a block where no switching was required.

(15 items)

5. Switch U-U:

An item requiring unconnected completion , following an item requiring unconnected completion, in a block where switching was intermittently required but not on this particular item.

(3 items)

6. Switch S-U:

An item requiring unconnected completion, following an item requiring sensible completion, in a block where switching was intermittently required and also on this particular item.

(3 items)

Because the status of the preceding trial was crucial to the task demand of each item, the first item of each block was omitted from the analysis.

The results of the switching task demand are presented in tables 9 to 11 (time and error scores).

Table 9

Experimental Switching Task: Sensible completions (Time)

Comparison of raw time scores (seconds) on conditions of increasing task demand for sensible completion (means and standard deviations of raw scores representing time taken to provide a response to complete the sentence).

(For explanation of conditions see section 6.6.1.2).

Block format	Previous item	Current item	MS group	Control group
Non switch	S	S	19.1 (17.6)	8.6 (8.0)
Switch	S	S	3.4 (4.0)	1.4 (1.7)
Switch	U	S	9.1 (8.2)	2.7 (1.9)

S= completion of sentence with SENSIBLE completions

U=completion of sentence with UNCONNECTED completions

The data in Table 9 were analysed using a 2 x 3 repeated measures analysis of variance. There was a significant main effect of group (MS versus control) ($F (1, 42) = 11.27$, $p = 0.02$) and switching condition (non switch S-S versus switch S-S versus switch U-S) ($F (2, 84) = 58.47$, $p<0.001$). There was no significant interaction between group and switching condition ($F (2, 84) = 2.00$, $p = 0.14$).

Experimental Switching task: Sensible completions (Errors)

All median raw error scores attained by both MS and control groups for all types of block format (non-switch S-S, switch S-S and switch U-S) were zero (0). Thus no further analyses were undertaken of this data since no significant differences were likely to exist between the groups.

Table 10

Experimental Switching Task: unconnected completions (Time)

Comparison of raw time scores (seconds) performance on conditions of increasing task demand for unconnected completion (means and standard deviations for raw time scores taken to provide a response to complete the sentence).

(For explanation of conditions see section 6.6.1.2)

Block format	Previous item task	Current item task	MS group	Control group
Non switch	U	U	57.0(61.9)	18.4 (15.7)
Switch	U	U	12.0 (15.9)	1.91 (2.2)
Switch	S	U	12.9 (10.6)	4.2 (4.3)

The data in Table 10 were analysed using a 2 x 3 repeated measures analysis of variance. There was a main effect of group (MS versus controls) ($F(1, 42) = 13.61$, $p = 0.001$) and of switching condition (non switch U-U versus switch U-U versus switch S-U) ($F(2, 84) = 73.55$, $p<0.001$), but no significant interaction effect between group and switching condition (F (2, 84) = 2.34, p = 0.10).

Table 11

Experimental Switching task: unconnected completions (Error)

Comparison of raw error scores on conditions of increasing task demand of unconnected completions (means and standard deviations for error scores in providing a response to complete the sentence).

(For explanation of conditions see section 6.6.1.2)

Block format	Previous item task	Current item task	MS group	Control group
Non switch	U	U	12.0 (10.1)	5.9 (3.3)
Switch	U	U	2.1 (2.2)	1.1 (1.8)
Switch	S	U	2.6 (3.1)	1.2 (1.9)

The data in Table 11 were analysed using a 2 x 3 repeated measures analysis of variance. There was a main effect of group (MS versus control) (F (1, 42) = 6.79, p = 0.01) and of switching condition (non switch U-U versus switch U-U versus switch S-U) (F (2, 84) = 75.86, p<0.001). There was no significant interaction effect (F (2, 84) = 0.66, p = 0.52).

6.6.2. Experimental Proverbs Task

This task involves conditions that require either the initiation of verbal responses or their inhibition. The latter condition also requires the generation of novel responses to replace responses that have been suppressed. The degree of demand on inhibitory processes was varied by including both well-known and less well-known proverbs. The inclusion of well-known proverbs aimed to increase the demand on inhibitory processes. The findings are presented in tables 12 and 13.

All data of the Proverbs Task were based on composite scores of the relevant raw scores of the task. The score for the 'Sensible Common' condition for each participant was calculated by adding up the participant's score for each common proverb in the task requiring completion with a sensible word. This method was repeated for both time and error scores per participant for each of the four combinations of task demands (sensible common, sensible rare, unconnected common, unconnected rare).

Table 12

Experimental Proverbs Task (Time)

Comparison of raw time scores (seconds) performance on different conditions of proverb completion (means and standard deviations for time taken to provide a response to complete the proverb).

(See key below for explanation of conditions).

Condition	MS group	Control group
Sensible Common	15.6 (19.8)	3.1 (4.5)
Sensible Rare	111.5 (75.3)	47.2 (43.7)
Unconnected Common	41.0 (31.3)	10.3 (8.9)
Unconnected Rare	52.8 (52.5)	14.6 (15.2)

Sensible = completion of proverbs with sensible responses

Unconnected = completion of proverbs with unconnected responses

Common = common English proverbs

Rare= Romanian or rare English proverbs

(18 items per condition)

A 2 x 4 repeated measures analysis of variance showed that there was a significant main effect of group (MS versus control) ($F(1, 42) = 22.99$, $p<0.01$) and of type of completion (sensible common versus sensible rare versus unconnected common versus unconnected rare) ($F(3, 126) = 67.24$, $p<0.01$). There was no significant interaction effect between group and type of completion ($F(2, 126) = 1.39$, $p = 0.25$).

Table 13

Experimental Proverbs Task (Errors)

Comparison of raw error scores performance on different conditions of proverb completion (means and standard deviations). (See key of table 12 for explanation of conditions).

Condition	MS group	Control group
Sensible Common	3.0 (4.3)	2.3 (2.1)
Sensible Rare	19.6 (4.5)	18.2 (4.3)
Unconnected Common	5.3 (6.3)	1.2 (2.3)
Unconnected Rare	5.1 (5.7)	0.8 (1.0)

A 2 x 4 repeated measures analysis of variance showed that there was a significant main effect of group (MS versus controls) ($F(1, 42) = 8.34$, $p<0.01$) and of type of completion (sensible common versus sensible rare versus unconnected common versus unconnected rare) ($F(3, 126) = 172.9$, $p<0.01$). There was a significant interaction effect between group and type of completion ($F(3,126) = 7.23$, $p<0.01$).

Further analysis of the significant main effects that were found was undertaken. A post hoc independent t-test revealed that there were no significant differences between groups in error scores when completing common proverbs with sensible words ($t(42) = 0.04$, $p = 0.97$) and rare proverbs with sensible words ($t(42) = 1.10$, $p = 0.28$). However, the MS group had a significantly higher error score than the control group when completing common proverbs with unconnected words ($t(42) = 2.98$, $p < 0.01$), and when completing rare proverbs with unconnected words ($t(30) = 3.78$, $p < 0.001$).

Further inspection using a post hoc paired samples t-test revealed that for both groups, participants had significantly greater error scores when completing rare proverbs with a sensible word than when completing common proverbs with a sensible word (MS: $t(21) = 14.76$, $p < 0.001$; controls: $t(21) = 17.61$, $p < 0.01$) and had significantly greater error scores when completing rare proverbs with sensible words than when completing rare proverbs with unconnected words ($t(21) = 11.14$, $p < 0.01$; $t(21) = 18.97$, $p < 0.01$). However, participants in the control group had significantly higher error scores when completing common proverbs with a sensible word than when completing proverbs with an unconnected word ($t(21) = 2.83$, $p < 0.01$) although this significant difference was not found for participants in the MS group ($t(21) = 1.60$, $p = 0.12$).

Nevertheless, there was no difference in error score between completion of rare and common proverbs with an unconnected word for participants in both groups (MS: $t(21) = 0.20$, $p = 0.85$; controls: $t(21) = 0.25$, $p = 0.81$).

6.7. The relationship between performance on baseline cognitive tests and other variables

Although not part of the formal hypotheses, analyses were undertaken to establish whether performance on baseline cognitive measures were affected by variables such as mood, fatigue, and disease variables. The relationship between mood (HADS anxiety and depression ratings (Zigmond & Snaith, 1983), disability (Ambulation Index disability rating, Hauser et al., 1983), fatigue (pre- and post testing), patients' own perspective of their difficulties (DEX rating, Wilson et al., 1986), and their actual performance on cognitive tests, may affect performance and should be taken in to consideration when interpreting the results. Separate correlations were computed for each group.

Table 14

Intercorrelation between age, mood, self ratings of executive difficulties, disease duration, and baseline cognitive scores for the MS group

	Age	HADS anxiety	HADS depression	DEX rating	Disease duration
Premorbid IQ	0.33	-0.14	-0.16	-0.49*	0.48*
VESPAR					
(IQ equivalent)					
Verbal analogy	-0.06	0.21	0.03	-0.16	-0.07
Spatial analogy	-0.15	-0.05	0.03	-0.13	-0.21
Digit Span					
Total score	-0.13	-0.11	0.15	-0.35	0.12
Forwards	-0.06	-0.08	0.14	-0.40	0.28
Backwards	-0.17	-0.11	0.12	-0.19	-0.09
PASAT					
3 secs	-0.30	0.33	-0.05	-0.23	-0.07
2 secs	-0.16	0.18	-0.14	-0.31	-0.09
Verbal fluency	0.05	-0.06	-0.12	-0.41	0.18

* $p<0.05$, ** $p<0.01$.

Table 14 highlights a significant negative correlation between the DEX rating (self reported difficulties with executive function in everyday life) by participants in the MS group, and Premorbid IQ ($r = -0.49$, $p = 0.02$). The results indicate that the higher the premorbid IQ which reflects higher premorbid intellectual functioning, the lower the DEX rating score which is indicative of fewer executive difficulties encountered in everyday life. A significant positive correlation was found between premorbid IQ and disease duration ($r = 0.48$, $p = 0.02$) indicating the higher the premorbid level of intellectual functioning, the longer the disease duration in this particular group of MS participants.

No significant correlations were found between rating of depression and performance on cognitive measures.

Table 15

Intercorrelation between age, mood, self-ratings of executive difficulties, and baseline cognitive scores for the control group.

	Age	HADS anxiety	HADS depression	DEX rating
Premorbid IQ	0.28	0.28	0.14	-0.06
VESPAR				
(IQ equivalent)				
Verbal analogy	0.30	0.17	0.44*	0.01
Spatial analogy	-0.01	0.01	0.25	0.22
Digit Span				
Total score	0.07	0.04	0.27	0.19
Forwards	0.04	0.11	0.39	0.10
Backwards	0.08	-0.03	0.13	0.23
PASAT				
3 secs	-0.05	-0.06	0.34	0.05
2 secs	0.31	0.14	0.36	0.12
Verbal fluency	-0.08	0.31	0.02	0.35

* $p<0.05$, **$p<0.01$.

Table 15 shows that only performance on the verbal domain of the VESPAR test ($r = 0.44$, $p = 0.04$) significantly correlated positively with the HADS depression score.

Table 16

Intercorrelation between fatigue, disability and baseline cognitive scores for MS group.

	Pre fatigue	Post fatigue	Ambulation index (disability)
Premorbid IQ	0.39	0.01	0.12
VESPAR			
(IQ equivalent)			
Verbal analogy	0.45*	0.07	0.02
Spatial analogy	0.28	-0.15	-0.07
Digit Span			
Total score	0.40	-0.19	0.58**
Forwards	0.48*	-0.04	0.55**
Backwards	0.24	-0.29	0.45*
PASAT			
3 secs	0.44*	0.02	-0.19
2 secs	0.30	-0.14	-0.13
Verbal fluency	0.29	-0.18	0.42

* $p<0.05$, ** $p<0.01$.

Table 16 highlights that level of fatigue prior to testing is significantly positively correlated with performance on the verbal domain of the VESPAR test ($r = 0.45$, $p = 0.03$), forwards digit span performance ($r = 0.48$, $p = 0.03$), and the PASAT (3 seconds) ($r = 0.44$, $p = 0.04$) in the MS group. This indicates that the higher the level of fatigue prior to testing, the higher the scores on the cognitive tasks. There was a significant positive correlation between the disability rating on the Ambulation Index and total digit span score ($r = 0.58$, $p = 0.01$), forward digit span score ($r = 0.55$, p = 0.01) and backwards digit span (r = 0.45, p = 0.04). This reflects a tendency for higher disability ratings to be associated with higher digit span scores, and thus better performance, in the participants with MS.

Table 17

Intercorrelation between fatigue and baseline cognitive scores for the control group

	Pre fatigue	Post fatigue
Premorbid IQ	-0.29	0.06
VESPAR		
(IQ equivalent)		
Verbal analogy	-0.32	-0.01
Spatial analogy	-0.50*	-0.41
Digit Span		
Total score	-0.29	0.27
Forwards	-0.15	0.34
Backwards	-0.44*	0.08
PASAT		
3 secs	-0.24	-0.24
2 secs	-0.45	-0.01
Verbal fluency	-0.07	-0.05

* p<0.05, **p<0.01.

Table 17 highlights a significant negative correlation between level of fatigue prior to testing and the spatial domain of the VESPAR test (r = -0.50, p = 0.02), and digit span backwards (r = -0.44, p = 0.04) in the control group. This indicates that higher fatigue ratings prior to testing were associated with lower scores on these cognitive measures and thus poorer cognitive performance.

CHAPTER 7

DISCUSSION

The discussion chapter will begin by briefly reviewing the demographic details, disease characteristics and general level of intellectual functioning of the MS sample in the present study. Secondly, a summary of the results in relation to each of the hypotheses of this study will be presented. Thirdly the chapter will consider the results in relation to previous findings and theoretical concepts outlined in the introduction chapter (2). Section 7.9 will provide a discussion on the limitations of the study followed by a section in which clinical implications of the findings will be considered. Suggestions for future research will be outlined in the final section of the discussion chapter.

7.1 Demographics of the present MS sample

The present sample of MS participants has a mean age of 53.3 years, with participants ranging between 25 and 70 years of age. More than half of the 22 participant sample is composed of females (16). The mean number of years of education is 13.8, ranging between 9 and 19 years. Five participants had relapse-remitting MS, four had primary progressive MS, one had 'general progressive' MS, and twelve participants had secondary progressive MS. The mean duration of the disease was 15.9 years and ranged between 4 and 38 years. The MS group had a significantly higher rating than the control group on the HADS (Zigmond & Snaith, 1983), with 14 % falling within the 'clinically depressed' range. The MS group were not significantly more tired than the control group before and after testing, although they became significantly more tired as the session progressed.

7.2. Premorbid and current level of intellectual functioning

The current sample did not differ significantly from the control group with respect to premorbid and current levels of intellectual functioning. Premorbid and current levels of intellectual functioning both fell within the average range. There was no significant difference between groups in the verbal and non-verbal domains of intellectual functioning, although the current IQ ratings (VESPAR, Langdon & Warrington, 1995) of the MS group were lower than that of the control group. There does not appear to be evidence of a global cognitive deterioration in the current sample of MS participants.

Several studies have reported small differences between MS and control groups in terms of current intellectual functioning, with level of intellectual functioning being lower in the MS group than the control group as found with the current sample (Rao et al., 1991a).

The demographics of the MS sample in this study appear to be broadly comparable with other studies in the area and the cognitive profile is largely typical of MS samples employed in other studies within the MS research literature (Aupperle et al., 2002; Camp et al., 1999). It is therefore considered that the findings of the present study may be generalisable to the wider MS population.

7.3. Hypotheses of study and summary of findings

7.3.1. Hypothesis 1

One of the aims of the present study was to investigate whether or not people with MS had significant difficulty in initiating and suppressing verbal responses. It was predicted that MS participants would either take longer or be less able to suppress over learned habitual verbal responses that were obvious choices to complete a series of sentences, and particularly when required to suppress over learned habitual verbal responses when completing a series of familiar proverbs. Thus, when required to complete a sentence with a word that is not connected to the context of the sentence (an unconnected word), the MS group would be more likely to complete a sentence with a word that did make sense in the context of the sentence (a sensible word). Sensible completions were taken as the best indicator of verbal initiation. Unconnected completions were taken as the best indicator of verbal inhibition and suppression, although they were not mutually exclusive.

7.3.1.1. Hayling test

Findings revealed that the MS group took significantly longer on section A of the Hayling test that requires the ability to generate words that will complete sentences in a sensible manner, compared to the control group. However, the MS group performed at a comparable level to the control group on section B of the Hayling test in terms of the time taken to respond and the errors made. Thus, the Hayling experiment supported the part of hypothesis 1 that related to initiation of verbal responses (Section A). It did not support the part of hypothesis 1 that related to suppression of responses (section B).

7.3.1.2. Experimental Switching task

In the first of the new experimental tasks, the switching task, differences in performance between completion of sentences with either a sensible word or an unconnected word, irrespective of type of block format (switch or non switch format), were examined. This was to highlight any differences between groups in their ability to generate and suppress verbal responses on novel sentences. This would allow for comparison with the Hayling result. The results showed that the MS group took significantly longer to both complete sentences requiring a sensible word, and to complete sentences requiring completion with an unconnected word, than the control group. Both groups took significantly longer to complete sentences with words that were unconnected to the sentence than with a sensible word.

The groups did not differ in error score when completing sentences with a sensible word. However, the MS group's error score was significantly greater than the control group's score when participants were required to complete sentences with an unconnected word. The error score for each group was greater when completing sentences with unconnected words than when completing sentences with sensible words. Thus the switching task provided partial support for hypothesis 1 relating to poorer MS performance in both initiation (for time but not errors), and suppression of verbal responses (for both time and errors).

7.3.1.3. Experimental Proverbs task

The second new experimental task, the proverbs task, allowed the performance of MS participants and healthy controls to be compared on a verbal inhibition task using familiar sayings that was similar in format to the Hayling test. Participants were required to suppress responses and to generate novel responses to complete sentences. However, in this task, the degree of demand on inhibitory processes was varied by including both well-known and less well-known proverbs.

Time

The results showed that the MS group took significantly longer than the control group on all types of sentence completion. The MS group took significantly longer than the control group to complete well-known English proverbs, and Romanian or rare English proverbs, with a sensible word. Similarly, the MS group took significantly longer than the control group to complete well-known English proverbs and rare English or Romanian proverbs with unconnected words.

Although there was no significant difference in performance times across type of condition, both groups took longer to complete Romanian or rare English proverbs with a sensible word than to complete well-known English proverbs with a sensible word. Both groups also took longer to complete well-known English proverbs with an unconnected word than with a sensible word, and took longer to complete Romanian or rare English proverbs with a sensible word than with an unconnected word.

Errors

Further findings revealed that there were no significant differences between groups in error scores when completing well-known English proverbs with sensible words, and when completing Romanian or rare English proverbs with sensible words. However, the MS group had a significantly higher error score than the control group when completing well-known English proverbs with unconnected words, and when completing Romanian or rare English proverbs with unconnected words.

Not surprisingly, participants in both groups had greater error scores when completing Romanian or rare English proverbs with a sensible word, than when completing well-known English proverbs with a sensible word. Both groups also had greater error scores when completing Romanian or rare English proverbs with sensible words than when completing Romanian or rare English proverbs with unconnected words. Surprisingly, participants in the control group had significantly higher error scores when completing well-known English proverbs with a sensible word than when completing these proverbs with an unconnected word, although this significant difference was not found for participants in the MS group. Nevertheless, there was no difference in error score between completion of Romanian or rare English proverbs and well-known English proverbs with an unconnected word for participants in both groups.

Thus the proverbs task also provided partial support for the part of hypothesis 1 relating to poorer MS performance in verbal initiation (timing in all sensible completion conditions, and error scores for both unconnected conditions). The proverbs task additionally provided support for the part of hypothesis 1 relating to poorer MS performance in suppression and inhibition (timing and error scores for both unconnected conditions).

7.3.2. Hypothesis 2

Participants with MS will perform significantly worse than normal controls in conditions that require the ability to switch from one task demand or instruction to another of the experimental task.

In the first experimental task, the switching task, conditions varied in their task demands: some conditions required participants to switch task, whereas other conditions did not. The task involved completing sentences with either a sensible word, or with a word that was unconnected to the context of the sentence.

Sensible completion of sentences

For the condition requiring sensible completion of sentences, the MS group took significantly longer than the control group across all conditions. Both groups took the longest time on the non-switch S-S condition. Their response rates were quickest on the switch S-S condition.

In terms of error scores, there were no significant differences between the groups for each switch condition. Similarly, there were no significant differences in error scores across switch conditions within each group.

Unconnected completion of sentences

For the condition requiring the completion of sentences with words that did not make sense in the context of the sentence (unconnected words), the MS group were found to have taken significantly more time than the control group across each switching condition. Both groups took longest to respond in the non-switch U-U condition. Their response rates were quickest in the switch U-U condition.

In terms of error scores, the MS group produced a significantly higher error score than the control group across all conditions. Both groups produced the highest error scores in the non-switch U-U condition with lowest error scores in the switch U-U condition.

The results provide little support for hypothesis 2. The MS group were significantly slower in their performance, and made more errors in the unconnected completion condition than the control group, across all block types, including those blocks requiring a switch in tasks demands. However, the MS group did not show a significantly greater impairment in performance on the switching tasks than on the non-switch task.

7.3.3. Hypothesis 3

Participants with MS will perform significantly worse than normal controls on tests of working memory.

The performance of the MS group was significantly poorer than the normal control group on the effort demanding measure of working memory, the PASAT, in two rates of item presentation. However, the MS group did not differ significantly from the control group in terms of their performance on the digit span backwards test. Since the PASAT is also considered a measure of speed of information processing (Archibald & Fisk, 2001), the findings suggest that speed of information processing in the MS group was significantly poorer than the control group. Further findings showed that the MS group did differ significantly from the control group in their forward digit span score. Thus hypothesis 3 is only partly supported by the findings of the present study.

7.4. Validity of the Proverbs experimental task

The experimental Proverbs task was designed to vary the demand on inhibitory processes by including both well-known and less well-known proverbs. The inclusion of well-known proverbs aimed to increase the demand on inhibitory processes involved in suppressing responses to incomplete, well-known phrases. Less well-known proverbs (Romanian, in English translation, or rare English proverbs) were included as a control for aphorism.

The results of this experimental task appear to support the validity of this task construction and experimental design. Although there was no significant difference in performance across type of condition, participants in each group took longer, and made greater error scores, when completing Romanian or rare English words with a sensible word than to complete well-known English proverbs with a sensible word. Well-known English proverbs were quicker to complete sensibly as expected, because such phrases are considered to be familiar, (usually over learned) phrases in the English language, and thus are likely to strongly cue the initiation of appropriate 'automatic' responses.

Both groups also took longer, and made greater error scores, when completing well-known English proverbs with an unconnected word (compared to sensible completion). This suggests that these phrases were familiar enough to the participant, to elicit a stronger, 'automatic' response during the presentation of the well-known proverbs with the last word missing. This 'automatic' response needed to be inhibited or suppressed to allow for completion of the proverb with a word that was unconnected to the context of the proverb. This pattern of performance that is supported by findings from both groups suggests that inclusion of well-known proverbs did increase the demand on inhibitory responses predicted in this experimental task.

The inclusion of Romanian or rare English proverbs on the proverbs experimental task aimed to control for aphorism. Should the Romanian or rare English proverbs be unfamiliar enough to the participants, these proverbs would be understood as unfamiliar sentences that do not strongly cue the initiation of 'automatic' responses as do proverbs. However, they have the same 'pithy' format and quality of metaphor. It is expected that participants would take longer, and produce a significantly greater error score, when completing unfamiliar Romanian or rare English proverbs with a word that does make sense in the context of the proverb (a sensible word) than a word unconnected to the context of the sentence, since careful consideration of the meaning of the Romanian or rare English proverb would probably not be required in order to select an unconnected word as would be required when selecting a 'correct' or sensible word. Such proverbs would be treated as unfamiliar sentences where a strong, 'automatic' response would not be elicited by the presentation of an unfamiliar proverb. Thus a strong need to suppress the response would not be required. This pattern of performance was found in both groups, and thus the employment of the Romanian and rare English proverbs in the current design as a control for aphorism is upheld.

In reviewing the performance of the MS group to that of the control group on tasks requiring the initiation and inhibition of verbal responses, a number of interesting findings have been highlighted in the present study. These, together with findings from the two experimental tasks and baseline cognitive measures, will now be discussed in the light of theoretical concepts that have been reviewed earlier in chapter 2.

7.5. Discussion of findings in the context of the hypotheses and the research literature

7.5.1. Response initiation and inhibition

7.5.1.1. Response initiation in MS

The longer response times taken by the MS group on the Hayling and two experimental tasks reflect a slowed rate at which the MS participants process information which impacts on the efficiency of the ability of this patient group to generate responses to complete sentences in a logical or sensible manner. Since the MS group appeared to have remained as accurate as the control group in initiating words (no difference in error scores) it is possible that a normal rate of accuracy was maintained by the additional time taken by the MS participants in providing a response.

7.5.1.2 Response inhibition in MS

The comparable performance of the MS group, to that of the control group, in terms of response time and errors made on section B of the Hayling test suggests that the MS group did not have significantly greater difficulty than the normal healthy control group in inhibiting strongly cued verbal responses. The MS group also appeared to have been able to generate novel responses to complete sentences as efficiently as the control group when a word unrelated to the context of the sentence was required. However, the significantly longer time taken, and higher error scores made by the MS group, when completing sentences on the switching task, lends some support for the evidence of disinhibition in the MS group, particularly in the light of the higher error scores produced by the MS group compared to the control group. The longer response times of the MS group may, again, have reflected a slower rate of information processing in this group.

7.5.1.3. Effect of increasing inhibitory demands on response suppression

The MS group were significantly slower than the control group, and produced a greater error score, when completing well-known English proverbs with unconnected words in the proverbs experimental task. The MS group appear to have been less able to inhibit 'automatic' prepotent responses as efficiently as the control group. Thus, when the degree of inhibitory control demanded by the task was increased by requiring completion of proverbs with unconnected words, the MS group were unable to maintain a normal rate of accuracy of response initiation and suppression comparable to the control group, and this provides evidence of disinhibition when demands on inhibitory processes are increased.

Similarly, the significantly greater error scores produced by the MS group compared to normal controls when participants completed sentences with unconnected words in the switching task in the context of a lack of a significant difference between the groups when participants completed sentences with a sensible word, lends further support to evidence for disinhibition in this patient group. It is possible that a greater cognitive demand was placed on participants when they were required to suppress undesired responses and initiate a new (unconnected) completion in the proverbs and switching experimental tasks.

7.5.1.4. Theoretical underpinnings of response initiation and inhibition in MS participants.

Various cognitive theoretical approaches have been described to understand the process of response inhibition as outlined in the introduction (section 2.3.5). More recently, response inhibition has been further investigated (Miyake et al., 2000), and various emerging theoretical concepts may be applied to the performance of the MS group on tasks of response inhibition.

7.5.1.4.1 Response initiation

It has been suggested that the initiation of verbal responses involves the retrieval of items from semantic memory. One idea is that items are generated or retrieved from semantic memory through the automatic process of 'spreading activation' where an association process involved in generating items is automatically initiated by the presentation of a stimulus (e.g. well-known English proverbs) (Posner & Snyder, 1975) (see section 2.3.5.1.).

Alternatively, response initiation may be considered to involved effort –demanding processes that require a certain degree of attentional or executive control (Fletcher & Henson, 2001). A similar process is thought to be involved when performing the verbal fluency task which requires the selection and generation of items from semantic memory (Lezak, 1995). Since the MS group were able to generate verbal responses as accurately as the control group, as shown in the switching and proverbs experimental tasks, the ability of the MS participants to select and retrieve items from semantic memory appears to have been relatively preserved.

This result appears to be inconsistent with the significantly poorer performance of the MS group on the COWAT test of verbal fluency which involves retrieval of items or lexical information quickly from memory (Beatty, 1999; Lezak, 1995). However, verbal fluency involves a phonological search. It is possible that the lack of semantic involvement in this task makes it more challenging for MS patients.

7.5.1.4.2 Response inhibition

When inhibition of a strongly cued, well-learned response is required, for example in the experimental proverbs task, various cognitive or executive processes are brought into play such as attention and inhibition (Smith & Jonides, 1999). The role of the Supervisory Attentional System (Norman & Shallice (1986) (see section 2.3.1.2.), which has been employed in understanding tasks of attention that involve the process of response suppression, may help explain the poorer performance of the MS group in inhibiting responses when the inhibitory demand was increased on this experimental proverbs task. Inhibiting schemata are called into play to suppress attention and to inhibit output (the automatic response which is inappropriate to the task demand) hence allowing attention to be directed to a non-salient, desired dimension (generation of novel responses). Response suppression requires greater effort and attention than conditions in which an automatic prepotent response is expected (Casey et al., 1997; Nathaniel-James et al., 1997). In the present proverbs experiment, it is possible that the MS group's ability to suppress attention to the 'salient dimension' (the well known English proverb), which allows for the inhibition of a dominant, 'automatic' response cued by the well-known English proverb, was less efficient compared to the control group, particularly when inhibitory demands were increased in the proverbs task. This may have been due to a reduction in the amount of attentional control or capacity that could be allocated to the non-salient dimension (generation of novel task) following inhibition of the response. Reduced attentional capacity appears to be evident in the present group of MS participants as reflected in their significantly poorer performance on the PASAT test (Gronwall, 1977), in comparison to performance by the healthy control group. Thus, the findings from the experimental tasks lend support to the suggestion that people with MS may have greater difficulty in inhibiting inappropriate or undesired verbal responses.

The findings from the present study are consistent with the evidence in the research literature that has revealed an impairment in ability of some groups of people with MS to inhibit undesired responses (Comi et al., 1999; Foong et al., 1997). Vitkovitch et al. (2002) employed the Stroop colour-word interference test to examine inhibition in MS and suggested that a partial breakdown in the inhibitory processes of their group may be a plausible explanation for their findings. It is possible that in the current study, the preserved ability of the MS group to inhibit their responses on the Hayling Test section B as efficiently as the healthy control group, while still showing significantly poorer performance than controls on conditions requiring inhibition in the experimental tasks, may similarly reflect a partial break down in inhibitory mechanisms in this group.

The performance of participants on the switching experimental task will now be discussed in order to examine the ability of participants with MS to switch between task demands. This is a second area of interest in the present study.

7.5.2. Task Switching

Prior to examining the performance of the MS group in terms of ability to switch task demand, the performance of the control group will first be analysed in relation to the literature on the set switching process and related theoretical concepts.

Work by Meiren (1996) has shown that switching between tasks within a block of trials takes a greater amount of time than when performing the *same* task in a block (task repetition). Performing the same task in a block means that participants are better able to predict the up coming task demand and thus prepare their response in advance, consequently reducing the time taken to complete the item. Switching between tasks within a block of trials will require a change in 'mental gear' that is likely to contribute to a switch cost effect when a switch occurs. Hence, switching is likely to produce greater response times and error rates (see section 2.3.6).

Figure 1 presents the 'classical' model of cognitive demands that are considered to be involved in the switching process (Meiran, 2000a).

Figure 1

A classical model of processing demands of switching (Meiran, 2000a)

Least processing demands	**No switch requirement**
Moderate processing demands	**Possible requirement to switch but not required to switch in this instance**
High processing demands	**Possible switch required and required to switch in this instance**

The findings of this task highlighted a particular pattern observed in the performance of the control group. Although the time taken to complete items, and error score produced, did not vary significantly between specific switch/ non switch conditions across the three conditions in the control group, the results showed that there was still some difference in the time taken to respond to an item, and the error score, between the different conditions. For both 'sensible' and 'unconnected' conditions, control participants took the longest time, and made the highest error scores, when completing a sentence (item) that required completion with a response following an item requiring the same type of completion, within a block where no switching was required (non switch S-S/ U-U). The group took less time, and produced lower error scores, when completing sentences that required a sensible (or unconnected) completion following an item requiring a different sentence completion, in a block where switching was intermittently required and also a switch on that item was required (switch S-U/ U-S). However, these participants took the least amount of time, and produced the lowest error scores, when completing sentences with a sensible (or unconnected) word that followed an item requiring the same type of completion, in a block where switching was intermittently required but not on that particular item (switch S-S/U-U).

Completion of a sentence with a particular response is likely to be affected by the type of completion undertaken on the preceding item or sentence in terms of time and accuracy, since it is known that successfully switching from one task to another without perseveration requires active disengagement from the previous task in order to allow for engagement with the new task, and effects such as proactive interference (Miyake et al., 2000) and inhibition (Shimamura, 1995) are to be overcome. The longer response time taken, and higher error score made, by the control group when completing sentences with a response that was different to the response required for the completion of the preceeding sentence (switch U-S / S-U conditions), may be understood as a switch cost effect (Monsell, 2003) when compared to the completion of sentences with a response similar to that required in the preceding sentence (switch SS / UU conditions).

Overcoming inhibition may be considered an important factor in contributing to shift costs in the current experimental task. The longer response times taken, and higher error scores made, by the control participants when completing a sentence with a sensible word following completion of a sentence with an unconnected word within a switch block (switch U-S), compared to completion of a sentence with a sensible word following completion of a sentence with a sensible word within a switch block but with no switching in this item (switch S-S), is like to reflect the residual cost of having to overcome a stronger demand in the preceeding sentence (Allport et al., 1994). It is likely that participants required more time to initiate or select a response for the current item after having completed a sentence with an unconnected word where some degree of inhibition was required.

The control participants' pattern of performance may be further understood as involving two types of 'cognitive costs', where costs are defined in terms of the time taken to provide a response and errors made in preparing and managing a switch in task demand. 'General' cognitive costs may be expended when completing items in a switch block where switching is intermittently required (switch S-S / U-U or switch S-U/ U-S conditions). Switching may or may not be required on the item currently being completed and is represented by the time taken by the participants on these switching blocks. 'Switching' costs are expended when participants are required to meet two task demands simultaneously. Participants are thus required to switch between type of completion (U-S or S-U) within a switching block where switching is intermittently required, and to manage a switch from a preceeding item. Thus, the longer response times taken, and higher error scores made, by the control group on switch S-U or switch U-S conditions compared to switch S-S/ U-U conditions, may be understood as reflecting the higher processing demands required for the task. Consequently, this pattern of time performance by the control group on these two switch conditions is considered to fit the classical model of switching demands presented in figure 1.

However, there appears to be an anomaly in the findings of the control group's performance in relation to theoretical concepts of set switching. The performance of the control group on the switching task is in some way inconsistent with the classical model of switching presented in figure 1 and the findings by Meiren (1996) described above. Performing the same task in a block means that participants are better able to predict the up coming task demand and thus prepare their response in advance which reduces the time taken to complete the item. In the current experimental task, however, the control group took longer to respond, and produced higher error scores, reflecting a greater switch cost, when completing items within a block where switching was *not* required ('no switch S-S' and 'no switch U-U conditions') than when completing items in blocks were switching was required (switch S-S/ U-U' or switch S-U/ U-S).

It is possible that the order of presentation of the 'non switch' blocks within the switching task played a role in contributing to this anomalous finding. The first point at which a non switch block was presented in the task was after two 'switch' blocks had been presented. This order of presentation of blocks was based on a randomisation procedure using random number tables. Randomisation prevented participants from learning to anticipate the next task demand in the sequence, that might occur when performing the same task within a block. It is possible that participants became accustomed to preparing themselves to having to switch task demands in 'switch' blocks and thus were less prepared for reconfiguring cognitive processes such as attentional control to perform the change in task demand to begin completing items where switching was not required within the block, and so contributing to a greater time taken on these items.

Set shifting experiments commonly involve training participants to undertaken simple tasks or trials at the initial stage of the experiment. It is possible that since the practice items in the current task mainly required participants to switch between items, participants were not as prepared as they could have been to efficiently complete items in purely 'non switch' blocks.

Finally, there is an inconsistency in the number of items to be completed according to a particular task demand across the six different task conditions. Non switch blocks ('non switch S-S' and 'non switch U-U' conditions) were composed of fifteen items each (see section 6.6.1.2, chapter 6). However, ' switch' blocks (switch S-S/ U-U and switch U-S/ S-U conditions) were composed of 3 and 6 items, respectively. It is possible that this difference in the number of items composing each condition may be considered an additional variable in the design that may have impacted on performance and should have been accounted for in the design.

7.5.2.1. Performance of the MS group in the set switching task

The MS group performed in a similar way to the control group in terms of the response times and error scores produced when they completed sentences with a sensible word or with an unconnected word. The MS group tended to take longer and produce higher error scores in the switch U-S/S-U conditions than the switch S-S/ U-U conditions, with best performance on the non switch S-S/ U-U conditions. This suggests that the manner in which the MS participants manage switching and non switch demands is similar to that of the control group.

Although the MS group took significantly more time than the control group on all conditions (switching and non switching), there does not appear to be any substantial evidence for an impairment in set switching in these MS participants. The MS group produced a higher error score and took longer to complete items in switch U-S/S-U conditions than switch U-U/S-S conditions, yet the group completed sentences in a similar manner to the control group in terms of time taken and error scores made across the conditions. There was no differential impairment across conditions in the MS group, and thus there was no evidence that the MS group was significantly more impaired on the switching conditions compared to the non-switch condition. The significantly longer times taken by the MS group across the conditions, may however, provide evidence of a reduced rate of information processing speed in this patient group. A reduced information processing speed may impair the ability of people with MS to meet cognitive challenges as efficiently as people who do not suffer from MS.

Several studies have described the difficulties MS groups have with the ability to switch set (Arnett et al., 1994; Beatty et al., 1989; Comi et al., 1999; Heaton et al., 1985; Swirsky-Sacchetti et al., 1992). It is possible that the lack of a significant finding is due to a difference between the current sample and samples in other studies in terms of background demographics and disease variables. However, this appears to be a less likely explanation given that the beginning of the discussion reported that the current MS sample were relatively comparable to samples in other studies in terms of these factors. An alternative explanation is that the experimental switching design was not challenging enough to the participants in terms of placing demands on switching and attentional resources. It would be valuable to repeat the study using a more stringent experimental switching design that might involve more items and a switching demand that would be considered to be more challenging to participants to establish whether, indeed, there is a deficit in task switching in this patient group.

7.5.3. Working memory in MS

The performance of the MS group was significantly poorer on both conditions of the PASAT because of the demanding nature of the test on working memory. This is consistent with previous findings (Litvan et al., 1998) (see section 1.2.6.4.) and suggests that the current sample of MS participants are performing in a typical manner to that expected for MS samples in other studies.

D' Esposito et al. (1996) have linked a slowing of information processing speed that is commonly observed in MS patients to an impairment of the Central Executive component of Baddeley's model, particularly with progression of the disease (Archibald & Fisk, 2000). It is possible that in the present study a slowing of information processing speed that appears evident in this group, may also be associated with an impairment in the CE. However, further work would be needed to confirm this hypothesis.

In terms of performance on the digit span test, previous studies have reported the immediate memory span to be preserved in the context of impaired performance on the backward digit span test (Rao et al., 1993; Ruchkin et al., 1994) (see section 1.2.6.5.). However, the present study showed the MS group to be impaired on the immediate memory span test where as backward digit span was normal.

One possible explanation for this inconsistency in findings in terms of the digit span results may be explained in terms of the control group's performance. The control group may have experienced particular difficulties with the backward digit span task. The effect of this was to lower their performance to a level that would no longer bring about a significant difference between the groups. The control group may have experienced difficulty with manipulating information over a period of a few seconds (backwards span), where as their ability to simply hold information in the short term memory span (digit span forwards) was relatively better.

The discrepancy in the MS group's performance between their backward digit span and the PASAT may be explained in terms of a difference in specific task demands required to complete both tasks. Although both tests examine working memory ability (see section 5.4.2.), it appears that task demands vary between both tasks in terms of degree of cognitive flexibility required. The PASAT task, unlike the digit span backwards test, does not involve the reversal of digits in memory, an activity that is likely to demand a degree of cognitive flexibility. Consequently, the MS group may have experienced a specific difficulty with reversal of digits that was not demanded by the other attention or working memory tasks. It may therefore be speculated that the MS group may indeed have found the backward digit span task difficult to complete, consistent with the PASAT findings, yet this impairment was masked by a poor performance by the control group.

7.5.4. Working memory and response inhibition

The relationship between working memory and response inhibition may be commented on based on the findings of the present study. The relationship between the two processes of working memory and response inhibition is considered to be closely linked (Roberts et al., 1994) (see section 2.3.5.2). Failures in inhibition of behaviour have been observed when working memory demand is varied due to a reduction in the capacity to hold in mind information in the short term and to divert attention to inhibit an undesired response.

It is possible that a reduced working memory capacity in the MS patient group, reflected by the significantly poorer performance of the MS group on the PASAT task in comparison to the control group, may have contributed to the reduction in the ability to inhibit prepotent automatic responses when inhibitory demands were increased. The impact of increasing the inhibition demand was reflected by the MS group's performance on the proverbs task where MS participants produced significantly greater error scores and took more time than the control group when completing well-known English proverbs with an unconnected word. Such a deficit in inhibition was not apparent on the Hayling task (section B) in which much less of an inhibitory demand is likely to have been placed on participants when completing sentences. It could be speculated that the MS group's poor working memory made less of an adverse impact on their performance which was maintained at a normal level. However, as the inhibitory demand was greater in the proverbs task, the MS group may have been less efficient in maintaining the unconnected items in working memory that they were temporarily suppressing, whilst allocating their attention to retrieval of a novel response during completion of a sentences with an unconnected word. The MS group may have had fewer cognitive resources that they could draw upon. Consequently, it may be speculated that poor working memory may have contributed to verbal disinhibition in the MS group. These findings may have implications for everyday functioning in people with MS as will be discussed in section 7.10.

Similar to the findings of the present study, Matotek, Saling, Gates & Sedal (2001) found a relationship between working memory and another executive process (verbal fluency), in a group of MS participants. The authors suggested that a reduced working memory capacity is likely to have contributed to a reduced verbal fluency, as reflected by the greater amount of errors made by the group than was normally expected. The authors consider that a reduction in working memory was likely to have been due to the effect of the disease process. In a similar way, the significantly reduced working memory capacity of the MS group in the present study is likely to have been an effect of the disease process.

Matotek et al. (2001) also found a correlation between cognitive impairments, for example in working memory and verbal fluency, and ratings of subjective difficulties in the MS group. Although the present study did not find a significant relationship between subjective ratings of difficulties in everyday life in terms of cognition, behaviour and personality change that are characteristics associated with dysexecutive syndrome (DEX rating scale), and scores on measures of working memory and verbal fluency, MS participants with lower premorbid IQ scores tended to report greater difficulties in every day life in terms of their cognition and behaviour. This suggests that the MS group appear to have some degree of insight into their executive difficulties and that they appear to be aware of the impact of these difficulties on their every day life. Awareness of difficulties is important in the rehabilitation setting since successful rehabilitation depends partly on the insight a patient has into their own difficulties.

7.6. Further consideration of cognitive functions in MS

7.6.1. Executive dysfunction

The findings suggest that there is evidence of a reduction in the efficiency of particular executive processes in this MS group, as shown by significantly poorer performance by the MS group compared to the control group in working memory (PASAT), inhibition (findings from the experimental switching and proverbs tasks) and the rapid retrieval of items from semantic memory (COWAT test). These findings appear to be consistent with those of several other studies in providing support for the evidence of executive impairment in patients with MS (Arnett et al., 1994; Rao et al., 1993; Swirsky-Sacchetti et al., 1992), including an impairment in inhibitory processes (Comi et al., 1999; Foong et al., 1997).

However, not all executive processes are impaired. The ability to switch between task demands (experimental switch task), to maintain and manipulate items in working memory (backwards digit span), and to reason about information using abstraction (verbal and spatial reasoning tasks), appears to be better preserved, reflecting a variability in the degree of impairment of executive processes in this group. The absence of a significant difference in premorbid and current intellectual functioning between both groups, suggests that the MS group shows selectively worse impairment in particular executive functions against a background of relatively preserved general cognitive function.

It is possible that the evidence for executive impairment in the current sample of MS patients may be indicative of frontal lobe pathology or damage to the frontal cortico-subcortical circuits that link the areas of the frontal cortex with other brain regions that are affected by the demyelinating process in MS. This has been highlighted in previous studies (Brassington & Marsh, 1998; Comi et al, 1999). However, since use of brain imaging methods to identify brain regions that are affected by the disease was not within the realms of the present study, this suggestion has not been confirmed and is only speculative. It is not clear whether the deficits in the cognitive processes highlighted by this study are representative of lesions to the frontal lobes or are indicative of more widespread dymyelination involving other brain regions as have been highlighted by studies showing widespread pathology involving both cortical and subcortical areas of the brain (Foong, et al., 1997; Foong et al., 1999).

7.6.2. Speed of information processing in MS

In the current study, slowed cognitive processing speed in the MS group may have contributed to poorer performance on more cognitively demanding conditions and tasks employed as supported by findings of previous studies (Beatty et al., 1988; De Sonneville et al., 2002).

The significantly longer response times taken by the MS group in comparison to the control group on the Hayling test (section A) and both experimental tasks (switching and proverbs) may reflect the need of the MS group to have additional time in preparing cognitive resources to manage the possibility of having to undertake a switch on the switching task, and having to complete sentences and proverbs with unconnected words in the proverbs and Hayling tasks. Both tasks are likely to place greater demand on cognitive processes since switching requires the reconfiguration of cognitive processes (Meiren, 1996), and completion of sentences and proverbs with an unconnected word requires both suppression of an undesired response and generation of a novel response to replace it. It is possible that the greater time taken by the MS group ensures that this group remain as accurate as the healthy control participants in meeting, or better compensating for, the greater cognitive demands they face. Consistent with the present findings, Demaree et al. (1999) showed that providing an MS group extra time to process information improved their accuracy rates to the level of the control group. This has implications for improving every day cognitive functioning in people who experience cognitive difficulties that impact on their every day life.

In summary, the MS group in the present study exhibited deficits in the areas of executive function, attention, and the speed of information processing. The general level of current intellectual functioning, and reasoning abilities in verbal and spatial domains, appeared to be relatively well preserved. This finding is consistent with those in the research literature (Brassington & Marsh, 1998; Rao et al., 1991a; Ron et al., 1991).

7.7. Further consideration of the findings in relation to MS

7.7. 1. Mood

The findings of the present study revealed that the MS group had a significantly higher depression rating than the control group. This finding is not surprising since studies have reported a lifetime prevalence in the rate of depression in people who suffer from MS of approximately 50% (Kroencke et al., 2001). However, the median score of the MS group on the HADS fell within the 'not clinically depressed' range. The lack of a significant correlation between depression ratings and performance on the cognitive measures in the MS group is consistent with previous studies (Camp et al., 1999; Krupp et al., 1994; Moller at al., 1994; Rao et al., 1991a).

7.7.2. Fatigue

The MS group did not differ significantly from the control group in terms of fatigue pre and post testing. However, the MS group did show a greater degree of change in their level of fatigue over the testing session and better test scores were associated with higher ratings of fatigue. This appears to be an unusual finding as, according to the research literature, it would be expected that test scores would increase, and therefore performance would improve, with lower ratings of fatigue (Sandroni et al., 1992). It might have been more valuable to have correlated change in fatigue ratings over time with performance on cognitive measures to clarify this finding.

The results for the control group were as might be expected. Higher fatigue ratings prior to testing were associated with lower scores on the cognitive measures of the VESPAR test (spatial domain), and digit span backwards, indicating poorer test performance in the control group. This is perhaps because such measures are demanding tasks of reasoning and attention which require a high degree of attention and effort.

7.7.3. Disease variables

7.7.3.1. Disability rating

The MS group's median score of 5 on the Ambulation Index suggests that the group had moderate difficulty in timed walking and ability to transfer between sitting and standing, and vice versa. Their ratings ranged from 0 (normal gait) to 9 (unable to walk or transfer independently). On the Troiano scale, a scale that assesses gait, activities of daily living and ability to perform a transfer between sitting and standing, or between one seating position to another, the group's median score of 5 indicated a moderate level of disability in these particular areas. A significant positive association was found between digit span scores and disability rating on the Ambulation Index (Hauser, 1983). This suggests that a greater ability to maintain and manipulate information for a very brief period of time in working memory is associated with higher ratings on this disability measure. It is possible that this reflects a relationship where, as degree of disability worsens and people with MS become less mobile, they are better able to compensate for the limitations this brings on their everyday life by relying more on working memory to cope with daily demands, thus efficiency of working memory improves with greater use.

7.7.3.2. Disease duration

The lack of a significant association between disease duration and cognitive performance on all cognitive measures apart from one, is consistent with other studies that have failed to find a similar relationship (e.g. Rao et al., 1991a). Perhaps examining the rate of change, rather than the duration of the disease, would have yielded more meaningful results.

7.7.4. Duration of testing

There was a disparity in length of testing of the two groups, with the MS group taking between 2 – 2 1/2 hours per person compared to the control participants who took in the region of 1 ½ hours per person. It is possible that effect of fatigue contributed to the greater testing time of the MS participants, particularly given that there was a significantly greater degree of change in level of fatigue rating over the session by the MS group when compared to the control group. This may have added to any initial cognitive difficulties by slowing further the rate at which MS participants could process information, increasing further the response times and errors on experimental tests.

The present findings have been considered in relation to cognitive function in MS. The findings will now be briefly reviewed at a more general level in terms of the current approach to the understanding of executive function before turning to consider the limitations of the current study.

7.8. Relating the present findings to the area of executive function: consideration of the relationship between different executive processes

Understanding executive functions in terms of separable processes is considered to be the current focus of thinking in the area of executive function (see section 2.3.2).

In terms of the present study, the design of the switching and proverbs task was based on a similar format to the Hayling task in that it allowed for the examination of response initiation and response suppression to be undertaken under similar task demands and conditions. Since the MS group were found to be as accurate as the control group when required to generate sensible words that would best complete the sentence in both experimental tasks, yet they produced a significantly greater error score than the healthy controls when completing sentences with unconnected words, then in the same task and within the same group of patients, there appears to be a discrepancy or separability in terms of these executive processes. Consequently, these findings provide further support for this approach in the current literature on executive function.

7.9. Limitations of the study

There are several points for consideration.

The lack of support for a deficit in task switching in the MS group may have reflected an experimental design that was not demanding enough, or one that failed to contain sufficient items, to produce a significant effect. Use of more items and a larger sample size may have helped to increase the demands of the task and the degree of power.

Several cognitive measures were included in the study in order to test the research hypotheses. It is possible that the inclusion of several measures and use of multiple t-tests may have increased the type I error rate in this study. There is also a possibility that type 1 errors may have arisen as a result of multiple correlational analyses having been undertaken, where sample sizes were relatively small. Type 1 errors reflect false positive findings that arise by chance which are misinterpreted as a significant finding. However, the potential problem of type 1 errors occurring in the correlational analyses was controlled for by employing a more stringent level of significance ($p<0.01$) to evaluate the findings. This reduced the likelihood that any significant findings arose simply by chance.

A proportion of the healthy control participants were recruited from a local organisation. It is possible that this method of recruitment may have led to a bias in the sample as reflected by the high proportion of control participants falling into the 'clinically anxious' range of the HADS mood scale. To have better avoided such a potential bias in the control sample recruited for the study, more participants should have been from a wider range of sources within the community.

When administering the battery of cognitive measures and experimental tasks, a hand held stopwatch was used to record the response times of participants. It is possible that use of a hand held stopwatch may have reduced the accuracy in the measurement of timed responses. Use of computers to record response times may increase the accuracy of recording, but they have their own problems when used in studies on MS in that they rely on visuomotor abilities that are commonly compromised in people with MS (Brassington & Marsh, 1998).

Using the total response score of the PASAT as an indication of whether there is an impairment of working memory and of speed of information processing has been criticised (Archibald & Fisk, 2001). The total number of correct scores, which is commonly used as the outcome measure of the PASAT, has been found to mask the difficulties that participants commonly experience with this task. Participants have been found to 'chunk' information presented to them by ignoring some of the items presented. This makes the test less difficult to perform since chunking the information ensures that the items becomes more manageable to process and this reduces the need to perform several cognitive tasks at once (Archibald & Fisk, 2001). Archibald and Fisk recommend that in addition to calculating the total response score on this test, that the scores be analysed by calculating the proportion of correct responses made that are consecutive ('dyads'). When reanalysing the responses using this method, the MS group were found to perform at a more comparable level to that of the control group at the faster, and thus more demanding, rate of presentation. This reanalysis of the scores was not undertaken in the present study but it would have been important to do so given that MS patients have been found to perform more comparably to the normal healthy controls when this new method of analysis is used.

An important issue in executive function research is the use of ecologically valid tests that go some way in correlating with how patients really cope with everyday demands in real life (see section 3.1.2.). Although the performance of the MS participants on the experimental tasks have not been specifically correlated with performance in everyday life, the performance of participants in completing familiar English proverbs in the proverbs task, and simple sentences in the switching task, with unconnected words may provide some insight into the difficulties that people with MS may face in everyday conversations involving the English language. The tasks therefore may be considered to have some degree of ecological validity.

The current study did not consider the possible effect of medication on cognitive test performance. Although several studies have failed to find a significant association between cognitive impairment and prescribed medication usage (Heaton et al., 1985; Rao et al.,1991a), examining the potential effect of medication on performance would have helped to ensure that significant findings were not attributable to the use of medication.

7.10. Clinical Implications of the study

There are several important findings in the present study and these are likely to have clinical implications for the lives of people with MS.

The MS group were found to have greater difficulty than healthy control participants in inhibiting prepotent or undesired verbal responses. Inhibiting undesired responses was particularly difficult when inhibitory demands were higher and undesired responses were likely to be more familiar or over-used (the experimental proverbs task). A difficulty in inhibiting more familiar or over-used verbal responses is likely to have a major impact on the life of a person with MS, particularly when communicating in social situations, at work or with the family. Some people with MS may have difficulty in stopping themselves from using particular words, for example, expletives. Expletives are terms that may be more strongly cued by particular situations or contexts, for example when the person is becoming angry, or may be triggered by the verbal responses of other people. Consequently, expletives may be more difficult to inhibit or suppress as compared to other terms in a person's vocabulary. In the light of the findings of this study, some people with MS may have real difficulties in preventing themselves saying particular words that they might not wish to say in everyday situations. The findings further suggest that some people with MS may also experience difficulty in stopping themselves from continuing to use familiar routines or actions that are cued by the context, but when they are no longer appropriate to the situation. This may include use of a walking stick that was once an appropriate aid, but that continues to be used unquestioningly despite subsequent reduced balance.

Consequently, the present findings have implications for rehabilitation since strategies to help people with MS to cope with the problem of disinhibition can be developed. Such strategies may include supporting the person with MS to monitor their own verbal output and to focus on the importance of providing feedback to the person.

The MS group were also found to take significantly longer than the normal control participants on several of the cognitive tasks. In everyday life, people with MS may have difficulty in completing tasks under timed conditions or that require speed. This will be a particular problem in the work or home setting where the ability of people with MS to meet cognitive challenges may be less efficient than people who do not suffer from MS. Since Matotek et al. (1999) showed that providing an MS group extra time to process information improved their accuracy rates to the level of the control group, people with MS who take longer to complete every day tasks may benefit from being given more time to complete activities. This may involve planning and organising tasks in advance so that there is sufficient time to complete them.

The significantly greater change in fatigue over the testing session found in the MS group compared to the control participants suggest that completing tasks can be a challenge for people with MS due to the fatigue they are likely to experience. Strategies to help people with MS cope better with fatigue can be developed and these can include encouraging the person to take frequent breaks.

It appears that the MS group have some degree of insight into their executive difficulties as reflected by their high self ratings on the DEX measure that indicated that participants were aware of the impact of these difficulties on their everyday life. If people with MS have a degree of awareness of their difficulties and how they impact on their everyday life, it is likely that they will be more motivated to engage in rehabilitation and ensure that the strategies developed to support the person in coping with their cognitive difficulties will be more successful.

The final part of the discussion will focus on suggestions for future research.

7.11. Suggestions for future research

A significant finding in the current study is that there is evidence of verbal disinhibition in a group of people with MS. Disinhibition appears to be a relatively under researched area in this patient group and since this is a problem that is likely to have significant implications for the life of a person with MS, further work in this area is needed. It may be valuable to replicate this study using the experimental proverbs task in order to look more carefully at the relationship between factors such as reduced working memory and information processing rate, and the effect of fatigue, on disinhibition.

The experimental switching and proverbs tasks may be replicated using more vigorous testing methods. These include using computers to time responses in order to improve the accuracy of the recording and to include more items in each of the tasks. Inclusion of more items would allow for the examination of the effect of fatigue, which is one of the main difficulties people with MS face in their everyday life (Brassington & Marsh, 1998), on the cognitive processes of switching and inhibition which will have further clinical implications in improving the quality of life of people with MS.

7. 12. Conclusion

The present study set out to examine the processes of verbal response inhibition and the ability to switch between task demands in a group of people with MS. The hypotheses of the study have been partly supported by the findings in which there is evidence of verbal disinhibition, although there is little support for an impairment in task switching in this group. There is evidence of a reduction in the efficiency of some executive processes in the MS group in the context of other areas of cognitive dysfunction such as speed of information processing. The findings of this sample are considered generalisable to the wider MS population and there are important clinical implications of these findings in improving the quality of life of people who suffer from MS.

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HARROW RESEARCH ETHICS COMMITTEE
(Chairman: Dr David Lubel)
Room 4B 011

8 October 2002

Dr D Langdon
Department of Psychology
Royal Holloway
University of London
Egham
Surrey
TW20 0EX

Dear Dr Langdon

Ethics Submission No 3039: Executive functioning in multiple sclerosis

The above project was approved by the Harrow Research Ethics Committee at its meeting on 7 October 2002. It would be appreciated if, in any future correspondence relating to this project or in any entry made in case-notes about procedures undertaken in the course of this study, you would refer to it as **EC 2761.** ***Please note that, before you can proceed with the study, you will need to obtain formal authorisation from the NHS institution where it is to be undertaken.***

Set out overleaf is the REC membership list which should, if applicable, be copied to the sponsoring organisation.

General Practitioners should be kept informed of research work affecting their patients, particularly when the patient's involvement continues after discharge from hospital.

All adverse events arising during the course of this study should be notified, but please note that the Committee is only concerned to receive such notifications as they relate to subjects participating in trials in Harrow. Investigators undertaking trials on behalf of drug companies are asked to refrain from sending other adverse event reports, unless there are very exceptional circumstances.

The Committee operates according to GCP in most important respects.

Yours sincerely

Brian Saperia
Administrator

3039

HARROW RESEARCH ETHICS COMMITTEE
(Chairman:
Room 5BB 013

24 February 2003

Yamna Satgunasingam
Sub-Department of Clinical Health Psychology
University of London
Gower Street
London WC1E 6BT

Dear Yamna

Ethics Submission No 3039: Executive functioning in multiple sclerosis

I am pleased to inform you that protocol amendments for the above study as notified in your letter of 10 February have been approved by Chairman's action.

Yours sincerely

Angela Barst

Ms Angela Barst
Acting Administrator

3039

Application no: 18/2003

ROYAL HOLLOWAY
University of London

ETHICS COMMITTEE

Result of Application to the Committee

Name of Applicant: Dr Dawn Langdon

Title of Project: **Executive Processes in Multiple Sclerosis**

This is to notify you that your research project:

✓	Has been approved under Chair's Action, this decision to be reported to the Committee at its next meeting

A. B. Wathey
....

Prof A B Wathey
Vice-Principal (Planning & Resources)

Chair

14 April 2003
....

Date

B. Davis
....

Dr B Davis
Principal's Executive Officer

Secretary to the Committee

14/4/03
....

Date

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON

INFORMATION SHEET

Thinking in Multiple Sclerosis

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 ask me if there is anything that is not clear. Take time to decide whether or not you wish to take part.

All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This study has been agreed by the Harrow Research Ethics Committee.

What is the purpose of the study?

We are investigating the ways in which people with Multiple Sclerosis (MS) think about information. This has relevance for everyday living because memory and concentration difficulties are reported by people with MS.

We are also studying people who do not suffer from Multiple Sclerosis so that we can compare findings. There is no treatment benefit from taking part in this trial but we hope that in the long run our results will enable us to improve existing methods of recognising difficulties and aid us in developing treatment methods.

Will you want to see my medical notes?

Yes. We will need to check your medical notes to collect information about your condition.

Will my General Practitioner be informed?

Yes. A copy of this information sheet and consent form that you will have signed if you have decided that you would like to participate in this study will be sent to your General Practitioner.

What will the study involve?

You will be asked to carry out a series of tasks involving reading, completing sentences, problem-solving, memory and learning. Some of these are pen and paper tests or puzzles, and some are presented on a computer screen or audiotape. Some of the tasks include giving spoken or written answers, and others involve pressing keys on a computer. We will be interested in how accurately you do the tasks, and in how quickly you do them.

You will also be asked to fill out questionnaires and to answer brief questions about your educational, occupational and medical history and any difficulties you may be having.

The testing will be arranged to suit your convenience and you will be able to take breaks if you feel tired. The time taken depends on how you work through the tasks and the number of breaks you choose to take. Most people take between 60 and 90 minutes. You will be reimbursed for agreed travel expenses. The date of the appointment, location and payment will be arranged with you by telephone by myself and confirmed in writing.

The research does NOT involve giving any blood tests or other medical procedures and you will not be given any drugs. In fact, there is no physical investigations of any kind and you will not be asked to do anything unpleasant or painful.

If you do decide to take part you will be asked to sign a consent form, and any information you give will be treated in strict confidence. It is up to you whether or not you take part. You may have a relative, or friend, or a nurse present if you so wish.

Will I be able to find out about the findings of the study?

You will be sent a copy of the summary of the findings of the research once the study has been completed if you wish. A copy of this summary will be sent to your General Practitioner at his or her request.

What happens if I do not want to take part in the study?

You do not have to take part in this study if you do not want to do so. If you decide to take part you may withdraw at any time without giving a reason. Your decision whether to take part or not will not affect your care and management in any way.

What should I do if I want further information?

If you would like more information, Yamna Satgunasingam can be contacted on:
07866536959

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

HOSPITAL NUMBER:

NAME:

DOB:

RESEARCH PROJECT CONSENT FORM

Title of Project: **EXECUTIVE FUNCTIONING IN MULTIPLE SCLEROSIS**

Ethics Committee (EC) No.:

Principal Investigator: Dr. D. W. Langdon

PART A: TO BE COMPLETED BY THE INVESTIGATOR:

I confirm that I have explained this research project to the patient in terms which, in my judgement, are suited to the understanding of the patient and/or one of the parents or guardians of the patient.

____________________	____________________	____________________
Name of Researcher	*Signature*	*Date*
Name of Person taking consent (if different from researcher)	*Signature*	*Date*

PART B: TO BE COMPLETED BY THE PATIENT AND/OR PARENT OR GUARDIAN: **Please initial box**

1. I confirm that I have read and understand the information sheet dated........................... 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 my identity will not be disclosed in any published or written data resulting from this study. ☐

4. I understand the above information and agree to take part in the above research project. ☐

____________________	____________________	____________________
Name of Patient (and/or Parent/Guardian)	*Signature*	*Date*

On completion, one copy of this form (the original) is to be inserted into the patient's case notes.
A copy must also be sent to the patient's General Practitioner and a copy handed to the patient to keep.

PARTICIPANT QUESTIONNAIRE

Name:

Address:
Telephone Number:

Live in own home?
Gender:
DOB: Age: (within 18 - 70?)
Left or right handed?

GP/ address:
Consultant Neurologist
Hospital no.
Diagnosis:

Educational and occupational history:

1. Is your first language English?
   If not:
   How fluent are you in English?
   Which langauges do you speak?
   At what age did you start to learn English?

2. Where did you receive your education?

3. What school did you attend? (primary/secondary)

4. What age did you leave school?

5. What qualifications, if any, did you obtain after leaving school?
incl. university

6. How long was the course of study?

7. Total number of years of education (primary & secondary/ university level)

8. What are the main types of work you have done/ main career, if any?

9. What is your main job now, if any?

10. How long held job ?

Medical

11. Do you have difficulty understanding conversations because of your hearing?
    If yes, do you use a hearing aid?
    Does this help?

12. Do you have any difficulties with your speech/ speaking eg dysarthria?

13. Do you have trouble with your vision that prevents you reading ordinary print?
    eg blurred vision/ rapid eye movements (nystagmus?)
    If yes: Do you wear reading glasses?
    Do these enable you to read ordinary print?

14. Have you every been diagnosed with having dyslexia?

15. Apart from the MS, have you ever had a serious illness?
    incl. diabetes / TB/ heart trouble/ thyrotoxicosis (as affects cognitive function) (please give details)

16. Have you ever suffered from any other neurological illness
eg meningitis / encephalitis / epilepsy / seizures/ fits (please give details)

17. Ever had a serious accident?
(please give details) esp. head injury.

18. Ever been unconscious?
eg length of time unconscious/ no. of times unconscious (please give details)

19. Previous surgical operations
If yes, under general anaesthetic?
Total no. of operations?
How long ago was last operation?

20. How would you describe your current mood state now?

21. Have you ever received treatment for mental health or emotional difficulties?
If yes, please give details
(condition/ how long/ treated?/ how treated?/ ever attempted suicide?)

22. Do you drink alcohol
How much per week?

23. Do you take recreational drugs- now or in the past?

24. Do you suffer from fatigue? (eg when most fatigued during the day?)

FOR MS PARTICIPANTS

25. Please give details of current prescribed medication
(name/ dosage/ side effects?) (obtain list from participant)
i) for the MS

ii) for other reasons/ conditions (eg antidepressants/ sleep tablets etc?)

26. Ever suffered from any problems such as difficulties with memory, problem-solving or planning or saying things that you don't want to say/ inappropriate things? If so, please give details

27. When were you first diagnosed with MS?

28. When did you first notice symptoms of MS?

29. Total number of years with MS?

30. What physical difficulties do you face? (eg walking/ mobility/ fine motor movements etc)

PRE

VISUAL ANALOGUE SCALE OF FATIGUE

Please rate on the scale below how tired you are feeling **at this moment** by picking the relevant label.
(There is no right or wrong answer)

Thank you.

Not at all tired	A little tired	Quite tired	Very tired	The most tired I have ever felt

<u>*Switching Test (experimental test 1)*</u> <u>INSTRUCTIONS</u>

(Based on Hayling Test instructions):
'In a moment I am going to play to you on a audiotape a series of sentences, each of which has the last word missing from it. Before hearing each sentence on the tape, I will ask you to give me a word that will complete the sentence according to a specific rule as follows:

I may ask you to complete the sentence with a word that would *best* completes the sentence (a sensible word)

OR I may ask you to complete the sentence with a word that does *not* fit at the end of the sentence (an unconnected word). In this case, I want the word you give me to be completely unconnected to the sentence in every way.

The sentences will be presented on a tape recorder in blocks of 6 sentences. Some blocks will require you to complete the sentences with only sensible words, some blocks will only require you to complete the sentences with only unconnected words. Other blocks will require you to **SWITCH** between completing the sentences with either a sensible word or an unconnected word.

You will know whether to complete the sentence with a sensible word or with an unconnected word because, ***BEFORE*** hearing each SENTENCE, the word 'sensible' or the word 'unconnected' will be spoken on the tape.

Do you understand? (Repeat if necessary until participant understands)

Before we start I'll play to you a few practice sentences on the tape recorder so that you can get the hang of what is required.

<<u>*playing on tape:*</u>
<u>*Practice items*</u>
***present on tape**
***check if participant able to hear sentences clearly enough**
****press pause button after end of EACH sentence (3 second gap)***
***(both practice items and main task)*>**
***allow one minute per response**

'Sensible: She decided to visit her ....'
'Unconnected: He planned to travel to ....'***
'Unconnected: They would arrive there by ....'
'Sensible: He saw her in the......................................'

***If the participant produces a sensible word instead of an **'unconnected' word on an 'unconnected' type sentences**, say the following to the participant:
'The word you have just given me *does* fit at the end of the sentence. But what I want is a word which doesn't fit at the end- one which is complete *unconnected* to it.

SO for example if you had given me the word 'egg' that would be right because 'egg' is unconnected to the sentence 'He planned to travel to.......'

<So can you think of a word which you could have given me instead of <participant's response>?

Let the participant try again, then move onto the next practice item, regardless of whether the participant produces an unconnected word.

If the response is **ACCEPTABLE** just say:
'That was very good, so I'll give you one/a couple more practice items.

If NOT ACCEPTABLE:-
'Well that word is still connected to the sentence, isn't it?
SO it is not an ideal kind of answer. But I'll give you another practice sentence to see if you can get the hang of it.'
<Give next practice item> (just **READ** it out)
If answer still strongly connected to sentence, point out its a connected answer, and so it is not what you are asking for. Give the participant an opportunity to think of another answer to the practice item, but move on regardless of success or failure.

IF USE SAME STRATEGY
****if repeat SAME word for sentences within a block,** this is ONLY strategy **NOT permitted in test:**
i.e. person to try and use DIFFERENT words within a block, but say following instructions only once (on first repetition):
-Say on FIRST repeat of response:
'You've ALREADY used that answer.
Repeating the same word to each sentence is a good way of approaching this test, but its makes it too easy, so I'm afraid that I'm going to have to ask you not to use it.
From now on I want a DIFFERENT word each time.'

****if use other** strategies:
-make clear that the only strategy NOT allowed is to REPEAT answers
-NEVER give eg.s of other strategies that could use.

MAIN TASK
'OK, that's the end of the practice items. Remember it is important for you to give me your answer **AS QUICKLY AS YOU CAN**. Are you ready?'

Played on tape: (1 min/ response)
(Key: S=sensible Reponses; U= Unconnected word)
(Blocks of 6 sentences have been randomised in terms of S/U/R blocks)

1. (U) The old house fell ....down
(S) They ran down the ....hill
(S) The tall tree leaned ....over
(U) They walked up the ....road
(U) The large bird flew ....away

RECORD SHEETS FOR EXPERIMENTAL TASKS
(1 min/ response)

A) SWITCHING TASK

Practice items | Participant's response | Time

Sensible: She decided to visit her ....
Unconnected: He planned to travel to..........
Unconnected: They would arrive there by..........
Sensible: He saw her in the..........

Main task

1. (U) The old house fell..........
   (S) They ran down the..........
   (S) The tall tree leaned..........
   (U) They walked up the..........
   (U) The large bird flew..........
   (S) They swam across the..........

2. (U) The cat drank his milk and then..........
   (S) The children got off their bikes and..........
   (U) The dog ate his biscuits before lying..........
   (S) The children searched for the paper and ....
   (U) The cow produced the milk for its..........
   (S) The children waited patiently to see their..........

(BREAK?)

3. (S) I went to the library and borrowed a..........
   (S) I got up and then switched on the..........
   (S) I went to the garage and bought some..........
   (S) I went out to lunch and lost my..........
   (S) I went to the cafe and ate a..........
   (S) Walking down the road I stopped at the..........

4. (U) She took out a book and began to..........
   (U) He struck a match and then lit the..........
   (U) She opened the fridge and took out the..........
   (U) She turned off the light and went to..........
   (U) He switched on the stereo and played the..........
   (U) She turned on the tap and filled the..........

(BREAK?)

CLASSIFICATION GUIDE FOR SWITCHING TASK

Please would you rate each of the participant's responses to sentences of the switching task on the sheets given according to the following classification guide (writing your classification rating next to each response)? Please refer to the examples of test items also attached. Many thanks. Yamna.

1) For sentences to be completed with a sensible word (i. e. sentences with an (S)):

	Classification	Error score
1. Does the word reasonably complete the sentence? (i.e. it's a word you might give yourself if asked to provide a word that would fit at the end).	G	0
2. Does the word make the sentence illogical or non-sensical?	H	1

2) For sentences to be completed with an unconnected word (i.e. sentencees with a (U)):
(Based on Burgess and Shallice, 1996)

Sensible completions (connected)	Classification	Error score
1. Does the word reasonably complete the sentence (i.e. it's a word you might give yourself if asked to provide a word that would fit at the end)	C	3
Semantically connected		
2. Is the word an opposite of what you might expect to answer?	SO	1
3. Is the word obviously semantically connected to the subject of the sentence?	SA	1
4. Is the word obviously semantically connected to the expected response?	SB	1
5. Does the word vaguely fit at the end of the sentence, but in a way that makes the sense of the sentence ludicrous -or is the word a slang semi-obscenity?	SC	1
Unconnected		
6. Is the word an item you might find in a room at home or in an office?	UR	0
7. Is the word semantically connected to the participant's last response?	UL	0
8. Is the word both an item you might find in the home or office and is also related to the last answer?	URL	0
9. Are none of the above true?	U	0

Appendix 3.4.1.

Proverbs used in Experimental Proverbs Task

Well-known English Proverbs (E) matched with Romanian or rare English proverbs (R)

1. A bird in the hand is worth two in the bush (E)
   Better an egg today than a hen tomorrow (R)
2. Action speak louder than words (E)
   Deeds are fruits, words are but leaves (R)
3. All good things must come to an end (E)
   The best of friends must part (R)
4. An apple a day keeps the doctor away (E)
   Where the sun enters, the doctor does not (R)
5. Beggars can't be choosers (E)
   The goat must browse where she is tied (R)
6. Curiosity killed the cat (E)
   He that gazes upon the sun shall at last be blind (R)
7. Don't cut of you nose to spite your face (E)
   Don't burn your house to frighten the mouse (R)
8. Do not count your chickens before they are hatched (E)
   Do not sell the bear's skin until you have caught him (R)
9. Easier said than done (E)
   From word to deed is a great space (R)
10. Give him an inch and he'll take a mile (E)
    Give the clown your finger and he will take your hand (R)
11. Honesty is the best policy (E)
    Plain dealing is best (R)
12. Look before you leap (E)
    Think on the end before you begin (R)
13. Rome was not built in a day (E)
    The oak is not felled at one stroke (R)
14. Strike while the iron is hot (E)
    Hoist your sail when the wind is fair (R)
15. Variety is the spice of life (E)
    Variety takes away satiety (R)
16. Practice makes perfect (E)
    Use makes mastery (R)
17. One swallow doesn't make a summer (E)
    One flower makes no garland (R)
18. Out of sight, out of mind (E)
    Saltwater and absence wash away love (R)

Appendix 3.4.2.

PROVERBS TEST

Practice items

Participant's response **Time**

Sensible: The cat sat on the...

Sensible: Better late than...

Unconnected: Many hands make light...

Unconnected: Home is where the heart...

Main task (1 min/response)

SENSIBLE - CCCRRR

Beggar's can't be...

Do not count your chickens before they are...

Give him an inch and he'll take a ....

The best of friends must...

Don't burn your house to frighten the...

Hoist your sail when the wind is...

UNCONNECTED- CRRCCR

Easier said than...

Better an egg today than a hen...

Salt water and absence wash away...

Honesty is the best...

Actions speak louder than...

The goat must browse where she is...

(BREAK?)

SENSIBLE -RRRCCC

The oak is not felled at one...

One flower makes no...

Variety takes away...

Curiosity killed the...

Out of sight, out of...

All good things must come to an...

SENSIBLE - RRCCCR

Think on the end before you...

Deeds are fruit, words are but...

Don't cut off your nose to spite your...

Look before you...

Rome was not built in a ....

He that gazes upon the sun, shall at last be...

(BREAK?)