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An investigation into fatigue and cognitive function in advanced multiple sclerosis

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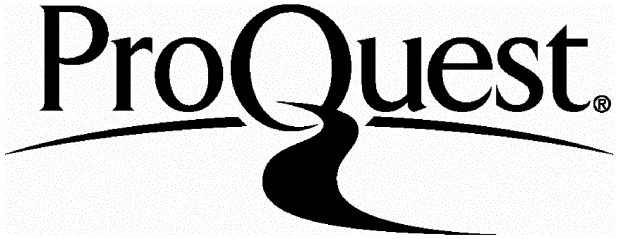

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Abstract

Fatigue is a common symptom of multiple sclerosis (MS) and the impact of fatigue on the quality of life of a person with MS is significant. It has been associated with overall mental health, perceived control over the illness and unemployment. Cognitive impairment in MS is also common. People with MS are often impaired on measures of speed of information processing, attention, memory, executive function and working memory. As with fatigue, the psychosocial impact of cognitive dysfunction on the individual with MS is significant. However, there are relatively few investigations of the link between the two symptoms of MS.

The present study aimed to examine the effects of fatigue on cognitive performance in MS. Of particular interest, were changes in cognitive performance within a task and across a session (which may be evidence of cognitive fatigue) and their relationship with self-reported fatigue and depression.

Sixteen people with advanced MS and 19 healthy control participants completed two neuropsychological testing sessions. Each testing session involved repeated administration of a continuous cognitive task (the n-back task). At the beginning and the end of one session participants completed the 0-back task, a test of sustained attention. In the other session they completed repeated administration of the 1-back task, which requires sustained attention and has an additional working memory load. A neuropsychological battery was administered between each n-back presentation in each session. In addition, self-reported fatigue was measured at regular intervals during each session. All participants also completed depression and fatigue questionnaires.

Overall, the performance of the MS group was worse than the control group on the n-back task and the neuropsychological tests. There was mixed evidence to support the notion that compared to a healthy control group, people with MS show more objective signs of cognitive fatigue (a decline in cognitive performance over time) during a continuous cognitive task. There was no significant evidence that people with MS showed a greater decline in performance across a neuropsychological testing session compared to a control group. However, participants with MS did report greater subjective changes in their level of fatigue across a testing session compared to the control group when the task had a working memory load. Also, ratings of the symptoms of fatigue were associated with symptoms of depression. However, a significant finding was the poor association between changes in subjective fatigue and changes in cognitive performance over the testing session.

These findings suggest that although people with MS may report subjective changes in fatigue across a testing session, their cognitive performance may not necessarily reflect the same pattern. In addition, there appears to be a relationship between depression and fatigue that has important treatment implications and should be examined in future studies.

1.0 Introduction Section

1.1 Multiple Sclerosis

1.11 What is Multiple Sclerosis?

The French neurologist, Jean-Martin Charcot, is generally credited with first naming the condition now know as multiple sclerosis (MS) (Charcot, 1877). By the early 20th Century, the disease that was previously only recognized in individual case reports had become one of the most common reasons for admission to neurological wards (Compston and Coles, 2002). There are approximately 2.5 million affected individuals worldwide, accounting for an estimated £1.2 billion expenditure per annum in the UK (Holmes et al., 1995).

MS is currently recognized as an autoimmune inflammatory disorder that affects the central nervous system (ffrench-Constant, 1994). The inflammatory response leads to damage in the myelin sheath covering of nerve cells (demyelination). This damage impairs the normal transmission of nerve impulses and the symptoms of MS ensue (Feinstein, 1999).

Individual presentations of MS vary, but symptoms may include visual disturbances, muscular weakness, ataxia, spasticity and bladder dysfunction. Two frequently reported symptoms that can cause distress and disability are cognitive difficulties and fatigue. The relationship between these two symptoms of MS will be the focus of this thesis.

1.12 Aetiology / epidemiology

MS has an incidence of approximately seven per 100 000 every year, prevalence of around 120 per 100 000 and a lifetime risk of one in 400 (Compston and Coles, 2002). Onset is most

common in early adult life and it is twice as prevalent in women as in men (Feinstein, 1999). Epidemiological studies have emphasized the importance of genetic and environmental variables.

A frequently reported finding is that the prevalence rate of MS increases as the distance from the equator increases. For example, Poser (1994) cites a prevalence rate of 99.4 per 100, 000 inhabitants in Iceland (latitude = 65°N), but only 4 per 100 000 in Malta (latitude = 36°N). However, there are a number of exceptions to the high latitude - high prevalence rule, with populations living on the same latitude having very different prevalence rates (Poser, 1994). This finding may be accounted for by genetic susceptibility. Compelling evidence for the role of genetic susceptibility in certain ethnic groups comes from the finding that the disease is extremely rare in populations including the Japanese (Kuroiwa et al., 1983), the Chinese (Yu et al., 1989) and the Maori population of New Zealand (Skegg et al., 1987).

Migration studies have provided additional information about the influence of the environment and genetics. People who move from a country with a high frequency of MS to a country of low frequency appear to bring the high risk with them if they immigrate after puberty. However, if they move before puberty they acquire the low risk of the country of destination (Alter et al., 1996; Dean and Kurtzke., 1971; Derels et al., 1978). There is also evidence to suggest that people who move from areas of low frequency to areas of high frequency bring with them the low risk of their country of origin (Dean et al.,, 1976). However, Poser (1994) argues that the conclusions drawn from migration studies should be treated with caution. He suggests that migrants may represent a select group fundamentally different from the general population in terms of health, age and sex.

The role of genetic influences in MS is also supported by twin studies, which indicate concordance rates of approximately 25% in monozygotic twins (Ebers et al., 1986). This concordance rate indicates that the mode of inheritance may be polygenetic, with Poser (1992) suggesting the presence of an MS trait. This trait is speculated to be a systemic non-pathological condition (a disease waiting to happen) which is acquired from a viral antigenic challenge in a genetically susceptible individual, from either vaccine or an infection (Poser, 1992). However, in order to clarify the influences of environment and genetics on acquisition of MS, future research is needed to compare similar ethnic groups under different environmental conditions (Poser, 1994). O'Connor (2002) suggests that at present the most widely accepted hypothesis for the aetiology of MS is that susceptibility to the disease is genetically determined and that onset is triggered by an environmental factor.

1.13 Pathogenesis and Pathology

The exact pathogenesis of MS is still uncertain (Feinstein, 1999). However, the conventional view is that it is an organ- or antigen-specific disease caused by immune-mediated injury to myelin, its cell of origin in the CNS (the oligodentrocyte) and to the underlying axon (O'Connor, 2002).

Post-mortem studies in people severely affected by MS often show a mild degree of brain atrophy, with ventricular dilation and sulcal widening (Allen, 1991). Plaques, which show evidence of demyelination, are often seen in the corpus callosum, the temporal and occipital lobes, and around the lateral ventricles. Plaques are also frequently found in the brain stem and

the spinal cord as well as in the white matter regions of the basal ganglia, thalamus and hypothalamus (Trötster, 1998).

1.14 Symptoms / clinical features

MS can present with very different neurological signs according to the location of the plaques (Feinstein, 1999). Initial symptoms often include weakness in the limbs, incontinence and retrobulbar or optic neuritis (Knight, 1992).

Making a diagnosis of MS can be difficult. There is no single clinical sign or diagnostic test that can provide enough information to make an accurate diagnosis. Instead, the process of diagnosis involves gathering information from clinical examination, clinical history and a variety of laboratory tests, all intended to rule out alternative causes of disease (McDonald et al., 2001). To assist clinicians in the process, an International Panel on MS Diagnosis recently revised existing diagnostic criteria (McDonald et al., 2001). In order to diagnose MS, objective evidence is needed of at least two lesions typical of MS separated in time and space. Radiological (e.g. MRI) and laboratory information (e.g. analysis of cerebrospinal fluid) may assist in the process of diagnosis. The outcome of a diagnostic evaluation can be MS, possible MS, or not MS.

1.15 Typologies / Disease course

As with the clinical features, the course of the disease is very difficult to predict. The pattern is usually characterized by "either episodic acute periods of worsening (relapses, exacerbations, bouts, and attacks), gradual progressive deterioration of neurological function, or

combinations of both" (Lublin and Reingold, 1996). As the disease progresses periods of remission can become shorter and relapses can leave people more impaired than before the attack (Brassington and Marsh, 1998).

In attempting to define the clinical course of MS, there has been a degree of confusion in the literature about terminology (Lublin and Reingold, 1996). This confusion has led to difficulties comparing clinical studies using different groups of patients. In an attempt to clarify the descriptive terms currently in use Lublin and Reingold (1996) conducted an international clinical survey, from which the Advisory Committee on Clinical Trials of New Agents in MS of the National Multiple Sclerosis Society (USA) agreed on the following disease types:

Relapsing-remitting MS

The consensus definition refers to clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression. The defining features of relapsing-remitting MS are episodes of acute worsening of neurological function followed by a variable degree of recovery, with a stable course between attacks.

Primary-progressive MS

The consensus definition refers to disease progression from onset with occasional plateaus and temporary minor improvements allowed. The essential feature of primary-progressive MS is a gradual, nearly continuously worsening baseline with minor fluctuations but no distinct relapses.

Secondary-progressive MS

This definition indicates an initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions and plateaus. As such, secondary-progressive MS is seen as the long-term outcome of the relapsing-remitting disease.

Progressive-relapsing MS

The agreed definition was a progressive disease from onset with clear acute relapses, with or without full recovery, and periods between relapses characterized by continuing progression. The consensus determined that progressive-relapsing MS was an additional, albeit rare, clinical course which deserved a separate definition.

Prior to the consensus definitions described above, the term 'chronic-progressive MS' was often used in research to describe primary progressive and secondary progressive disease courses. It was abandoned as it lacked specificity (Lublin and Reingold, 1996), but continues to be used as a classification system where there is insufficient information about the early disease course for someone who has clearly moved to the progressive phase of the disease.

Consensus definitions were also provided for two levels of disease severity. *Benign MS* is a disease course in which the patient remains fully functional in all neurological systems 15-years after disease onset. *Malignant MS* refers to a disease with a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

However, Feinstein (1999) suggests that these definitions are rarely static and that patients can often be defined as having different types of MS as the disease progresses. For example,

Goodkin et al., (1989) followed a group of 254 people with MS over a period of between one and five years and found that adherence to the initially defined disease course varied considerably.

There is currently no explanation for the relapses, remissions and progression in the disease (Brassington and Marsh, 1998). However, Grant et al., (1989) found that many people experienced stressful life events in the year prior to symptom onset. In addition, Warren et al (1991) compared patients experiencing an exacerbation and patients in remission. The group who were having an exacerbation of symptoms scored more highly on measures of emotional disturbance and intensity of stressful events than the group in remission.

1.16 Psychological issues associated with MS

MS is associated with a number of psychological symptoms, of which the most frequently reported include depression and other affective disorders (e.g. euphoria, or manic episodes), cognitive dysfunction and fatigue.

Lifetime prevalence for major depression in people with MS varies between 25 and 50% (Minden and Schiffer, 1990), which is almost three times the lifetime prevalence in the US population (Kessler et al., 1994). However, the heterogeneity of the individual symptoms comprising the syndrome of depression (e.g. low mood, anger, irritability, sleep problems and fatigue) and the potential confusion with somatic complaints of MS (e.g. fatigue and sleeplessness), may lead to increased prevalence rates (Feinstein, 1999). Even so, if the somatically loaded items are removed from depression scales such as the Beck Depression Inventory (Beck and Steer, 1987), the prevalence rates of depression amongst MS samples has

still been reported to be significantly higher than in healthy control groups or many other neurological disorders (Minden et al., 1987). In addition, it has been suggested that the clinical features of a major depressive disorder due to MS may differ from those in people without MS. Symptoms such as irritability, worry and discouragement are commonly found in people with MS, whereas withdrawal, apathy, guilt and worthlessness seem more common in depression without MS (Minden et al., 1987). A lower frequency of reported guilt and self reproach in MS has also been reported by Johnson et al., (1996) and high rates of reported irritability have been found by Ron and Longsdale (1989).

In a large scale controlled study, Rao et al., (1991a) suggest that just under half (43%) of their entire community based sample of people with MS were impaired on four or more of a battery of thirty-one neuropsychological tests. The impact of cognitive dysfunction on the individual with MS is wide reaching. Rao et al (1991b) compared people with MS and cognitive impairment to MS participants without cognitive impairment in a number of social and occupational areas. They found that the cognitively impaired group was less likely to be working, engaged in fewer social and vocational activities, reported more sexual dysfunction, experienced greater difficulty in daily household tasks and exhibited more psychopathology than a cognitively intact group.

Up to 90% of people with MS report fatigue as a major problem (Krupp et al., 1988). As with depression and cognitive dysfunction, the impact of fatigue on the quality of life of a person with MS is significant. It is suggested to be related to overall mental health and perceived control over the illness (Schwartz et al., 1996) and is strongly associated with unemployment (Edgely et al., 1991).

1.2 Cognitive Function in MS

Rao's (1991a) finding that just under half of his sample of people with MS were impaired on four or more neuropsychological tests represents a relatively recent acceptance that cognitive decline is a common symptom for many people with MS (Feinstein, 1999). As recently as 1970, Kurtzke had suggested that less than 5% of people with MS were affected by cognitive difficulties. This underestimation may be accounted for by two related factors (Fischer, 2001). Firstly, that MS related cognitive decline is difficult to detect during brief clinic visits (frequently the method used for assessing cognitive dysfunction) and secondly, the prevailing belief that cognitive impairment rarely occurred in MS and then in the late stages of the disease. However, more recent studies using community and clinic based samples and neuropsychological testing (Rao et al., 1991a; Heaton et al., 1985), have found prevalence rates of cognitive impairment of approximately 45%.

1.21 Common deficits

With a growing acceptance that MS is frequently associated with cognitive deficits, there has been interest in delineating specific cognitive impairments due to the MS disease course. Research has tended to concentrate on general intellectual functioning, memory, attention / information processing, working memory and executive function.

1.211 General Intellectual Functioning

Rao et al (1991a) found that 100 people with MS had a significantly lower Verbal IQ on the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981) than a healthy control group. In addition, Ron et al (1991) compared the current intellectual functioning (WAIS-R) and estimated premorbid IQ (National Adult Reading Test (NART), Nelson, 1982)

of a group of people with MS, a group with clinically isolated lesions and a healthy control group. They found that compared to the NART scores, the WAIS-R scores of the MS group indicated a decline of 6.8 IQ points. The healthy control group showed a small improvement on their WAIS-R scores, whilst the group with clinically isolated lesions had a decline of 2.2 points. Furthermore, in a longitudinal study, Penman (1991) reported a small but significant decline in general intellectual functioning over time. Performance IQ was more affected than verbal IQ, perhaps a function of psychomotor difficulties associated with MS. However, Feinstein (1999) suggests that considerable variability exists in the IQ scores of people with MS and that focusing on group scores may obscure significant individual differences.

1.212 Memory

People with MS often complain of memory problems, which appear to be present in around 40-60% of all patients (Rao et al., 1993). However, the term 'memory' refers to a number of distinct (though related) neuropsychological processes which may be affected to differing degrees in MS (Feinstein, 1999).

Implicit and procedural memory are not reliant on conscious recall and include memory processes such as priming, conditioning and motor skill learning. These facets of memory are commonly found to be intact in people with MS (e.g. Beatty et al., 1990).

Long-term memory is commonly subdivided into episodic memory (e.g. memory for events) and semantic memory (e.g. memory for facts and concepts). There is very little evidence to suggest that semantic memory difficulties occur in MS (Rao et al., 1993). However, a number

of studies have demonstrated difficulties with episodic memory, in both verbal and visual domains (Camp et al., 1999; Rao et al., 1991a).

Rao et al (1986) noted that problems with long term memory in MS are more evident in recall rather than recognition. This discrepancy led some authors to conclude that memory problems were due to specific difficulties in retrieval whereas encoding processes were relatively spared (Beatty et al., 1989; Rao et al., 1989a). In support of the retrieval deficit hypothesis are findings that people with MS have normal rates of forgetting (Rao et al., 1989a) and normal immediate recall of short spans of information (Litvan et al., 1988). However, there is contradictory evidence to suggest that people with MS may have difficulty with encoding and storage but not retrieval. Using a word list learning task, DeLuca et al (1994) found that although people with MS required more trials to learn a word list, once the information was learned retrieval was comparable with the control group. Furthermore, Arnett et al (1997) found that people with MS were less likely to use learning strategies such as semantic clustering to facilitate encoding and retention of information. Similarly, Armstrong et al (1996) suggested that some of the long term memory difficulties in MS may be due to limited use of temporal order information. A number of authors (Armstrong et al., 1996; Beatty et al., 1996; Ryan et al., 1996) have suggested that there may be subgroups of memory impairment in MS that would warrant further investigation. However, at present the available evidence only allows the conclusion that MS can result in impaired encoding, storage and retrieval of long term memory. Some of these difficulties may be due to slowed information processing and / or executive impairments (see below).

1.213 Speed of Information Processing / Attention

Many people with MS report feeling mentally "slowed down" (Fischer, 2001). Indeed, over a century ago, Charcot described slowness of thinking as one of the hallmarks of cognition in people with MS (Feinstein, 1999). It has been suggested that slowed information processing may underlie many of the cognitive problems exhibited by people with MS (Litvan et al., 1988; Rao et al., 1989c). Using the Sternberg Memory scanning test Rao et al (1989c) compared a group of 36 people with MS to a group of 26 healthy control subjects. They found that the MS group had an overall slower reaction time than the control group. In addition, their scanning rate, a measure of pure cognitive speed (independent of the effects of physical impairment), was also significantly slower than the control group. The results suggested that people with MS exhibit a slowing of mental processing that is independent of motor involvement.

Many people with MS also have attentional problems (Fisher, 2001). William James (1890) described attention as "the taking possession by the mind in clear and vivid form of one out of what seem several simultaneous objects or trains of thought". However, now attention is conceptualised as a function of an interaction of at least four component processes under the influence of multiple brain systems (Cohen et al., 1998). Coull (1998) suggests that attention can be divided into the following four sub-processes: 1) attentional orientation (the direction of attention to a particular stimulus); 2) selective attention (giving priority to one stimulus over another); 3) sustained attention (attending to a particular stimulus for a prolonged period of time; and 4) divided attention (dividing attention between two or more different stimuli). In MS deficits in selective (Camp et al., 1999; DeLuca et al., 1993; Litvan et al., 1988) and sustained (Kujala et al., 1995; Nocentini et al., 2001) attention have been identified.

Coull (1998) defines selective attention as "attending to one location or stimulus *in favour* of another". The Stroop colour-naming test (Stroop, 1935) is often used as a measure of selective attention (Coull, 1998). In the Stroop test, participants are asked to name the colour of the ink in which a colour word is written. The word may be of a congruent colour (i.e. 'green' written in green ink) or an incongruent colour ('green' written in red ink). This task has been associated with activation in the anterior cingulate area of the frontal lobes (Pardo et al., 1990). A number of studies (Foong et al., 1997; Kujala et al., 1995; Nocentini et al., 2001) have demonstrated impaired performance on the Stroop test in MS.

The Paced Auditory Serial Addition Task (PASAT)(Gronwall, 1977) is frequently used as a measure of selective attention (e.g. Camp et al., 1999) and as such has been used in a number of studies with participants with MS. The PASAT requires the person to add consecutive numbers as they are presented on an auditory tape and respond orally with the accurate sum. As each digit is presented, the patient must add that number to the digit that was presented prior to it. DeLuca et al (1993) found that participants with MS and Chronic Fatigue Syndrome exhibited difficulties on the PASAT compared to healthy participants. Litvan et al (1988) also found that people with MS were significantly worse than a control group on the PASAT. The MS participants were impaired compared to the control group when the stimuli were presented at a rapid rate (1.2 and 1.6 seconds) but not at slower rates (2.0 and 2.4 seconds); a finding which is consistent with the research on selective attention described above. This finding suggests that the degree to which selective attention may or may not be impaired in MS depends on the task demands (Fisher, 2001). On self-paced tasks, in which the participant can slow their responses to ensure accuracy, people with MS are often unimpaired

compared to a control group. Moreover, the performance of people with MS is comparable with healthy participants when there are few stimuli or response choices (Demaree et al., 1999; Kujala et al., 1994; Paul et al., 1998b).

Fockert et al (2001) suggest that the concept of working memory (see below) may overlap with selective attention. They asked healthy participants to perform a selective attention task that required them to ignore distractor faces while holding in mind a series of digits that were in the same order (low working memory load) or a different order (high working memory load) on every trial. Higher working memory load was associated with increased interference effects and increased neural activity in areas of the frontal lobes associated with working memory load (Cohen, 1997). They argue that working memory is crucial for reducing distraction by maintaining the prioritisation of relevant information. Their finding may help to explain why selective attention is impaired under some conditions in MS (on the PASAT) but not others (Fischer, 2001). Faster rates of stimulus presentation on the PASAT are likely increase working memory load, which may be impaired in people with MS (D'Esposito et al., 1996; Rao et al., 1993).

Coull (1998) suggests that sustained attention is the ability to "maintain attention to a particular stimulus or location for prolonged periods of time". Sustained attention appears to involve arousal more than other attention tasks as length of time between targets continues. The term 'vigilance' is often used interchangeably with sustained attention, although Coull argues that vigilance is required on sustained attention tasks when the target stimuli occur at very low frequency. Vigilance has been defined as a "state of readiness to detect and respond to certain small changes occurring at random time intervals in the environment" (Mackworth,

1957). Seidman et al (1998) suggest that sustained attention tasks require participants to not only sustain attention, but also minimise distractibility to irrelevant stimuli and to maintain adequate alertness over time.

Wilkins et al (1987) found that participants with lesions in the right frontal lobe were impaired on a simple vigilance task that required them to count stimuli presented at one-second intervals. Similarly, Ruekert and Grafman (1996) found that participants with frontal lobe lesions were impaired relative to a control group on a task that required participants to respond selectively to one letter and to ignore distractors. Using a visual vigilance task Kujala et al (1995) demonstrated impaired performance in a group of people with MS who were also mildly cognitively impaired. Moreover, Nocentini (2001) found that people with secondary progressive MS were impaired on a sustained auditory attention task. Taken together, these findings suggest that impaired sustained attention may be an important feature of MS.

1.214 Working Memory / Executive Function

The concept of working memory has a number of different definitions, but all seem to agree that it refers to a "multi-component set of processes involving temporary storage and manipulation of information for use in various cognitive operations" (Seidman et al., 1998). To a certain extent, the brain structures involved in working memory tasks appear to overlap with those involved in attentional tasks (Seidman et al., 1998), particularly the central executive component (Baddeley, 1986) and the supervisory attentional system (Norman and Shallice, 1986). Specifically, there is overwhelming evidence (Gazzaniga, Ivry and Mangun, 2002) to suggest that the lateral prefrontal cortex is an essential neural substrate for working memory. Two main hypotheses have been put forward to explain the relative contributions of areas of the lateral prefrontal cortex: content-based hypotheses and process based accounts.

The working memory model described by Alan Baddeley (1986) is a content-based hypothesis. In the model, working memory is not a unitary process, but is comprised of a central executive controlling and directing verbal (the phonological loop) and spatial (visuo-spatial sketchpad) slave systems. Within the model, there is an expectation that the phonological loop is represented in the left hemisphere of the lateral prefrontal cortex and the visuo-spatial sketchpad in the right hemisphere of the prefrontal cortex. A meta-analysis by D'Esposito et al (1998) supported the notion that spatial working tasks are associated with activation in the right prefrontal cortex and nonspatial tasks with the left hemisphere. Rao et al (1993) found that people with MS had an exaggerated word length effect, despite normal digit-span. This was thought to reflect an impairment in the articulatory rehearsal process of the phonological loop. Furthermore, D'Esposito et al (1996) investigated the hypothesis that the central executive system of working memory is impaired in people with MS using a dual-task paradigm. Participants were asked to carry out a judgement of line orientation task whilst concurrently finger tapping, humming a melody, or reciting the alphabet. They found that the MS participants were significantly more impaired than the healthy control group during the demanding dual-task conditions. This was taken as evidence that people with MS have a working memory deficit reflecting an impaired central executive system.

Process based accounts of working memory (Owen et al., 1996) suggest that the type of processing necessary for task completion determines the recruitment of specific neural areas. The model suggests that ventrolateral areas of the prefrontal cortex are activated when memory content has to be "maintained", but that additional "monitoring" and "manipulation" leads to activation of the dorsolateral prefrontal cortex, a hypothesis that is supported by

current neuro-imaging data (D'Esposito et al., 1998). Delayed matching paradigms, such as the 'n-back' tasks are commonly used to vary working memory load. The n-back task requires the participants to respond when the stimulus matches a target shown n trials before (usually n = 0, 1, 2, or 3).

The finding that people with MS have difficulty on faster rates of stimulus presentation on the PASAT is consistent with a hypothesis that tasks that place additional working memory demands are more likely to be impaired.

Norman and Shallice (1986) described a model of executive control to account for goal oriented behaviour. In the model, our actions are governed by schema control units which compete with one another for dominance. The schema control units receive input from the perceptual system, contention scheduling and a supervisory attention system. The model suggests that contention scheduling facilitates the selection of schemas for routine actions (e.g. riding a bike). However, when the demands of the situation are non-routine, the supervisory attentional system provides a flexible response selection mechanism. Gazzaniga et al (2002) suggest that the supervisory attention system may be required in situations such as: 1) when a task requires planning or decision making; 2) when the task requirements are novel or not well learned; 3) when the situation requires a response that competes with a strong habitual response; 4) when the situation requires error detection; and 5) when the situation is difficult or dangerous. They also propose that the supervisory attention system is unlikely to be represented in a single brain area, but is more likely to be a distributed network of neural structures.

Many of the executive functions described in the Norman and Shallice (1986) model may be impaired in people with MS. Foong et al (1997) demonstrated that people with MS had difficulties on the Tower of London Test (Shallice 1982) a task that requires planning. In addition to assessing selective attention, the Stroop test examines the ability to inhibit a strong habitual response. As described above, performance on the Stroop test has been shown to impaired in participants with MS (Nocentini et al., 2001). People with MS have also been shown to have difficulties on the Wisconsin Card Sorting Test (WCST) (Heaton, 1981) which requires error detection and cognitive flexibility (Rao et al., 1987). It is also likely that these deficits in executive function are likely to affect a number of other cognitive tasks which are frequently shown to be impaired in MS, such as explicit memory tasks (Fischer, 2001).

1.215 Summary

In summary, slowed information processing speed appears to be an important feature of the cognitive difficulties displayed by people with MS (Brassington and Marsh, 1998). These difficulties are likely to interact with a number of other impairments associated with MS that have a greater cortical involvement, such as verbal memory (DeLuca et al., 1994; Litvan et al., 1998; Rao et al., 1989b). Moreover, the pattern of increased impairment with greater task complexity, which has been illustrated in the literature on attention and MS, is hypothesised to be associated with the concepts of working memory and executive functions. People with MS are frequently impaired on tasks that place demands on the working memory system (D'Esposito et al., 1996; Rao et al., 1993; Litvan et al., 1998) and executive functions (Foong et al., 1997).

1.22 Neuroanatomy and physiology of cognitive decline

Attempts to clarify the relationship between disease pathology and cognitive decline have been facilitated by the development of neuroimaging techniques such as Magnetic Resonance Imaging (MRI). Using imaging techniques, a number of studies have attempted to identify localized brain abnormalities and specific cognitive deficits (Feinstein, 1999).

MRI is a sensitive technique for identifying lesions due to the MS disease (Feinstein, 1999). Using MRI, patients with cognitive impairments have consistently been shown to have more lesions than those who remain cognitively intact (Rao et al., 1989b; Ron et al., 1991). In the study by Rao et al (1989b) total lesion area was significantly correlated with 25 out of a battery of 34 cognitive tests. The authors suggested that when total lesion area exceeded a particular cut-off point, the probability of cognitive dysfunction was high.

Ryan et al (1996) found that visuospatial ability correlated with corpus callosum lesions and that impaired memory performance was linked to white matter lesions in the left parietal lobe. Furthermore, Rao et al (1989b) found that corpus callosum abnormalities were associated with speed of information processing and rapid problem solving.

Foong et al (1997) examined the relationship between frontal lobe pathology and executive function in a group of 42 people with MS. They found that although a number of executive tasks correlated with the severity of frontal lobe lesion load (MRI), it was difficult to disentangle the specific contribution of frontal lobe pathology to the impairment on executive tasks in the presence of widespread lesions. Specifically, they found that a significant correlation between frontal lobe pathology and impaired executive skills disappeared when

total lesion load was controlled, a finding which was also reported by Rovaris et al (1998) and Nocentini et al (2001). Foong and colleagues (1997) argued that their findings provided evidence for the hypothesis that executive functions are subserved by a different, widely distributed neural systems (Burgess and Shallice, 1992). However, in a recent study, Benedict et al (2002) identified a strong correlation between frontal cortex atrophy and performance on neuropsychological tests commonly associated with frontal lobe activity.

There are also reports of cognitive dysfunction being associated with periventricular lesions (Feinstein, 1999). Anzola et al (1992), found that periventricular demyelination was associated with difficulties in concept formation, non-verbal reasoning and verbal memory tests. Similarly, Maurelli et al. (1991) identified an association between memory impairment and periventricular demyelination. Feinstein (1999) suggests that periventricular lesions may affect the function of more distant sites, through the process of disconnection, or interruption of neural circuitry. Maurelli et al (1991) propose that the disconnection may be between limbic and prefrontal structures.

1.23 Clinical correlates

The relationship between cognitive function in MS and disease course, time since diagnosis, severity of symptoms, depression and fatigue have been the focus of a number of investigations. However, Fischer (2001) suggests that efforts to identify clinical variables predictive of MS related cognitive impairment have been disappointing.

Severity of MS is frequently assessed using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983); a measure used to assess the severity of disability within eight functional

systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral (mental) and 'other'). Despite being the gold standard research tool for measuring impairment in research studies the EDSS has been criticized for a lack of sensitivity for clinical changes that do not affect mobility (Brassington and Marsh, 1998). EDSS is only a modest predictor of overall cognitive function (Heaton et al., 1985; Rao et al., 1991a).

The lack of association between depressed mood and cognitive function in MS has been well documented (Moller et al., 1994; Rao et al., 1991a). In a sample of 25 people with MS, Moller et al (1994) found that depression was unrelated to age, gender, status of disability, or the results of a cognitive assessment.

Unlike a number of other clinical variables, disease course does appear to be related to cognitive function. People with a primary progressive disease course have been shown to be more cognitively impaired than healthy control groups (Camp et al., 1999) and those with a relapsing remitting course (Heaton et al., 1985). In addition, Comi et al (1995) reported a greater frequency of cognitive impairment in a sample of people with secondary progressive MS when compared to a group with a primary progressive disease course.

A large number of people with MS take psychotropic medication to reduce psychiatric morbidity. Stenager et al (1994) investigated the association between medication and cognitive performance in a sample of 92 people with MS in which approximately two thirds were taking medication. The majority of the participants were taking medication with a sedative effect. When administered a battery of cognitive tests, there was no association between performance and the use of sedatives. Similar findings were also reported by Rao et al (1991a).

In addition, Rao et al (1991a) failed to find a significant association between duration of illness and cognitive function. However, in a longitudinal study, Amato et al (1995) examined changes in cognitive function over a 4-year period. They found that most patients had a decline in cognitive performance at 4-years follow-up. However, in a 3-year follow-up study, Kujala et al (1997) found that cognitive decline only occurred in patients who had shown an initial cognitive impairment. They suggest that cognitive function can remain stable in MS, but that incipient cognitive decline is widespread and progressive in nature.

Fisher (2001) suggests that the relationship between cognitive function and fatigue is not yet clear. This issue will be investigated further in section 1.4.

1.24 Psychosocial impact

The functional impact of cognitive dysfunction in MS is profound. Rao et al (1991b) classified 100 people with MS as either cognitively intact, or cognitively impaired. The two groups were compared on a number of measures of mood and social functioning. The cognitively impaired group were less likely to be working, engaged in fewer social activities, reported greater sexual dysfunction, more difficulty performing routine household tasks and exhibited greater psychopathology than the cognitively intact group.

1.25 Treatment

Treatment of cognitive decline in MS is still in its infancy (Fisher, 2001). Approaches have included cognitive rehabilitation and pharmacological interventions.

Compensatory strategies for cognitive difficulties are frequently employed by people with MS. Sullivan (1990) noted that the use of an external memory aid was commonly used. In addition, daily planners, lists and other written cues may help to alleviate some of the memory and planning problems reported in many people with MS (Bennett et al., 1991). Very little attention appears to have been paid to remedial (as opposed to compensatory) strategies in people with MS. Feinstein (1999) suggests that this may be due to the progressive nature of cognitive decline in MS, which is unlike other conditions such as head injury or stroke, where the insult is followed by a period of expected recovery. However, promising results have been presented in a controlled trial of cognitive rehabilitation (Jonnson et al., 1993). The study compared remediation plus compensation to non-specific diffuse mental stimulation. They found that the remediation plus compensation group showed improved visual perception and visuo-spatial memory. The gains were maintained at six months follow-up.

There is preliminary evidence to suggest that disease-modifying treatments may also have a beneficial effect on cognitive function. IFN-β-1b (Betaseron) was shown to lead to improvements in visual memory (Pliskin et al., 1996). Similarly encouraging improvements in complex attention, concentration, visual learning and recall have been reported by Barak and Achiron (2002). In addition, IFN-β-1a (Avonex) was shown to have a beneficial effect on complex attentional processes and memory (Fisher et al., 2000). There was also a trend towards improved executive functioning and memory. Fisher (2001) suggests that clinicians should consider monitoring cognitive functioning in patients undergoing disease modifying treatments.

1.3 Fatigue in MS

Krupp and Pollina (1996) define fatigue in progressive neurological disorders as:

> *"an overwhelming sense of tiredness, lack of energy and feeling of exhaustion. It is distinguished from symptoms of depression, which include lack of self-esteem, despair, or feelings of hopelessness. Fatigue is also distinguished from limb weakness"*

In MS, fatigue appears to be a particularly common and disabling symptom of the disease. A study (Freal et al., 1984) which defined fatigue as "tiredness or exhaustion distinct from depressed mood or limb weakness", reported that 87% of patients considered fatigue to be a problem. Other studies (Fisk et al., 1994; Krupp et al., 1988; Krupp et al., 1989) have cited prevalence rates of between 76 and 92%. Fatigue was described as the worst symptom (14%) or one of the worst (55%) in a sample of 85 people with MS in a study by Fisk et al (1994). Similarly, Krupp et al (1988) reported 28% of their sample described fatigue as their "most troubling symptom". Amato et al (2001) found severity of fatigue to be an independent predictor of quality of life. Fisk et al (1994) suggest that the disruption of MS patients' lives caused by the need to accommodate fatigue or its potential occurrence, adversely affects their mental health.

Though fatigue is ubiquitous, Lauren Krupp and colleagues (1988) propose that the following features distinguish MS fatigue from 'normal fatigue': it comes on easily; it is worsened by heat; it prevents sustained physical activity; it interferes with responsibilities; it interferes with physical functioning; and it causes frequent problems. In general, it appears that the major feature distinguishing fatigue in MS from fatigue in people in normal health is the persistent

incapacity associated with MS fatigue (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Recently, the importance of distinguishing the symptom called fatigue and the signs of fatigue has been emphasized (Iriarte, Subirá and Purificación de Castro, 2000). The symptoms of fatigue include tiredness, lack of energy and exhaustion (Krupp and Pollina, 1996), whilst the signs of fatigue in a system are the lower effectiveness of this function as time passes.

1.31 Measurement of Fatigue in MS

A variety of self-report measures have been developed to quantify fatigue in MS. These measures rely on the participant's subjective assessment of functioning (Krupp and Pollina, 1996). Two of the most commonly used measures are the Fatigue Severity Scale (FSS) (Krupp et al., 1989) and the Fatigue Impact Scale (FIS) (Fisk et al., 1994). The FSS is a nine-item scale which has been used to assess the effects of fatigue on activities of daily living. It is brief, easy to administer and is reliable (Krupp, 1997). However, it may not be sensitive to changes associated with treatment. The FIS is a 40 item scale which assesses physical, cognitive and social dimensions. It has been shown to distinguish fatigue in MS from fatigue in people with hypertension (Fisk et al., 1994). However, compared to the FSS the FIS is rather lengthy.

In attempt to distinguish the symptom and the signs of fatigue, Iriarte and de Castro (1994) have developed the Fatigue Descriptive Scale (FDS). Iriarte et al (2000) suggest that the scale differentiates fatigue as a symptom that includes three different clinical entities: asthenia (fatigue at rest); fatigability (fatigue with exercise), and worsening of symptoms. Using the paradigm of Iriarte et al (2000) it is possible to examine the signs of fatigue and their

relationship to the symptom fatigue. In a recent investigation into to the association between muscular fatigue (measured by maximum strength on a hand dynamometer) and symptom fatigue (measured using the FSS and FDS), Iriarte and de Castro (1998) found that not only did the MS group show more physical fatigue, but that there was also a negative linear correlation between baseline strength and fatigue as a symptom.

Recent studies (Krupp and Elkins, 2000; Kujala et al., 1995) have suggested that in addition to experiencing physical fatigue (in a maximal force output paradigm), people with MS may suffer from cognitive fatigue. In these studies cognitive fatigue has been operationalized as a decline in cognitive performance over time. This issue will be reviewed in greater detail in section 1.4.

Considering physical fatigue (measured by an inability to sustain a specified force during exercise) and cognitive fatigue, Chaudhuri and Behan (2000) suggest a distinction between central fatigue and peripheral fatigue. Central fatigue represents a failure of physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness. They suggest that pathological central fatigue is similar to the brief episodes of self-limiting central fatigue that may follow periods of acute stress or viral infections. In contrast, they suggest that peripheral fatigue is associated with physical fatigue but not mental fatigue.

In conclusion, there is an emerging tendency to not only measure the symptom of fatigue (quantified using self report measures such as the FSS), but also to measure the signs of fatigue (Iriarte, 2002). In questioning the validity of traditional measures of fatigue (such as

the FSS) Giovannonni (2002) suggests that specific and well validated fatigue outcome measures should be developed.

1.32 Fatigue in other conditions

Fatigue is a common complaint in a number of other chronic medical disorders. In Parkinson's disease, fatigue is common (Friedman and Friedman, 1993), and can often antedate the development of the motor symptoms of the disorder (Chaudhuri and Behan, 2000). Cimprich (1995), found that patients with cancer had difficulty with sustained attention tasks, which may be evidence of cognitive fatigue. In addition, many people with HIV and AIDS report fatigue as a symptom at some point during the disease (Tindall et al., 1988).

Post-Concussional Syndrome (PCS) is a term often used to describe symptoms that follow a brain injury (e.g. headache, dizziness, irritability, and fatigue) and persist past the initial post-traumatic period. McMillan and Glucksman (1987) suggested that within the first seven days of sustaining a traumatic brain injury, 75% of patients report fatigue as a symptom. Thereafter the incidence of symptoms of PCS appears to decline. At three months post injury up to 37% of patients may continue to report disturbing levels of fatigue (Keshavan et al., 1981). LaChapelle and Finlayson (1998) compared 30 people with brain injuries to a matched healthy control group on three subjective and one objective measure of fatigue. The FSS and FIS were used as two of the subjective measures, and fatigue was objectively measured by comparing four 40 second intervals of continual thumb pressing. The mean length of time between brain injury and participation in the study was 44.3 months (SD=45.2). Their findings indicated that the participants with brain injuries had significantly greater subjective ratings of fatigue compared to the control group. The brain injury group evidenced greater fatigue on the thumb-

pressing task but the difference between groups did not reach statistical significance. It is of note that 50% of the brain injury group described fatigue as one of their worst symptoms. However, Riese et al (1999) failed to find evidence of cognitive fatigue after very severe head injury on two continuous divided attention tasks.

Chronic fatigue syndrome is a controversial diagnostic entity (Marshall et al., 1996), but which has persistent, debilitating exhaustion as its hallmark feature. People who complain of chronic fatigue syndrome also report significant functional disability in activities of daily living and social activities (Chistodoulou et al., 1998). Moreover, cognitive difficulties are often reported, with consistently documented impairments in the areas of complex information processing speed and efficiency (Tiersky et al., 1997). There appear to be few differences between people with MS and those with chronic fatigue syndrome on a number of neuropsychological test measures (Krupp et al., 1994). However, people with MS often have more extensive neuropsychological impairment (DeLuca and Johnson, 1993).

1.33 Clinical correlates

People who are depressed often report fatigue. Moreover, it is a one of the features of the DSM-IV (American Psychiatric Association, 1994) diagnosis of major depressive disorder. Depression is also common in MS (Feinstein, 1999), and disentangling fatigue as a symptom of MS and fatigue as a symptom of depression is complex. Some studies have shown a positive correlation between fatigue severity and depression (Fisk et al., 1994; Kroencke et al., 2000), whilst others have not (Krupp et al., 1989; Möller et al., 1994; Vercoulen et al., 1996). Medications such as amantadine have been shown to be useful in reducing fatigue but appear to have little effect upon depression (Krupp et al., 1995). These findings suggests that whilst

fatigue and depression in MS often overlap, future research is needed examining the way that they co vary (Kroenke et al., 2000). This research appears to be particularly important as Chauhudri and Behan (2000) point out that there has been a tendency of clinicians to equate fatigue with depression. As such, they suggest that clinicians have often chosen to ignore fatigue in conditions such as MS or felt it necessary to equate fatigue with depression, somnolence or disinclination, seeking to explain the mechanism of fatigue by paradigms based on psychoanalytic models.

As with depression and fatigue, some authors (Kroenke et al., 2000; Krupp et al., 1995) report a correlation between self reported fatigue and level of physical impairment, as measured by the Expanded Disability Status Score (EDSS)(Kurtzke, 1993), whilst others do not (Fisk et al., 1994; Vercoulen et al., 1996).

In addition, there are reports of more severe fatigue in progressive MS (Mainero et al., 1999) than in relapsing-remitting MS, although contradictory findings have also been found (Giovannoni et al., 2001)

1.34 Neuroanatomy of fatigue

Columbo et al (2000) found structural differences between people with MS who complain of fatigue and those who do not. Lesion load in a T2 weighted MRI was found to be higher in MS patients complaining of fatigue than in those not doing so. There were significant differences in the parietal lobe, internal capsule, and trigone. Large differences were also found in the in frontal lobes and periventricular areas. They suggest that fatigue may be due to either a functional deafferenation of the cortex due to cortico-sub-cortical interconnection

damage, or of a demyelination in critical sites of the CNS such as the cortico-spinal tract. However, using magnetization transfer and diffusion tensor MRI, Codella et al (2002) failed to find an association between FSS scores and MRI derived quantities. They suggest that the severity of overall pathology in the brain is not a critical factor in the development of fatigue in MS.

Roelke et al (1997) compared a group of participants with MS who complained of fatigue to one that did not using a PET scan. The study measured regional cerebral glucose metabolism, which they suggest is closely related to regional cerebral blood flow and local synaptic activity. Reduced glucose metabolism in the frontal cortex and basal ganglia was found in the participants who complain of fatigue but not in those who did not. Reduction was marked in the bilateral prefrontal cortex, premotor and supplemental motor cortex, putamen and in the white matter extending from the rostral putamen to the head of the caudate nucleus. The authors suggest that the abnormal pattern of glucose metabolism at rest may reflect abnormal neuronal activity which makes patients susceptible to fatigue. Codella et al (2002) suggest that these grey matter metabolic abnormalities may be attributed to functional impairment of nerve conduction along frontal cortical – subcortical circuits rather than to their disruption. Roelke et al (1997) speculate that the "dorsolateral-prefrontal" and "motor" circuits (Alexander et al., 1990) may have a specific role in the pathogenesis of fatigue, and that fatigue may be associated with an impaired interaction between functionally related areas in the basal ganglia and the frontal lobes.

Moreover, Chaudhuri and Behan (2001) propose that 'central' fatigue may occur due to a failure in the integration of the limbic input and the motor functions within the basal ganglia

affecting the striatal - thalamic - frontal cortical system. In the context of disease pathology, they accept that multiple pathologies can affect the input to the frontal cortex e.g. anatomical changes and biochemical changes.

It is apparent that more research is needed on the physiopathology of fatigue in MS, but existing data strongly suggests a dysfunction of metabolic and structural pathways in the basal ganglia and frontal lobes. Most existing studies have utilized self report measures to quantify fatigue, which are subjective and rely on an individual accurately appraising their own functioning. It appears to be particularly important to elucidate the changes occurring when the signs of fatigue occur, not just in the people who report fatigue as a symptom.

1.35 Treatment

Comi et al. (2001) suggest that in treating fatigue in MS, the first step is to inform the patient and the family that the symptom is genuine. They propose that the patient's self esteem is enhanced when they are informed that the sense of exhaustion is not a mere psychological reaction to the disease but rather is due to nervous tissue damage produced by the disease. Subsequent management strategies for fatigue may include medication, and exercise programmes.

Amantadine (an antiviral agent with anti-parkinsonian effects) and pemoline (a stimulant) are commonly used in the management of fatigue in MS. Krupp et al (1995) compared amantadine, pemoline, and a placebo in a double-blind randomized controlled trial. They found that amantadine led to significantly greater reductions in self reported fatigue than both placebo and pemoline, which were not significantly different to one another. The benefit of

amantadine was not due to changes in sleep, depression, or neurological disability. However, the authors suggest that the mechanism for amantadine's treatment effect is not known.

Given the effectiveness of medication in treating fatigue, and the potential association between fatigue and cognitive function in MS, Geisler et al (1996) investigated effects of amantadine and pemoline on cognitive function. They found that amantadine and pemoline did not improve cognitive function. Based on their results they proposed that cognitive functioning is independent of fatigue in MS. However, their study failed to find a time by group interaction of fatigue measured before and after treatment, which is in contrast to the findings of the Krupp et al (1995) study. The authors suggest that this may have been due to insufficient drug doses or duration of treatment, a suggestion which calls into question their conclusion that cognitive functioning and fatigue are independent.

Exercise appears to be important in combating deconditioning (Comi et al., 2001). Di Fabio et al., (1998) found that participation in a 15 week programme of aerobic exercise led to a reduction of fatigue and an improved quality of life. In addition, Comi et al., (2001) suggest that behavioural therapy may be useful for patients with fatigue and mood disorders. However, controlled studies are lacking in this area.

1.4 Fatigue and Cognitive Function in MS

In summary, the existing literature indicates that both cognitive difficulties and fatigue are particularly prevalent and pernicious features of MS. The domains of cognitive function which seem most vulnerable to the MS disease process are memory, executive function, attention, and speed of information processing. MRI lesion load is correlated with cognitive dysfunction,

and brain areas associated with specific deficits include the corpus callosum, periventricular areas, and the deep white matter of the frontal lobes.

It has been suggested that fatigue in MS is qualitatively different to 'normal' fatigue. Fatigue in MS is associated with greater incapacity and reduced quality of life. Neuroanatomical findings have suggested an association between MRI lesion load and severity of fatigue. There is emerging evidence implicating a disconnection between the basal ganglia and the frontal lobes in the pathogenisis of fatigue in MS.

However, despite the large literature on cognitive function in MS and fatigue, there have been relatively few investigations of the link between the two symptoms.

1.41 Neuro-anatomical considerations

There are converging lines of evidence from neuroimaging studies to suggest an association between fatigue and cognitive dysfunction in MS. Roelke et al (1997) suggested that fatigue in MS may be due to frontal cortex and basal ganglia dysfunction. The dorsolateral-prefrontal circuit (Alexander and DeLong, 1990), which links the dorsolateral prefrontal cortex with the lateral head of the caudate nucleus, was implicated as a potential neuroanatomical substrate for the pathogenesis of fatigue. Lesions of the dorsolateral prefrontal cortex have been associated with deficits in the control, regulation and integration of behaviour (Lezak, 1995), whilst lesions to the caudate nucleus frequently result in low initiative, motivation, and poor task maintenance (Cummins, 1993). By implication, it seems plausible to link fatigue in MS with specific cognitive deficits associated with disruptions to the dorso-lateral prefrontal circuit.

Sandroni et al (1992) studied ten people with MS and complaints of fatigue using reaction times and event related potentials accompanying the performance of auditory memory tasks.

Participants were compared when they were rested and when fatigued. When fatigued reaction times became longer and there were changes in the potential latency and amplitudes of the evoked potentials. On the basis of their findings, the authors postulated that fatigue in MS affects neural processes acting after stimulus evaluation but before activation of the primary motor pathways. The Multiple Sclerosis Council for Clinical Practice Guidelines (1998) suggest that the findings of Sandoni et al (1992) and Roelke et al (1997) are consistent with the hypothesis that fatigue in MS has a cortical component, perhaps a conduction block involving intracortical circuits.

1.42 Neuropsychological Investigations

There have been relatively few investigations into the link between neuropsychological functioning when people with MS are fatigued. Moreover, the results of the existing studies are at times contradictory.

A recent study by Parmenter et al (2003) asked a group of people with MS to complete a battery of neuropsychological tests on two occasions: during a period of the day when they reported the highest severity of fatigue and during a period of relatively low fatigue. The findings showed that although people with MS thought that they had performed more poorly during the period of high fatigue, there were in fact no differences between the two time periods.

Kujala et al (1995) compared two groups of participants with MS, one with mild cognitive impairments and one without cognitive impairment, to a healthy control group on a number of neuropsychological tests. One of the measures was a 'visual vigilance task', in which

participants were visually presented with 600 letters on a computer screen and asked to press the space bar every time they saw the letter Y or L. Performance (reaction time, correct and incorrect responses) was compared over three, five-minute periods to explore the effects of fatigue. Their findings indicated that both the MS groups exhibited an increased decline in performance (reaction time) over time when compared to the control group. Their conclusion was tentatively attributed to mental fatigue.

Schwid et al (2000) also examined the effects of fatigue during a cognitive task. Participants with MS were asked to complete the PASAT and their within task performance was examined. They found during the three-minute test administration, participants with MS experienced an average decline in correct responses of 17.8 percent. They also found that individual declines in cognitive performance were unrelated to self-reported fatigue (FSS), level of disability (EDSS), cognitive impairment (total PASAT score), or motor fatigue. Unfortunately, there was no control group in the study, so it is unclear if the observed decline in performance was due to the symptoms of MS.

However, contradictory findings have been reported in two studies (Johnson et al., 1997; and Paul et al., 1998a). Johnson et al (1997) compared participants with MS, Chronic Fatigue Syndrome (CFS), or Depression, to fifteen healthy participants on repeated administrations of the Paced Auditory Serial Addition Test (PASAT) during a single three-hour long testing session. Between repeat PASAT administrations, participants were asked to complete a series of "standard neuropsychological tests" primarily included to induce fatigue. The findings indicated that all groups showed the same improvement in PASAT scores over time. This was despite self-reported changes in subjective fatigue from the MS group. Paul et al (1998a)

compared a group of participants with MS to healthy participants on grip strength, verbal fluency, vigilance, and subjective fatigue, before and after the administration of a "cognitive work battery" (verbal fluency and WAIS-R subtests) intended to induce fatigue. The battery lasted for thirty minutes and included the WAIS-R vocabulary and comprehension subtests, a famous faces test, and verbal and category fluency tasks. Despite subjective ratings of increased fatigue over time in the MS group there were non-significant changes in performance on the "objective" measures of fatigue (grip strength, verbal fluency, and vigilance). Both studies question the assumption that fatigue in MS leads to a cognitive decline, and propose that people with MS overestimate their level of fatigue. However, a major criticism of both studies is that they used non-specific "work batteries" to induce fatigue (Krupp and Elkins, 2000) and did not examine within-task declines in performance.

Krupp and Elkins (2000) compared 45 participants with MS to 14 healthy participants on a modified form of a neuropsychological test battery sensitive to MS related cognitive decline (Brief Repeatable Battery) before and after a "continuously cognitively effortful task" (the Alpha-Arithmetic Test). The MS group were recruited from an outpatient clinic and were all ambulatory, with EDSS scores of less than 6.5. Eight participants had primary progressive MS, 13 had secondary progressive MS, and 24 had relapsing remitting MS. The neuropsychological test battery included tests of verbal planning, visual memory, verbal memory, verbal fluency, and digit-span. The Alpha-Arithmetic Test (Logan and Klapp, 1991) was administered by computer and required participants to add the numbers 0, 2, 3, or 4 to the letters A through to T of the alphabet. The participant is shown an equation and is asked to judge if it is true or false (e.g. B + 2 = D or D + 2 = G). Performance was measured using reaction time. Their findings indicated that the MS group's performance during the Alpha-

Arithmetic Test declined significantly more than the control participants. Moreover, they found that the MS group performed significantly worse than the control group on tests of visual memory, verbal memory, and verbal fluency by the end of the session, despite no difference in performance at the start of testing. The comparative decline in the performance of the MS group was believed to reflect mental fatigue. In addition, it was notable that there was a poor correspondence between self reported fatigue and performance, leading the authors to emphasize the importance of using subjective and objective measures of fatigue. However, in total the testing session for all participants lasted approximately 4 hours. It may be of interest to determine if similar declines in performance can be seen in a much shorter session.

So, from the Kujala et al (1997), Krupp and Elkins (2000), and Schwid et al (2000) studies there is a strong suggestion that participants with MS show a greater decline in performance during a single attention task when compared to healthy participants, which may be taken as evidence of mental fatigue. Demonstrating a decline in cognitive performance following a task intended to induce fatigue appears to have been more difficult. The findings of Krupp and Elkins (2000) contradict those of Paul et al (1998a) and Johnson et al (1997). Differences between the studies may be attributed to the sensitivity and specificity of the measures. It is also possible that different cognitive tasks have different impacts on fatigue. Specifically, the Alpha-Arithmetic task used by Krupp and Elkins (2000) may have caused more mental fatigue than the "standard neuropsychological tests" used by Johnson et al (1997).

Speculation about the nature of the cognitive task required to cause mental fatigue in MS can be linked to research on the neuroanatomy of attention and process based accounts of working memory. Seidman et al (1998) examined the brain activation (using fMRI) of a group of

healthy men whilst engaged in two auditory continuous performance tests (CPTs) of different cognitive demand. One task was a working memory test (Q3A) and the other was a simple vigilance task (QA). The Q3A test was made more demanding than the QA test by increasing working memory and interference filtering demands. The findings indicated that the Q3A test, when compared to the QA test, produced a significant signal change in lateral and medial prefrontal cortex, precentral cortex, temporal lobe, parietal-occipital cortex, cingulate, thalamus, and superior colliculus. Moreover, Braver et al (1997) used functional MRI (fMRI) to probe prefrontal cortex activity during a sequential letter task in which memory load was varied in an incremental fashion. In all nine participants studied, dorsolateral and left inferior regions of the prefrontal cortex were identified to exhibit a linear relationship between activity and memory load. So, existing research strongly suggests that tasks that have a higher working memory demand lead to more brain activity in areas such as the dorsolateral prefrontal cortex; the same brain area which has been linked to fatigue in MS (Roelke et al., 1997).

1.5 Rationale for the Study

The need for research to investigate the association between cognitive function and fatigue in MS has been emphasized (Krupp and Elkins, 2000; MS Council for Clinical Practice Guidelines, 1998). Krupp and Elkins (2000) suggest that future studies of cognitive fatigue should broaden the range of cognitive domains evaluated and further explore whether continuous cognitive activity is necessary to precipitate fatigue.

The findings of Krupp and Elkins (2000) and Paul et al (1998a) indicate that self-reported fatigue may not be an accurate predictor of objective mental fatigue, demonstrated by a decline in cognitive performance over time. This conclusion is consistent with Iriarte's (2002) suggestion that research into MS fatigue must distinguish the symptom fatigue and the signs of

fatigue. It seems important to develop accurate methods of identifying and measuring the signs of fatigue (Giovannoni, 2002). This in turn may be useful for monitoring the efficacy of pharmacological, psychological, or environmental interventions for fatigue in MS.

Finally, research is needed into fatigue in the advanced stages of MS. Most of the existing studies into fatigue and cognitive function have used mildly or moderately impaired (as measured by the EDSS) MS participants. Identification of the impact of fatigue on cognitive functioning in severely impaired people with MS may contribute to greater awareness of fatigue in advanced MS, and to the development of remediation strategies.

1.6 Research Questions

This study aims to examine the effects of mental fatigue on cognitive performance in advanced MS. Specifically, the research will address the following questions:

1. Do participants with MS demonstrate a greater objective decline in cognitive performance over time (which may be evidence of fatigue) compared to healthy participants during a continuous cognitive task?
2. Does the cognitive performance of people with MS decline more than a healthy control group over a neuropsychological testing session (which may be evidence of fatigue)?
3. Would a greater working memory load lead to a greater change in cognitive performance within a task and across a testing session?
4. Do people with MS report greater subjective fatigue compared to a healthy control group?
5. Is there an association between subjective mental fatigue and objective mental fatigue (as demonstrated by any decline in performance)?
6. Is there an association between depression and fatigue?

2. Methods

2.1 Design

A mixed within and between subjects design was used to compare 16 adults with MS to a group of 19 healthy control subjects.

2.2 Participants

A total of 35 participants were tested for the study. The MS and control groups were matched according to age, gender, years of education, and scores on the Spot the Word Test (Baddeley et al., 1992).

2.21 MS Group

Initially, 20 participants with MS were recruited from the Royal Hospital for Neuro-disability (RHN), a specialist hospital for people with neurological disabilities. The RHN is a national charity that provides treatment and rehabilitation for people with a variety of profound neurological disabilities. Of the 20 participants, 13 were inpatients and seven were outpatients who accessed a day-service facility within the hospital. However, two people did not meet the inclusion criteria (see below) so were not included in the study. Furthermore, two participants became distressed during the first testing session and asked to withdraw from the study. This left a sample of 16 people with MS.

To be included in the study, participants had to be over 18 and diagnosed with MS (McDonald et al., 2001). It was anticipated that the participants with MS would be heterogeneous in terms of the severity and symptoms of the disease. To increase the homogeneity of the experimental

group and the likelihood of severe fatigue (Kroenke et al., 2000), participants were selected who had advanced MS, evidenced by an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score of 7.0 or above. People with an EDSS score of 7.0 or above are wheelchair bound (see measures section for further details). Participants were included in the study if they were taking concurrent antidepressants, anti-spasticity agents, anti-cholineric medications, and disease modifying therapies as long as the dosage has been constant for at least one month before the evaluation.

Participants were excluded from the study if they had an additional neurological or psychiatric disease, which might affect their performance. People who scored 16 or above on the anxiety or depression scales on the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) were classified as 'severe cases' (Snaith and Zigmond, 1994) and so were excluded from the study. Also, participants were excluded if they had a Spot the Word scaled score of four or less (below the 5^{th} percentile), a history of drug and alcohol dependence, a history of learning disabilities or a diagnosis of dyslexia. In addition, people with visual difficulties that prevented them from reading the consent form were excluded from the study. Initially, participants were only included if they were able to press the response keys used on the n-back task. However, two participants were unable to press the response keys but were capable of providing verbal responses, so were included in the study (see section 2.424 for further details).

2.22 Control Group

The control group consisted of healthy adults with no history of neurological or psychiatric illness. They were comprised of staff and relatives at the RHN. People were excluded from the

study if they had a history of drug and alcohol dependence, learning disabilities, dyslexia, or if they were classified as 'severe cases' of anxiety or depression on the HADS (Snaith and Zigmond, 1994). None of the control group were taking medication known to affect cognitive functioning.

2.23 Demographics

The MS and control groups were matched according to gender, age, years of education, and Spot the Word scores (an estimate of verbal intelligence). There were 12 women (63.16%) and 7 men (36.84%) in the control group and 11 women (68.75%) and 5 men (31.25%) in the MS group. As table 3.1 illustrates, there were no significant differences between the two groups on age, years of education and Spot the Word score.

2.24 Characteristics of the MS group

The mean number of years since diagnosis was 25.56 years (S.D 14.37). From a detailed examination of their medical notes, all MS participants were classified as having the chronic progressive form of MS. There was inadequate information to determine the initial disease course that would enable classification into primary progressive, progressive relapsing or secondary progressive MS.

The mean EDSS score of the MS group was 7.69 (S.D. 0.34) with a range of between 7.0 and 8.0. This indicates that all participants were unable to walk more than about five metres even with aid. All of the MS group were restricted to a wheelchair.

In the MS group, 14 participants were taking prescribed medication. The number of people taking medication and the type taken are described in table 2.2. Only medication with fatigue, drowsiness, or cognitive impairment listed as possible side effects are listed.

Table 2.2: Medication taken by the MS group

Type of medication	Medication name	Number of people taking it
Anti-depressant (SSRI)	Venlafaxine	1
	Paroxetine	1
Anti-depressant (Tricyclic)	Amitriptyline	1
	Lofepramine	1
Hypnotic	Temazepam	2
	Diazepam	2
	Zopiclone	2
Anti-psychotic (Atypical)	Olanzapine	1
Anti-spasticity	Baclofen	7
	Tizanidine	1
Anti-epileptic	Cabamazepine	1

2.3 Ethics

The Royal Hospital for Neuro-disability has its own Medical Research Advisory Committee (MRAC) from which ethical approval has to be granted before an application can be submitted to the local ethics committee. Approval from the MRAC was granted on the 11th July 2002, which allowed submission of an application to the Riverside Research Ethics Committee. Ethical approval for the study was granted by Riverside Research Ethics Committee on the 19th September 2002.

Copies of the approval notices, information sheets, and consent forms are provided in the Appendices.

2.4 Measures

2.41 Screening measures

2.411 The Fatigue Severity Scale (FSS, Krupp et al., 1989). See Appendix 6. 1

The FSS (Krupp et al., 1989) was developed as method of evaluating fatigue in MS and other conditions such as Parkinson's disease, CFS, and Systemic Lupus Erythmatosis (Krupp, 1997). It is a nine-item scale that assesses the effect of fatigue on activities of daily living. Participants are asked to indicate their level of agreement with each of nine statements where 1 indicates strongly disagree and 7 indicates strongly agree.

Krupp et al (1989) administered the FSS to 25 people with MS, 29 people with Systemic Lupus Erythmatosis, and 20 healthy adults. Their results indicated that the scale distinguished the two patient groups from the control subjects, correlated well with a Visual Analogue Scale measure of fatigue, and could detect clinically predicted changes in fatigue over time. In addition, FSS scores were unrelated to depressive symptoms. The internal consistency of the scale was high, with a Cronbach's alpha of .88 for the entire sample. Test retest-reliability was also good, with no significant changes in FSS score when administered on two separate occasions.

Krupp (1997) suggests that the advantages of the FSS are that it is brief, easy to administer, and has proven reliability. She suggests that it is most useful in the classification of patients, but may be less sensitive to changes associated with treatment.

2.412 The Expanded Disability Status Scale (EDSS, Kurtzke, 1983) – see Appendix 6. 2

The EDSS (Kurtzke, 1983) was developed to assess the severity of disability in any given individual with MS. It is comprised of a combination of grades within eight functional systems and an overall disability status score that has 20 grades / steps ranging in ½ point increments from 0 (normal) to 10 (death due to MS). The functional systems are pyramidal, cereballar, brain stem, sensory, bowel and bladder, visual, cerebral (mental) and 'other'. Scores from 4.0 to 8.0 on the EDSS were designed to reflect difficulties with ambulation. People with an EDSS score of 7.5 and above are essentially unable to walk, and scores between 8.0 and 9.0 are based primarily on upper limb dysfunction (Rudick, Weinshenker, and Cutter, 2001).

In a trial of inter-rater reliability, Noseworthy et al (1990) demonstrated 80% agreement in EDSS ratings where perfect agreement was defined as +/- 0.5 EDSS points. However, Rudick et al (2001) offer a number of criticisms of the EDSS, two of which have relevance for the present study. Firstly, steps at the upper range of the EDSS represent extremely large changes in functional ability and consequently lack sensitivity for the purposes of clinical trials. Secondly, cognitive assessment is not used to contribute to the EDSS even though cognitive impairment is a common cause of disability in MS. Despite these criticisms, the EDSS remains the most widely accepted rating scale of disease severity in MS.

2.413 The Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983)

The HADS is a 14-item self-assessment scale for detecting states of anxiety and depression (Zigmond and Snaith, 1983). The measure was developed for use in hospital outpatient clinics, but now is widely used in research and clinical practice.

Participants are asked to rate their agreement with seven statements about symptoms of anxiety (e.g. "worrying thoughts go through my mind") and seven symptoms of depression (e.g. "I have lost interest in my appearance"). Snaith and Zigmond (1994) suggest that on the anxiety and depression scales, scores of 8-10 identify mild cases, 11-15 moderate cases, and 16 or above, severe cases. Zigmond and Snaith (1983) argue that the anxiety and depression scales can be treated as separate. However, Crawford et al (2001) argue that it would be legitimate to combine scores on the anxiety and depression scales to obtain a total score of psychological distress.

The internal consistency of the scale was examined by comparing Spearman's correlations between each item and the total score for the remaining items in the subscale (Zigmond and Snaith, 1983). On the anxiety scale correlations ranged from +0.76 to +0.41 with a significance level of $p<0.01$. The depression items in the final scale had correlations ranging from +0.60 to +0.30, which were significant at $p< 0.02$. When compared to psychiatric ratings of caseness based on a clinical interview, the anxiety and depression scales also demonstrated good criterion validity. Using the same ratings, the HADS was also shown to be sensitive to the severity of anxiety and depression. The correlation between psychiatric rating and HADS score was $r = +0.70$ for the depression scale and $r= +0.74$ for the anxiety scale, both of which were significant at $p= <0.001$.

2.414 The Health Screening Interview – See appendix 6.3

All participants completed a health-screening interview from which background information was gathered.

2.42 Experimental measures

2.421 The Brixton test (Burgess and Shallice, 1997)

The Brixton test is a concept or rule attainment task (Burgess and Shallice, 1997). Failure on such tasks is a commonly reported dysexecutive sign in the formal examination of people with frontal lobe lesions. The Wisconsin Card Sorting Test is another example of a concept and rule attainment task.

The Brixton test consists of a 56-page stimulus book. Each page has the same basic design of 10 numbered circles in two rows of five. One of the circles is coloured in blue. The position of the coloured circle is determined by a rule or pattern and the participant is asked to predict where the coloured circle will be on the next page. At regular intervals, the pattern changes and the person is required to detect and follow the new rule. There are three broad classes of error on the test (Burgess and Shallice, 1996): perseverations (repeating a response); the misapplication of a strategy; or 'guessing' or 'bizarre' responses.

In the standardisation of the test (Burgess and Shallice, 1997), four groups were compared: people with bilateral frontal lobe lesions; people with unilateral frontal lobe lesions; a group with posterior lesions; and a group of healthy control subjects. Both the frontal lobe lesion groups were found to have significantly poorer test performance than the control or posterior

lesion groups. The two frontal lobe lesion groups did not significantly from one another, although the bilateral frontal group were poorer than the unilateral group. The split half reliability of the test for the entire standardisation sample was found to be 0.62 ($p<0.001$). In addition, the test-retest reliability of the test was 0.71 ($p<0.001$).

2.422 The Spot the Word Test (Baddeley, Emslie, and Smith, 1992)

The Spot the Word test is a silent lexical decision task that provides a relatively crystallised and robust estimate of verbal intelligence. The National Adult Reading Test (NART, Nelson and Willison, 1991) is a commonly used method of estimating verbal ability, which is often preserved following neurological damage. However, Baddeley et al (1992) suggest that it has a number of limitations. They mention that the NART cannot be used with subjects suffering from visual or articulatory problems and penalises the self educated, who may have acquired their vocabulary through reading and may understand words but be unable to pronounce them. The test authors argue that the Spot the Word test is a useful supplement to the NART as it does not require the subject to read out loud and that it requires familiarity with a word but not necessarily the capacity to pronounce the word.

In the Spot the Word test, subjects are presented with 60 pairs of letter strings, each pair comprising one genuine word and one non-word, for example "slank – chariot"). Subjects are asked to choose the letter strings that form real words. Two parallel forms (version A and version B) are available for repeat testing.

The validity of the test was established by comparing the performance of a standardisation sample on the NART and the Spot the Word test. The correlation between the two tests was

0.83 for version A and 0.86 for version B, indicating good convergent validity (Baddeley et al., 1992). There is also a strong correlation between Spot the Word scores and years of education, another method of estimating cognitive ability (Crowell et al., 2002). The reliability between the two forms is also adequate with a correlation of +0.883. The Spot the Word test also appears to be insensitive to the effects of brain damage (Crowell et al., 2002). A sample of 16 elderly participants with dementia was compared to a healthy control group on the Spot the Word and the NART (Law and O'Carroll, 1998). No significant differences were found between the groups.

2.423 The Ravens Coloured Progressive Matrices (Raven et al., 1999)

The Coloured Progressive Matrices (CPM)(Raven et al., 1999) is an assessment of general intellectual ability. The test is comprised of 36 items, grouped into three sets. Each item contains a pattern with one piece removed. Subjects are instructed to choose from six inserts, one of which completes the pattern. Each set contains progressively more difficult items, requiring different principles of reasoning. The test was designed for use with young children, older people, and for clinical work. The test authors suggest that it can be used with people who are suffering from physical disabilities, aphasia, as well as people who are intellectually impaired or who have deteriorated.

Studies of the reliability of the CPM have generally confirmed that it is extremely satisfactory, whether assessed by split-half or retest methods (Raven et al., 1999). The validity of the measure in clinical settings has been established for people with Dementia of Alzheimer's Type (Knopman and Ryberg, 1989). Furthermore, Halligan et al (1988) were able to show that

CPM scores decline progressively with the MS disease process. Duration since diagnosis with MS correlated – 0.35 with CPM score.

2.424 The N-Back task

This study used the N-back task, widely used as a delayed response measure (e.g. Braver et al., 1997). The N-back test is a working memory task that measures the ability to hold, update, and manipulate information in a temporary memory store. Working memory tasks particularly those with interference following delay, are sensitive to dorso-lateral prefrontal lobe lesions (D'Esposito et al., 1998).

In this task, a series of six blocks of 40 single letters were presented on a laptop computer screen. Each block was comprised of 10 target stimuli and 30 distractor trials. Participants were asked to respond to a target letter by pressing a large "yes" response key and "no" if it did not appear. Stimulus presentation was self-paced, so a new letter only appeared after the participant had responded to the previous one. The effects of working memory load were examined by comparing performance in the 0-back condition to the 1-back single condition. In the 0-back condition participants were asked to press the "yes" key every time they saw a single target letter (e.g. "B") and the "no" key when they see any other letter. In the 1-back single condition, participants were asked to respond "yes" if a single target letter was preceded by the same target letter (e.g. "yes" if the letter "P" is preceded by the letter "P"). Performance was examined on accuracy (percentage of correct responses) and reaction time. To examine the possible effects of fatigue within each task, performance was compared across the first, second and third pairs of blocks in the test. In addition, each n-back task was administered

twice in each session. Fatigue effects across the session were examined by comparing performance on the first test presentation to the second.

Two MS participants were unable to press the response keys on the n-back task, but were able to provide verbal responses. Therefore, they were asked to say "yes" or "no" and the researcher pressed the response keys on their behalf. To ensure matching of the two experimental groups, the same procedure was carried out with two members of the control group.

Braver et al (1997) examined the effects of increasing working memory load (i.e. increasing *n* from 0 to 3) on activity in the prefrontal cortex using functional magnetic resonance imaging (fMRI). Their findings indicated that dorsolateral and left inferior regions of the prefrontal cortex exhibited a linear relationship between activity and working memory load. They also identified load-sensitive activity in areas including motor, premotor, and supplementary motor areas as well as the posterior parietal cortex and the caudate nucleus of the basal ganglia.

2.425 The Fatigue Rating Scale (FRS) – See Appendix 6.4

In order to assess changes in the level of subjective fatigue during the testing sessions, a simple fatigue rating scale was developed. Participants were asked to choose a number from 0 to 8, depending on how tired / fatigued they felt at the time, from 0 ("not at all") to 8 ("extremely – the most tired / fatigued I've ever been"). All participants completed the FRS on four occasions within each testing session.

The use of simple rating scales, similar to the one used in the present study, is well documented (Johnson et al., 1997; Krupp and Elkins, 2000; Paul et al., 1998a; Schwid et al., 2000). Recently, Flachenhecker et al (2002) illustrated the convergent validity of a visual analogue scale as measure of fatigue in MS. They compared a scale in which participants were asked to indicate their fatigue on a 100mm line to the FSS (Krupp et al., 1989) and the Modified Fatigue Impact Scale (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). There were significant correlations between the visual analogue scale and both the FSS ($r = 0.38$; $p<0.0001$) and the Modified fatigue Impact Scale ($r = 0.47$; $p<0.0001$). The advantage of visual analogue scales is that they are quick and easy to administer. However, Krupp (1997) argues that they are also vulnerable to impulsive responses and do not assess qualitative aspects of fatigue.

2.5 Procedure

The experimental procedure had two components: screening measures and neuropsychological testing.

The screening measures were the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983), the Fatigue Severity Scale (FSS, Krupp et al., 1989), the Expanded Disability Status Scale (EDSS, Kurtzke, 1983) and the health screening interview.

All participants were then asked to engage in two neuropsychological testing sessions, separated by no less than three days and no more than one month. Testing was arranged to suit the convenience of the participants and took place between 9:30am and 3:30pm. To minimise

the effects of time of day on fatigue, the time of the second session was arranged within 2½ hours of the first session.

The order of test presentation was the same in both sessions:

1. First fatigue rating (FRS)
2. First presentation of either the O-Back or the 1-Back
3. Second fatigue rating (FRS)
4. Neuropsychological battery. Ravens Coloured Progressive Matrices, or the Spot the Word Test and the Brixton Test.
5. Third fatigue rating (FRS)
6. Second presentation of either the O-Back or the 1-Back
7. Fourth fatigue rating (FRS)

The order of test presentation (n-back variant and neuropsychological battery) was randomised and counterbalanced across the groups. Therefore, half the participants in each group were administered the 0-bach task on two occasions in the first testing session followed by the 1-back in the second session. The other half of each group received the 1-back followed by the 0-back. Similarly, half of each group were given the Coloured Progressive Matrices in the first session, followed by the Brixton and Spot the Word tests in the second session. The other half of each group received the opposite order of presentation.

3. Results

3.1 Analysis of data

The computerised statistical package SPSS version 10.1 for Windows was used to analyse the data.

The data were first examined to check that they did not violate the assumptions of normality that underlie parametric tests.

Outliers were identified by converting all data to z-scores and examining their distribution. All z-scores that were more than +/- 3 standard deviations from the mean were classified as outliers. The degree of skewness was calculated for each variable and compared against the standard error for skewness using Tabachnick and Fidell's (1983) formula. The standard error for skewness (sS) is as follows for the MS group:

$sS = \sqrt{6/N} = \sqrt{6/16} = 0.61$

The standard error for skewness (sS) for the control group is:

$sS = \sqrt{6/N} = \sqrt{6/19} = 0.56$

Where N is the number of cases. The probability of obtaining a skewness value of this size is:

$$Z = \frac{S - 0}{sS}$$

Where S is the value for skewness. At the 1% level, a Z value greater than $\pm$ 2.58 would lead to rejection of the assumption of normality.

Entering this into the table for the MS group,

$S = \pm 2.58 \times sS = \pm 2.58 \times 0.61 = \pm 1.57$

The same approach was applied to the control group,

$S = \pm 2.58 \times sS = \pm 2.58 \times 0.56 = \pm 1.44$

So, criterion of $\pm$ 1.57 for the MS group and $\pm$ 1.44 for the control group were used for the data in this study as a cut-off point for normality.

Where there were outliers or skewness for a particular measure, the data were transformed so that they more closely approximated a normal distribution. Square root transformations were used where there was mild to moderate skew (HADS depression and the Fatigue Severity Scale). Logarithmic transformations were used for more substantial skewness (n-back reaction time, FRS fatigue ratings). When the data were re-examined, they were found to approximate a normal distribution. Where transformation was unsuccessful (n-back fatigue ratings, total n-

back RT and accuracy and n-back accuracy), untransformed scores were used in the data analysis and any use of parametric tests where ANOVA was used for repeated measures was also checked using non-parametric tests.

A significance level of $p = <0.05$ was adopted throughout and for the sake of clarity, all descriptive statistics are reported using untransformed variables.

3.2 Results for neuropsychological measures and matching variables

Table 3.1 shows the results for matching variables and the neuropsychological measures.

The data for the matching variables (age, years of education and the Spot the Word Test score) were compared between groups using independent samples t-tests. The results showed that the two groups did not significantly differ from one another on any of the variables. This shows that the two groups were matched according to age, years of education and estimated verbal intelligence (Spot the Word score).

The data for the neuropsychological measures (Ravens CPM and the Brixton test) were compared between groups using independent samples t-tests. The results showed that there were significant differences between the two groups on both tasks. This shows that the MS group performed more poorly than the control group on a test of executive functioning (Brixton test) and a measure of general intellectual functioning (the Ravens CPM).

Table 3.1: Results for neuropsychological measures and demographic variables

	Control group (n = 19) Mean (S.D)	**MS group** (n = 16) Mean (S.D)	**t value**	**2-tailed sig**
Matching variables				
Age	59.16 (16.42)	57.12 (12.85)	0.39	0.70
Years of Education	12.89 (2.88)	12.75 (3.28)	0.14	0.89
Spot the Word scaled score (Max =16)	9.73 (2.42)	10.0 (2.34)	0.32	0.75
Neuropsychological measures				
Brixton scaled score (Max =10)	6.84 (1.64)	3.69 (1.58)	5.47	>0.001
Ravens CPM (Max = 36)	32.89 (2.83)	27.62 (5.99)	3.15	0.002

3.3 The n-back

3.31 The 0-back (sustained attention task)

The descriptive data for 0-back performance are shown in table 3.2. The results of the ANOVAs are described in table 3.3 and 3.4.

ANOVA was used to compare performance on the 0-back for the MS and Control groups. The within-subjects factors were block (first, second and third pair of blocks) and time (first and second n-back presentation within the session). The between-subjects factor was group (MS or Control). Separate analysis was performed for the two dependent variables, Log RT and accuracy. The pattern of findings for the accuracy data was also confirmed using Mann-Whitney tests.

3.311 Accuracy

As table 3.3 shows, the only significant interaction on the 0-back was between group and block. The main effect of group was also significant, with the MS group less accurate on the 0-back compared to the control group. It can be seen in table 3.2 that the performance of the MS group declined with continued performance on the task (across blocks) in both sessions, whilst the control group performed close to ceiling in both sessions.

The interaction between group and time was not significant, and the main effects of block and time were also not significant. These findings show that changes in cognitive performance between the first and second n-back presentation did not depend on group.

3.312 Reaction Time

Table 3.4 shows that there was a significant interaction between time and block and a main effect of time. There was also a main effect of group, with the MS group slower than control group. However, there were no significant interactions involving group, and there was not a main effect of block. This analysis shows that there was no effect of group on changes in RT both within a task and across a session.

Table 3.2. Cognitive performance on the 0-back across blocks and time

0-Back		Control Group (N = 19) Mean	(S.D)	MS group (N = 16) Mean	(S.D)
Accuracy (%)					
Time 1	1st Pair of Blocks	98.29	(2.54)	96.72	(3.62)
	2nd Pair of Blocks	99.54	(0.95)	95.47	(5.66)
	3rd Pair of Blocks	98.95	(1.20)	94.69	(7.82)
Time 2	1st Pair of Blocks	99.21	(1.04)	94.69	(7.46)
	2nd Pair of Blocks	99.28	(0.76)	93.75	(9.60)
	3rd Pair of Blocks	99.47	(0.76)	93.44	(13.07)
Median Reaction Time (Seconds)					
Time 1	1st Pair of Blocks	0.66	(0.27)	1.48	(1.0)
	2nd Pair of Blocks	0.61	(0.23)	1.33	(0.98)
	3rd Pair of Blocks	0.59	(0.21)	1.43	(1.32)
Time 2	1st Pair of Blocks	0.57	(0.21)	1.21	(0.83)
	2nd Pair of Blocks	0.60	(0.25)	1.23	(0.94)
	3rd Pair of Blocks	0.63	(0.37)	1.21	(0.75)

Table 3.3. Analysis of Variance for 0-back accuracy

	F	df	P
	Within Subjects		
Group x Time x Block	0.21	(2,32)	0.81
Group x Block	3.82	(2,32)	0.03
Group x Time	1.74	(1,33)	0.20
Time x Block	0.59	(2,32)	0.56
Time	0.66	(1,33)	0.42
Block	0.38	(2,32)	0.69
	Between Subjects		
Group	7.41	(1,33)	0.01

Table 3.4. Analysis of Variance for 0-back median RT

	F	df	P
	Within Subjects		
Group x Time x Block	0.52	(2,32)	0.60
Group x Block	1.53	(2,32)	0.23
Group x Time	0.81	(1,33)	0.37
Time x Block	0.98	(2,32)	0.03
Time	0.81	(1,33)	0.01
Block	1.20	(2,32)	0.15
	Between Subjects		
Group	16.61	(1,33)	>0.001

3.32 The 1-back (sustained attention plus working memory)

The descriptive data for 1-back performance are shown in table 3.5. The results of the ANOVAs are described in table 3.6 and 3.7.

Performance on the 1-back was compared between the MS and Control groups using ANOVA. The within-subjects factors were block (first, second and third pair of blocks) and time (first and second n-back presentation within the session). The between-subjects factor was group (MS or Control). Separate analyses took place for the two dependent variables, Log RT and accuracy.

3.321 Accuracy

Table 3.6 shows that the main effect of group was significant. It can be seen in table 3.5 that the MS group were less accurate than the control group.

There were no significant interactions and no significant main effects of time or block. However, the interaction between group and time approached but did not reach statistical significance. From table 3.5 it can be seen that the performance of the MS group was less accurate during the second n-back presentation within the session compared to the first, while the Control group showed a pattern of improvement and ceiling effects.

3.322 Reaction Time

Table 3.7 shows that the interaction between time and block and the main effect of time were significant. There was also a main effect of group, with the MS group slower than the Control

group. There were no significant interactions involving group. In addition, the main effect of block was not significant. So, there was no effect of group on changes in RT within a task and across a session.

Table 3.5. Cognitive performance on the 1-back across blocks and time

1-back		Control group (N = 19) Mean	(S.D)	MS group (N =16) Mean	(S.D)
Accuracy (%)					
Time 1	1st Pair of Blocks	98.09	(2.18)	94.37	(7.17)
	2nd Pair of Blocks	99.21	(1.12)	92.73	(9.21)
	3rd Pair of Blocks	99.21	(0.85)	93.51	(8.49)
Time 2	1st Pair of Blocks	99.34	(1.28)	92.19	(10.32)
	2nd Pair of Blocks	99.27	(1.05)	90.94	(12.22)
	3rd Pair of Blocks	99.08	(1.17)	89.45	(12.97)
Median Reaction Time (Seconds)					
Time 1	1st Pair of Blocks	0.72	(0.33)	1.59	(0.87)
	2nd Pair of Blocks	0.64	(0.32)	1.38	(0.84)
	3rd Pair of Blocks	0.65	(0.36)	1.34	(0.71)
Time 2	1st Pair of Blocks	0.58	(0.25)	1.18	(0.56)
	2nd Pair of Blocks	0.58	(0.26)	1.18	(0.70)
	3rd Pair of Blocks	0.60	(0.31)	1.26	(0.79)

Table 3.6. Analysis of Variance for 1-back accuracy

	F	df	P
	Within Subjects		
Group x Time x Block	1.21	(2,32)	0.31
Group x Block	1.84	(2,32)	0.17
Group x Time	3.62	(1,33)	0.07
Time x Block	0.24	(2,32)	0.24
Time	2.00	(1,33)	0.17
Block	0.63	(2,32)	0.54
	Between Subjects		
Group	10.85	(1,33)	>0.001

Table 3.7. Analysis of Variance for 1-back median RT

	F	df	P
	Within Subjects		
Group x Time x Block	0.20	(2,32)	0.82
Group x Block	0.35	(2,32)	0.71
Group x Time	0.66	(1,33)	0.42
Time x Block	7.11	(2,32)	0.003
Time	30.36	(1,33)	>0.001
Block	1.20	(2,32)	0.15
	Between Subjects		
Group	20.94	(1,33)	>0.001

3.33 Speed versus accuracy

The data on the n-back were examined for a speed versus accuracy trade-off. That is, were participants responding quickly but inaccurately, or were people responding accurately but slowly?

The association between n-back RT and accuracy was examined using Spearman's correlations. For the MS group, the correlations between total RT and total accuracy approached, but did not reach statistical significance for the 0-back ($r = -0.43$, $p = 0.09$) and the 1-back ($r = -0.46$, $p = 0.07$). For the control group, the correlations did not meet statistical significance for the 0-back ($r = 0.04$, $p = 0.87$) or the 1-back ($r = -0.28$, $p = 0.24$). The directions of the correlations suggest that participants with MS who were slower tended to be less accurate, so there is no evidence of a speed versus accuracy trade-off.

3.34 Summary

Overall, the results of the tests reported so far show that the MS group were significantly worse than the control group on RT and accuracy on both n-back tasks.

There was mixed evidence to support the hypothesis that people with MS show signs of a deterioration in performance during a continuous cognitive task. There was a significant interaction between group and accuracy during the 0-back task (across blocks), but a similar pattern did not emerge on the 1-back or when RT was the dependent variable.

There is less evidence to support the hypothesis that the cognitive performance of people with MS deteriorates across a testing session. There was a tendency for people with MS make more errors on the 1-back when it was repeated at the end of the session. However, this effect approached but did not reach statistical significance. Data analysis did not reveal a similar pattern of findings on the 0-back, or when RT was the dependent variable.

There is no clear evidence to support the hypothesis that the 1-back would lead to a greater decline in cognitive performance than the 0-back as the two tasks were not compared in a statistical analysis. However, the only significant interaction involving group was found on the 0-back. This suggests that a change in cognitive performance within a task or across a session is no more likely when working memory load is increased from 0-back to 1-back.

3.4 Self-reported fatigue and depression

Self reported fatigue was measured on the FRS and the FSS. Depression was measured on the HADS. The descriptive data for the FRS, FSS and HADS depression are reported in table 3.8.

3.41 The Fatigue Rating Scale (FRS)

The results for the FRS are shown in tables 3.9 and 3.10.

Repeated-measures ANOVA was used to compare the ratings of participants on the FRS across each session. The within-subjects factor was time (1^{st}, 2^{nd}, 3^{rd}, and 4^{th} FRS rating) and the between-subjects factor was group (MS or Control). FRS ratings for the 0-back and the 1-back were analysed separately.

As table 3.9 indicates, on the 0-back the interaction between group and time approached, but marginally failed to achieve statistical significance. There was a significant main effect of time but not of group. Table 3.8 shows that across the testing session, FRS scores increased for both groups. However, this effect was more pronounced for the MS group.

As shown in table 3.10, on the 1-back there was a significant interaction between group and time. There was also a main effect of time but not of group. Table 3.8 demonstrates a similar pattern to that described on the 0-back. There was an increase in FRS scores over the session, and this effect was more pronounced for the MS group.

Overall, the results demonstrate that ratings on the FRS increase over time and the degree of change varies according to group. This effect was statistically significant on the 1-back, but marginally failed to achieve significance on the 0-back.

3.42 Fatigue Severity Scale (FSS)

The descriptive data for the FSS are shown in table 3.8.

The results for this measure were analysed using an independent samples t-test. This showed that there was a significant difference between the two groups ($t(33) = 2.37$, $p = 0.02$). From table 3.8 it can be seen that the MS group reported more fatigue than the control group.

3.43 HADS Depression

The descriptive data for the HADS ratings of depression are shown in table 3.8

The two groups were compared on the HADS depression scores using an independent samples t-test. This showed that there was a significant difference between the two groups ($t = (33) = 3.03$, $p = 0.005$). From table 3.8 it can be seen that the MS group reported more symptoms of depression than the Control group.

Table 3.8. Mean FRS, FSS and HADS depression scores.

Measure		Control group (n = 19) Mean	(S.D)	MS group (n = 16) Mean	(S.D)
Fatigue Rating Scale (Max = 8)					
0-back	1st rating	1.68	(1.70)	2.25	(2.14)
	2nd rating	2.00	(1.63)	2.44	(2.10)
	3rd rating	2.10	(1.56)	2.62	(2.25)
	4th rating	2.26	(1.56)	3.37	(2.73)
1-back	1st rating	1.89	(2.05)	1.25	(1.84)
	2nd rating	2.05	(1.98)	2.06	(1.95)
	3rd rating	2.16	(2.06)	2.44	(2.13)
	4th rating	2.42	(2.14)	3.06	(2.20)
FSS (Max = 7)		2.22	(1.24)	3.19	(1.32)
HADS depression (Max = 21)		2.26	(2.40)	5.12	(3.77)

Table 3.9. Analysis of Variance for 0-back Fatigue Rating Scale scores

	F	df	P
	Within Subjects		
Group x Time	2.78	(3,31)	0.057
Time	5.87	(3,31)	0.003
	Between Subjects		
Group	1.07	(1,33)	0.31

Table 3.10. Analysis of Variance for 1-back Fatigue Rating Scale scores

	F	df	P
	Within Subjects		
Group x Time	3.56	(3,31)	0.02
Time	11.40	(3,31)	>0.001
	Between Subjects		
Group	0.01	(1,33)	0.91

3.44 The association between subjective mental fatigue, depression and changes in cognitive performance over time

In order to examine the association between subjective fatigue and changes in cognitive fatigue over time (which may be evidence of objective cognitive fatigue), the n-back data were converted to a format that represented the percentage change in performance over time (n-back fatigue). An assumption was made that participants would be at their least fatigued at the very beginning of each session (first two blocks of the first n-back presentation), and their most fatigued at the end of each session (the last two blocks of the second n-back presentation). Indices of n-back fatigue were developed that represented the percentage change in performance over time. These indices were calculated separately for the 0-back and 1-back using the following formula for the accuracy data:

$$\text{n-back fatigue (accuracy)} = \left[\frac{\text{Accuracy for } 3^{rd} \text{ blocks, n-back time 2} - \text{Accuracy for } 1^{st} \text{ blocks, n-back time 1}}{\text{Accuracy for } 3^{rd} \text{ blocks of n-back time 2}} \right] \times 100$$

In addition, the indices of fatigue for RT on the n-back were calculated separately for the 0-back and 1-back using the following formula:

$$\text{n-back fatigue (RT)} = \left[\frac{\text{RT for } 3^{rd} \text{ blocks, n-back time 2} - \text{RT for } 1^{st} \text{ blocks, n-back time 1}}{\text{RT for the } 3^{rd} \text{ blocks, n-back time 2}} \right] \times 100$$

A similar approach was applied to develop a single index of subjective fatigue. The index of fatigue for the FRS was calculated separately for the 0-back and 1-back using the following formula:

$$\text{FRS fatigue} = \left[\frac{4^{th}\ \text{FRS rating} - 1^{st}\ \text{FRS rating}}{1^{st}\ \text{FRS rating}} \right] \times 100$$

Correlations were calculated between ratings on the FSS, HADS depression, FRS fatigue (0-back and 1-back), and the indices of n-back fatigue (0-back fatigue (accuracy), 1-back fatigue(accuracy), 0-back fatigue (RT) and 1-back fatigue (RT)). Spearman's correlations were used as the n-back fatigue data were more suitable to non-parametric analyses.

As can be seen in table 3.10, there was a significant correlation between FSS and HADS depression scores for the MS and Control groups. However, no correlations between fatigue ratings on the FSS and FRS, and n-back fatigue reached significance for MS group. The data for the MS group also showed that there were no significant correlations between HADS depression and n-back fatigue or FRS fatigue ratings. In addition, there was no association between subjective fatigue on the FRS and subjective fatigue on the FSS. Two correlations reached significance for the Control group (between 1-back fatigue (accuracy) and both the HADS and the FSS).

These findings show that there was a significant association between symptoms of fatigue on the FSS and symptoms of depression on the HADS for both groups. However, there were no significant correlations between ratings of subjective fatigue across a testing session (FRS

fatigue) and measures of change in cognitive performance across a session (n-back fatigue). In addition, for the MS group there were no significant correlations between a measure of the symptoms of fatigue (FSS), and changes in cognitive performance, which may be evidence of cognitive fatigue (n-back fatigue). For the MS group, ratings of depression (HADS) and changes in cognitive performance (n-back fatigue) were not significantly associated.

Table 3.10: Spearman's correlations between fatigue ratings, depression and cognitive performance

			FRS fatigue 0-back	FRS fatigue 1-back	FSS	HADS
MS group (N = 16)	0-back					
		Fatigue (accuracy)	-0.09	–	0.26	-0.19
		Fatigue (RT)	-0.19	–	-0.44	-0.46
		FRS fatigue	–	–	-0.18	0.16
	1-back					
		Fatigue (accuracy)	–	0.24	0.49	0.26
		Fatigue (RT)	–	0.16	-0.11	-0.08
		FRS fatigue	–	–	-0.31	0.02
	FSS		–	–	–	0.56*
Control group (N = 19)	0-back					
		Fatigue (accuracy)	0.28	–	-0.06	-0.04
		Fatigue (RT)	0.01	–	-0.17	-0.21
		FRS fatigue	–	–	0.06	-0.24
	1-back					
		Fatigue (accuracy)	–	-0.14	-0.46*	-0.50*
		Fatigue (RT)	–	0.03	-0.22	-0.11
		FRS fatigue	–	–	-0.09	-0.33
	FSS		–	–	–	0.46*

P = <0.05*

4.0 Discussion Section

4.1 Summary of the main findings

This study compared people with advanced MS to a healthy control group on a number of psychiatric and neuropsychological measures. Of interest were six research questions concerned with advanced MS, fatigue and cognitive performance. Firstly, would people with MS demonstrate a greater decline in cognitive performance over time within a continuous cognitive task (which may be evidence of fatigue) compared to healthy participants. Secondly, would the cognitive performance of people with MS decline across a testing session, which may be evidence of fatigue? Thirdly, would a higher working memory load lead to a greater change in cognitive performance within a task and across a testing session? Fourthly, would people with MS report greater subjective fatigue compared to a healthy control group. Fifthly, would there be an association between subjective mental fatigue and cognitive fatigue, demonstrated by a decline in performance? Finally, would there be an association between depression and fatigue?

Considering the first research question, the findings demonstrated that people with MS showed evidence of a greater decline in accuracy compared to the control group during a continuous cognitive task (the 0-back). Initially, the MS group made more errors than the control group and as the task progressed, the performance of the MS group declined whilst the control group continued to perform close to ceiling. However, a similar effect was not found when a working memory load was introduced on the 1-back task.

Compared to the control group, there was no evidence of a significantly greater deterioration in the cognitive performance of the MS group when compared at the beginning and the end of each testing session. However, on the 1-back task there was a tendency for the accuracy of the MS group to decline across the testing session while the control group performed close to ceiling.

The third research question was concerned with the effects of working memory load (0-back vs. 1-back) on changes in cognitive performance. When the MS group were compared to the control group, there was no evidence that the working memory load on the 1-back task led to a greater deterioration in cognitive performance over time, both within a task and across a session. However, on the 0-back, which has a lower working memory demand, there was evidence of a greater deterioration in cognitive function within a task for the MS group. These findings provide tentative evidence to suggest that in the present study, deterioration in cognitive performance within a task and across a session was not more pronounced when a working memory load was introduced to a continuous cognitive task.

The fourth research question was concerned with self-reported fatigue. The FSS and the FRS were used as measures of subjective fatigue. On the FRS the MS group reported a significantly greater increase in subjective fatigue across the 1-back testing session. There was also a tendency for the MS group to report a greater change in their levels of fatigue on the 0-back test but in the data analysis this effect approached but did not reach statistical significance. On the FSS the MS group reported more symptoms of fatigue than the control group.

The association between subjective measures of fatigue and objective changes in performance were examined for both groups. The findings demonstrated that for the MS group, self reported fatigue (FSS and FRS) was poorly associated with changes in cognitive performance across a testing session.

The sixth question of this study was concerned with the association between depression and fatigue. As a group the participants with MS reported significantly more symptoms of depression than the control group. In addition there was a significant association between HADS depression scores and subjective fatigue on the FSS for both groups. Participants who reported greater symptoms of depression also reported more symptoms of fatigue. However, for the MS group there was not a significant association between depression and changes in cognitive performance or subjective fatigue (FRS) across a testing session.

4.2 Neuropsychological test performance

The two neuropsychological tests used in the present study were used as cognitively demanding tasks between the two n-back presentations. They were also used to obtain information about the general intellectual ability and executive functioning of the two groups. This information helped to contrast the sample in the present study with other samples of people with MS and cognitive impairment.

In this study, the MS group achieved lower scores than the Control group on two measures of neuropsychological function, namely the Ravens CPM and the Brixton test. Their performances on both tests were broadly consistent with the literature on cognitive function in progressive MS, which is often associated with cognitive impairment (Camp et al., 1999).

Nocentini et al (2001) examined the performance of a sample of people with secondary progressive MS on a number of neuropsychological measures that included the Ravens Standard Progressive Matrices. The MS group were divided into three separate groups: those with no cognitive deterioration, those with frontal and memory impairment and those who were cognitively deteriorated. These MS groups were then compared to a healthy control group. The findings of the study indicated that the performance of the cognitively deteriorated group on the Progressive Matrices differed from all the other groups but that the other groups did not differ from one another. Rao et al (1991a) reported similar findings in a community sample of people with MS. It is of note that the Standard Progressive Matrices differs from the CPM as used in the present study. The Standard Progressive Matrices is presented in black and white, rather than colour, contains 60 rather than 36 items and contains more complex task demands. Despite these differences it is proposed that in this study, the impaired Ravens CPM performance of the MS group is consistent with the existing MS literature and that this sample is similar to the cognitively deteriorated sample in the study by Nocentini et al (2001).

As with the Ravens CPM the Brixton test was not only intended to be a cognitively demanding buffer between n-back presentations, but also to provide information about the cognitive status of the MS group. A literature search suggested that at the time of writing there were no studies that had examined performance on the Brixton test in an MS sample. However the literature on executive functioning in MS has identified deficits on tests including the Wisconsin Card Sorting Test (Heaton, 1981), the Stroop test (Nocentini et al., 2001) and the Tower of London test (Foong et al., 1997). The findings of this study showed that people with advanced MS were impaired on the Brixton test when compared to a healthy control group. This finding is

consistent with the literature on samples of people with MS who are also cognitively impaired. It is possible that poor performance of the MS group on the Brixton test is indicative of frontal lobe pathology. However attempts to link frontal lobe pathology in MS with impaired performance on neuropsychological tests associated with frontal lobe damage have produced mixed findings (Benedict et al., 2002; Foong et al., 1997). It has been argued that it is extremely difficult to attribute specific cognitive abnormalities to focal brain pathology in the presence of a widespread disease such as MS (Foong et al., 1997).

In conclusion, the MS sample was impaired on a test of executive function (the Brixton test) and a test of general non-verbal intelligence (the Ravens CPM). The pattern of impairment was consistent with the available literature on cognitive impairment in MS. These findings suggest that the cognitive profile of the MS sample in the present study was similar to other cognitively impaired samples of people with MS.

4.3 Cognitive fatigue on the n-back

The term 'cognitive fatigue' has been used in previous studies (Krupp and Elkins, 2000; Paul et al., 1998a Schwid et al., 2002) to describe a decline in cognitive performance during a task or across a session. For the purpose of this study, a decline in cognitive performance over time (both within a task and across a session) will be described as 'cognitive fatigue'. It should be noted that this approach makes the assumption that fatigue causes the change in cognitive performance over time. This assumption may not necessarily be accurate as changes in performance may be due to other factors such as decreased effort or poor motivation.

4.31 Cognitive fatigue during a continuous cognitive task

The present study showed that during the 0-back task the accuracy of the MS group declined as the task continued. However this effect was not found on the 1-back task or when RT was examined. It is hypothesized that this effect may have been due to cognitive fatigue. As the task progressed the MS group may have found it more difficult to sustain attention on the 0-back task, which may have resulted in fewer correct responses.

Kujala et al (1995) showed that on a simple vigilance task people with MS showed signs of cognitive fatigue (evidenced by a decline in performance over time) when compared to control participants. Similarly Krupp and Elkins (2000) demonstrated that during the Alpha-Arithmetic test the performance of people with MS declined significantly more than a healthy control group. However in both these studies the decline in performance over time was observed for RT. For example, in the Kujala et al (1995) study it was noted that reaction times tended to be shortest in the last period of the task in the control group, compared with the first period in the MS patient groups. Although there were group differences in accuracy, there was no evidence of fatigue. The Krupp and Elkins (2000) study did not report any accuracy data in their findings. It is of note that the present study failed to find a fatigue effect within a task on reaction time. Instead, the observed cognitive fatigue effect was found on accuracy.

Schwid et al (2000) have also provided preliminary evidence of the effect of cognitive fatigue on task accuracy over time. The performance of a group of thirty people with MS was examined on the first ten items of the PASAT and compared to the last ten items. There was an average decline in accuracy of 17.8% during the task, which was taken as evidence of

cognitive fatigue. However, the study did not have a control group so it is unclear if the fatigue effects are specific to people with MS.

The mixed findings in the present study and in the existing literature suggest that there may be a number of possible factors that lead to cognitive fatigue during a task. Contributory factors may include task duration or task difficulty. It is hypothesised that task duration is unlikely to be a contributory factor as the duration of the n-back in the present study is similar to the tasks described by Krupp and Elkins (2000) and Kujala et al (1995). Moreover, in the study by Schwid et al (2000) fatigue effects were observed during a three-minute long task (PASAT). Alternatively, it is possible that the demands of working memory tests and measures of sustained attention are particularly fatiguing for people with MS, perhaps because of the cortical regions recruited for such tasks. Both the PASAT and the Alpha-Arithmetic tests are working memory tasks that require temporary storage and manipulation of information. The 0-back and the vigilance task used by Kujala et al (1995) require sustained attention. However in this study the lack of a cognitive fatigue effect on the 1-back, which is a sustained attention task with a working memory component, does not appear to be consistent with this hypothesis.

4.32 Cognitive fatigue during the testing session

In this study, performance on the n-back was examined at the beginning of each testing session and at the end of the session, after a neuropsychological battery had been administered. As described above, there was no statistical evidence to support the hypothesis that people with MS would show a greater decline in performance compared to a healthy control group across a testing session. However, there was a tendency for the accuracy of the

MS group on the 1-back task to decline over the course of the session. This effect marginally failed to meet statistical significance.

The existing literature contains equivocal findings about the effects of a neuropsychological testing session on cognitive performance in MS. Lezak (1995) noted that:

'Patients who no longer have the stamina to accept even part time work often report that the approximately two-hour examination I give exhausts them for the rest of the day and the next'

Krupp and Elkins (2000) found that on repeat administration of a battery of neuropsychological tests after a demanding continuous cognitive task, a group of people with MS performed significantly worse in a number of cognitive domains. The performance of the MS group declined on visual memory, verbal memory and verbal fluency. However, other studies (Johnson et al., 1997; Paul et al., 1998a) have failed to find evidence of a decline in performance across a single testing session. Differences between these studies include the nature of the task intended to induce fatigue. Krupp and Elkins (2000) used a working memory / sustained attention task (the Alpha Arithmetic Task), Johnson et al (1997) used a different sustained attention / working memory task (PASAT), and Paul et al (1998a) used a 'cognitive work battery', which included subtests from the WAIS. Other differences between the studies include the duration of the testing session and the characteristics of the MS sample.

The findings of the present study are consistent with those of Johnson et al (1997) and Paul et al (1998a) in that there was not a significantly greater decline in the cognitive performance of the MS group across the testing session. It is hypothesised that this may have been due to

insufficient task demands of the neuropsychological battery. Krupp and Elkins (2000) hypothesise that continuous cognitive activity may be necessary to precipitate cognitive fatigue. It is possible therefore that the cognitive demands of the tasks used in the present study may not have been sufficient to lead to cognitive fatigue.

It is also hypothesised that difference between the findings of Krupp and Elkins (2000) and the present study may have been due to the duration of the testing session. In the present study, testing lasted for less than one hour. This is in striking contrast to the four-hour long session described by Krupp and Elkins (2000). However, the sample in the study by Krupp and Elkins (2000) was less physically disabled than the present sample. Extending the duration of the session would have been too demanding for a number of the MS participants. It is of note that two participants withdrew from the study after the first n-back presentation because of self-reported fatigue. A number of other participants said that they would not have been able to continue if the session had lasted for longer than one hour.

4.33 Different n-back conditions

A consistent finding in the present study is that the MS group were slower and less accurate than the control group on both the 0-back and the 1-back task. The slower reaction time is consistent with the existing literature on speed of processing in MS (e.g. Rao et al., 1989c). Feinstein (1999) suggests that slowing of information processing may be due to the slowness of the visual input system (i.e. delayed conduction in the optic nerves, even without cerebral involvement may lead to slowed processing). In addition, the motor difficulties and upper limb spasticity of some of the MS group in the present study may have also contributed to slower RT. However, it has been argued that when people with MS are given sufficient time to

process information, performance accuracy on cognitive tasks can improve dramatically (Demaree et al., 1999). Stimuli on the n-back task were self-paced so that the MS participants would be given adequate time to process the information before responding. Despite this, they were still less accurate than the control group. Possible reasons for the group differences on the tasks are outlined below.

The 0-back is a sustained attention task. The results of the present study suggest that the MS group had poorer sustained attention than the control group, demonstrated by slower RT and less accurate responses. This finding is consistent with the literature on cognitive function in MS. People with MS often have sustained attention problems, which may lead to slowed and less accurate responses on tasks requiring the participant to maintain attention for a prolonged period of time (Kujala et al., 1995). In addition, people with neurological damage involving areas in the frontal lobes (Reukert and Grafman, 1996; Wilkins et al., 1987) are often impaired on tasks requiring sustained attention. Seidman et al (1998) suggest that sustained attention tasks also require people to minimise distractibility to irrelevant stimuli and to maintain adequate alertness over time. It is hypothesised that the poorer accuracy of the MS group on the 0-back may have been due to an impaired ability to minimise distractibility. A number of participants in the MS group became more distractible as the tasks and sessions progressed. It was notable how these participants appeared to have their attention captured by environmental stimuli such as items in the testing room and an earlier conversation with the researcher. When distracted, they were slow to return to the n-back task and may have produced more errors.

The MS group also performed significantly worse than the control group on the 1-back task. The 1-back also requires sustained attention but has an additional working memory

component. Given the similarity of the task demands between the 0-back and the 1-back, it is possible that the poorer performance of the MS group can be explained by the sustained attention difficulties described above. It is also of note that the 1-back has been shown to place greater demands on working memory than the 0-back. Braver et al (1997) demonstrated that on the n-back task, there is a 'dose-responsive curve' that describes the relationship between working memory load on the n-back and activity in circumscribed areas of the prefrontal cortex. Specifically, they demonstrated that on the 1-back there was more activity bilaterally in the mid-dorsolateral prefrontal cortex when compared to the 0-back. Further increases in working memory load led to more activity in the prefrontal cortex. In the present study, the difficulties of the MS group on the 1-back are consistent with hypothesis that working memory is often impaired in MS (e.g. D'Esposito et al., 1996).

In this study, the effect of different n-back conditions on cognitive fatigue was of particular interest. It was hypothesised that increased working memory load on the n-back would make cognitive fatigue more likely. However, as described above, there was no clear evidence that the 1-back task was more fatiguing than the 0-back.

No other studies into cognitive fatigue in MS have systematically varied the demands of the continuous cognitive task intended to induce fatigue as in the present study. At the time of writing, the only other study to investigate performance on the n-back in a MS sample was by Lengenfelder et al (2003). Using the n-back task, they attempted to identify specific working memory impairments in a sample of people with MS that included participants with and without cognitive impairment. The MS groups were compared to a healthy control group on the auditory n-back. The auditory n-back was similar to the procedure in this study, but the

letters were presented auditorily rather than visually, on the computer screen. Therefore, the auditory n-back was hypothesised to place demands on the phonological loop component of Baddeley's (1986) working memory model. They compared 0-back, 1-back, 2-back and 3-back versions of the auditory n-back. The findings indicated that on the 0-back and 1-back, there were no group differences between the cognitively impaired MS group and the other groups. However, when there was an increased central executive involvement, such as on the 2-back, group differences were found.

In the present study, group differences were found on the 0-back and 1-back, but the 1-back appeared no more likely to cause cognitive fatigue than the 0-back. These group differences (RT and accuracy on the 0-back and 1-back) were not found in the Lengenfelder (2003) study. This finding illustrates the severity of the cognitive impairment in the MS sample used in the present study. In addition, the task demands of an auditory n-back paradigm used by Lengenfelder (2003) are likely to be functionally different from a visual n-back paradigm used in this study. Within the Baddeley (1986) model, the visual n-back used in the present study would be expected to involve the visuo-spatial sketchpad instead of, or together with the phonological loop. Despite these differences in the two studies, a consistent finding is that increasing working memory demands from the 0-back to the 1-back has relatively little effect on cognitive performance.

Given the hypothesis that increased working memory load may lead to more fatigue, it would be interesting to examine the performance of an MS sample during the 2-back task. Also, as there appears to be a linear relationship between n-back load and dorsolateral prefrontal cortex

activity (Braver et al., 1997), a study involving the 2-back task may also further elucidate the link between cognitive fatigue and cortical activity.

4.4 Self reported fatigue and depression

4.41 The Fatigue Rating Scale (FRS)

The FRS was used to describe changes in subjective fatigue across the testing sessions. The MS group reported a greater increase in their level of fatigue across both testing sessions compared to the control group. This pattern was significant on the 1-back but not the 0-back, a finding that may have occurred because the MS group experienced the 1-back as more fatiguing than the 0-back. It is also possible that there was an expectation that the 1-back would lead to greater fatigue, although if this were the case we may not have expected to see a difference between the groups.

Increases in subjective fatigue during a neuropsychological testing session, such as the present study, have been reported elsewhere. Johnson et al (1997) noted that over the course of a demanding neuropsychological testing session, people with MS reported a significantly greater increase in their level of subjective fatigue compared to people with depression and a group with Chronic Fatigue Syndrome.

4.42 The Fatigue Severity Scale (FSS)

The FSS was used to obtain a global estimate of fatigue severity. The findings indicated that the MS sample experienced more symptoms of fatigue than the control group. This is consistent with existing evidence, which suggests that fatigue is a symptom of MS (e.g. Krupp et al., 1989).

It is also possible that the higher FSS scores in the MS group may have been due to additional factors that influenced the symptoms of fatigue. For example, the elevated FSS scores of the MS group may have been due to iatrogenic factors. Many participants in the MS sample were taking prescribed medication, which may have caused fatigue as a side effect. In addition, the significant association between depression and FSS scores in the present study suggests that depressive symptomatology may account for the group differences. This issue will be explored in more detail in section 4.44.

4.43 The association between subjective fatigue and cognitive fatigue

The present study found that there was poor association between subjective measures of fatigue and cognitive fatigue. This finding is consistent with the existing literature on fatigue and MS. A number of studies (Johnson et al., 1997; Parmenter et al., 2003; Schwid et al., 2000) have noted that there are poor correlations between subjective ratings of fatigue and demonstrable changes in cognitive performance. However, the mechanisms of this dissociation are poorly understood.

A possible explanation for the poor association between self-reported and cognitive fatigue is that people with MS experience subjective fatigue across a testing session but compensate by increasing their effort on the task. This hypothesis is consistent with the observation that compared to the control group, the participants with MS reported a significantly greater increase in their level of subjective fatigue on the 1-back task, despite no significant differences in cognitive performance across the testing session. The 1-back task may have been experienced as fatiguing but increased effort may have enabled the MS group to maintain

their cognitive performance across the session. It would be of interest to examine the effects of increasing the task demands on perceived effort and the ability to sustain cognitive performance. A measure such as the Borg Scale (Borg, 1970) could be used to assess perceived effort.

There are also parallels to the limited association between subjective and cognitive fatigue in other clinical contexts, such as the association between subjective and objective memory complaints. Many people present themselves to neuropsychology services with subjective memory complaints, often concerned that there is an organic cause for their perceived difficulties. However, studies have shown that in normal and also in brain-damaged populations the correlation between subjective and objective memory is poor (Scogin, 1985). Typically, people overestimate the severity of their memory difficulties although the opposite pattern has also been noted (Sawrie et al., 1999. It has been suggested that the poor correlation between subjective and objective memory complaints may be due to the influence of factors such as depression (Bolla et al., 1991) or internalised stereotypes about memory decline and ageing (Levy and Langer, 1994). However, Hertzog et al (2000) suggest that the self-report of memory problems is accurate when the measures directly relate to specific memory-related behaviours in everyday contexts. Their 'behavioural specificity' hypothesis proposes that, "Ask and ye shall receive. But, remember to be specific in asking what you want to know".

The literature on subjective and objective memory complaints provides a number of potential explanations for the findings of the present study. It is possible that the poor correlation between subjective and cognitive fatigue may have been due to the effects of factors such as depression or beliefs about fatigue in MS. In the present study there was a significant

correlation between symptoms of depression and subjective fatigue on the FSS but HADS scores were not associated with cognitive fatigue (see section 4.4 for a more detailed discussion of the relationship between depression and fatigue). It is also possible that beliefs about the effects of fatigue in MS may have led to an overestimation of subjective fatigue. As fatigue is common symptom of MS, participants in this study may have believed that they were fatigued when there was no objective evidence to support their subjective experiences. However, an alternative explanation derives from the behavioural specificity hypothesis of Hertzog et al (2000). In the present study, it is hypothesised that the questions used to assess subjective fatigue (FRS and FSS) were poorly related to a behavioural context similar to the n-back task. The n-back task requires sustained attention, but neither the FRS nor the FSS ask about this cognitive function in an everyday context.

An alternative measure of subjective fatigue, with potentially greater behavioural specificity, is the Fatigue Impact Scale (FIS) (Fisk et al., 1994). The FIS distinguishes between cognitive, psychosocial and physical manifestations of fatigue. It contains 40 items, ten of which ask about the severity and impact of cognitive fatigue. One item in the cognitive domain is, "because of my fatigue I have trouble paying attention for a long time". This item would appear to have good face validity as a measure of fatigue during a sustained attention task. The FIS was not used in the present study as it is rather lengthy. However, it is argued that the presence of a subscale relating to cognitive fatigue suggests that the FIS may be a particularly useful self-report measure to compare against objective indices of cognitive fatigue in future studies. Therefore, it is hypothesised that the lack of association between subjective and cognitive fatigue in the present study and previous studies (Johnson et al., 1997; Schwid et al., 2000) may have been a product of the behavioural specificity of the fatigue rating scales used.

Iriarte et al (2000), who used the Fatigue Descriptive Scale (FDS) (Iriarte and de Castro, 1994) to evaluate fatigue in a sample of 155 people with MS, also provide support for this hypothesis. The FDS enables the classification of fatigue into three forms, asthenia (fatigue at rest), fatigability (fatigue with exercise) and worsening of symptoms. The study found that asthenia and fatigability could be distinguished and appeared to have different origins. Asthenia was strongly associated with immune system activation, while pyramidal tract involvement was more closely associated with fatigability. Therefore they suggest that it is not realistic to deal with fatigue as one symptom. In the present study the FSS was used as a measure of the symptom fatigue, whilst the change in performance over time on the n-back task was used as a measure of fatigue with exercise (fatigability). The finding that there was no significant association between the symptoms of fatigue (FSS) and fatigability (decline in performance on the n-back) is consistent with the findings of Iriarte et al (2000). In future studies of cognitive fatigue it may be useful to examine the relationship between the fatigability items on the FDS and cognitive decline. This may be of particular interest given the association between fatigability and pyramidal tract involvement and the current research into the neurophysiological correlates of fatigue in MS (e.g. Chaudhuri and Behan, 2000; Roelke et al., 1997).

4.44 Depression and fatigue

The results of this study indicate that the MS group had higher ratings of depression on the HADS compared to a healthy control group. In addition, the ratings of fatigue on the FSS were significantly correlated with HADS depression scores. However, the severity of depression did not appear to be associated with cognitive fatigue.

The present study supports the existing literature, which indicates that there are much higher rates of depression in MS than in the general population (Kessler et al., 1994). The literature on the relationship between fatigue and depression in MS is equivocal. Some studies have reported a positive correlation between fatigue severity and depression (e.g. Fisk et al., 1994), whilst others have not (e.g. Giovannoni et al., 2001). The present study found that there was a positive correlation between symptoms of depression on the HADS and scores on the FSS. This finding is supported by studies by Bakshi et al (2000) and Kroencke et al (2000) who both found that fatigue scores on the FSS were associated with depression in an MS sample. However, for the MS group there was no association between any of the objective indices of fatigue and HADS depression scores. This finding is consistent with the results of Johnson et al (1997) who failed to find a significant association between depression and overall performance decrement on the PASAT.

It is hypothesised that differences in existing research findings may be due to the measures used to assess depression and fatigue. Many measures of depression also contain items that relate to fatigue. For example, the BDI (Beck and Steer, 1987), which was used in the study by Bakshi et al (2000), contains one item that specifically asks about 'tiredness' (question 17) and three other items that appear related to fatigue (question 13, 15, and 16). Therefore, the HADS was selected for the present study as it does not contain items that directly relate to symptoms of fatigue.

Bakshi et al (2000) suggest that the relationship between depression and fatigue on the FSS may be due to common underlying mechanisms secondary to the MS disease process. They

hypothesise that MS depression and MS fatigue may be related to white matter lesions interrupting limbic and frontal systems. However, Bakshi et al (2000) fail to distinguish fatigue on the FSS from the signs of fatigue such as fatigability. The findings of the present study and the results of Johnson et al (1997) suggest that there is no association between depression and objective cognitive fatigue.

In summary, the association between depression and FSS scores has equivocal support from the existing literature on fatigue and depression in MS. Bakshi et al (2000) suggest that the association may be due to a similar underlying mechanism. However, is also possible that the association between the two symptoms is in fact a consequence of imprecise measurement tools. Future research is necessary to further examine the relationship between fatigue and depression.

4.5 Limitations of the research study and suggestions for future studies

4.51 Sample size

It is of note that the present study involved a small sample size. When the sample size is small and statistical power is not high there is an increased risk of missing an effect that is present (Type II error). Therefore, in this study there was increased possibility of missing any effects. For example, the null findings regarding cognitive fatigue on the n-back task across a session may represent a problem with statistical power. However, the differences in performance between the two groups were large for each of the three n-back blocks on each testing occasion, and any deterioration over time for the MS group appeared relatively small on the basis of mean scores, suggesting only a subtle effect. A recent statistical power analysis of

clinical neuropsychology research by Bezeau and Graves (2001) concluded that although sample sizes are often smaller than those recommended by Cohen (1992), effect sizes are generally larger than those found in experimental psychology and power is generally adequate.

4.52 Level of disability in the MS group

The present study investigated a sample of individuals with advanced chronic progressive MS. This population are not normally represented in the MS literature (Kenealy et al., 1999) but were hypothesised to be more prone to severe fatigue. Kroenke et al (2000) suggest that level of disability is a significant predictor of self-reported fatigue. Also, Mainero et al (1999) propose that fatigue is more likely in samples of people with progressive MS compared to samples with a relapsing-remitting course. However, as mentioned above it was very difficult to recruit adequate numbers of people with advanced MS. There were a number of other difficulties faced when studying a group of people with such advanced MS that may be important for future studies to consider.

Two members of the MS group in the present study had upper limb spasticity that was severe enough to prevent them from pressing the response buttons. As they were able to provide verbal responses the problem was overcome by instructing them to say "yes" or "no" and the researcher pressed the keys on their behalf. To ensure matching between the groups, the same procedure was carried out with two of the control group. However, it is possible that providing verbal responses to the stimuli on the n-back was a functionally different task to that performed by the rest of the two groups, potentially more or less fatiguing than providing motor responses. This problem could be overcome in future studies of people by providing a different response method (e.g. a voice recognition system).

An additional difficulty faced when investigating a group of people with severe neurological difficulties is finding an adequate matching sample. The control group were matched with the MS group according to age, gender, estimated verbal IQ and years of education. However, it is of note that none of the MS group were in full time employment and nine of the group were hospital in-patients. In addition, many of the MS group were taking at least one prescribed medication which may affect cognitive function and cause drowsiness. It would be helpful for future studies to match the MS group with another hospital sample without cognitive impairment or significant fatigue, such as people with spinal cord injuries.

4.53 Fatigue Rating Scales

The present study used two fatigue rating-scales to describe subjective fatigue, the FSS and the FRS. The use of the FSS and simple self-report scales similar to the FRS is well documented in the research literature on fatigue in MS (Krupp, 1997). However, in the present study the FRS and FSS were not associated with objective signs of fatigue. In section 4.43 it was hypothesized that this may be because the measures may lack behavioural specificity, or that they were insensitive to cognitive effort. There were also other aspects of both measures that suggest that future studies into fatigue and cognitive function in advanced MS may wish to consider using alternative scales.

The FSS scores of the sample used in the present study are lower than the mean score in the standardisation sample reported by Krupp et al (1989). It is argued that this finding is not necessarily due to the MS sample in this study experiencing less fatigue than other samples of people with MS, but rather that the FSS contains a number of items that are less appropriate

for the level of physical disability of the sample tested. For example, items seven and nine (see appendix 6.1) ask if fatigue interferes with certain duties and responsibilities, or with work, family or social life. A number of the respondents in the MS group said that because of the advanced symptoms of MS (i.e. physical disability) they no longer had any duties or responsibilities. Furthermore, none of the sample were in work, and many of the participants indicated that their social lives were restricted by their physical disability rather than by fatigue. Schwid et al (2002) support this criticism of the FSS. They argue that items five, seven and nine on the FSS are particularly problematic for patients with confounding reasons for such consequences, such as motor and cognitive impairment from MS.

The FRS was developed specifically for this study, and the use of simple rating-scales similar to the FRS is well documented in the research on fatigue in MS (Johnson et al., 1997; Krupp and Elkins, 2000; Paul et al., 1998a; Schwid et al., 2000). However, in section 4.43 it is argued that the FRS may be insensitive to the actual subjective changes that occur across a neuropsychological testing session (e.g. finding it hard to concentrate). It is argued that future studies should ask questions that are closely related to the tasks intended to induce fatigue. It may also be helpful for future research to also participants about their perceived effort.

The lack of association between the various measures of fatigue (n-back, FRS and FSS) suggests that fatigue is not a single, clearly recognisable symptom of MS. Instead, the findings of this study are in agreement with Iriarte's (2002) recent suggestion that if all types of fatigue are grouped as one symptom, then it loses specificity and research on the pathogenesis or treatment will be inaccurate. Schwid et al (2002) argue that the questionable validity of existing methods of measuring fatigue have impeded research on the mechanisms and

therapeutics of fatigue in MS. They propose that generally accepted conclusions about the incidence and correlates of fatigue in MS that are based on self-report measures deserve reappraisal. The present study provides tentative evidence to suggest that the change in performance over time on a sustained attention task (0-back) may be a useful measure of cognitive fatigue. However, the duration of the task and its cognitive demands are still in need of more detailed investigation. Giovannoni (2002) has argued that there is a pressing need for the development of more specific and well validated measures of the signs and symptoms of fatigue.

4.54 The N-Back task

The n-back task was selected for the present study as it allowed incremental changes to be made in working memory load. In addition, the literature on brain activity at different levels of n-back (Braver et al., 1997) made it possible to link performance on the task to dorsolateral prefrontal lobe function. The link between the cognitive task and specific brain areas was important given the hypothesis of Roelke et al (1997) that fatigue in MS may be due to disruptions in dorsolateral – prefrontal circuits (Alexander et al., 1990).

During the design phase, the n-back task was adapted for the MS group. Large response keys were developed to attempt to accommodate upper limb difficulties. The stimuli were unpaced as many people with MS find it difficult when stimuli presentation is delivered at a fast pace (Litvan et al., 1988). In addition, the n-back was presented with n set at zero and one as it was hypothesized that the level of cognitive impairment in the MS group may have made the 2-back too demanding a task.

However, the decision to make the n-back task self-paced meant that many of the MS group were slower than the control group. Consequently the MS group took longer to complete the task. If duration on a task is a critical factor in leading to fatigue, then the two groups were unevenly matched. This problem could have been overcome by pacing the stimuli presentation at a rate that has been shown to be acceptable in previous studies. For example, Litvan et al (1988) found that on the PASAT the performance of a group of participants with MS was comparable to a control group when stimuli were presented at two-second intervals but not at 1.6-second intervals.

It is argued that future studies of cognitive fatigue in MS should examine the effects of tasks in which working memory load can be varied. For example, comparing the fatiguing effects of the 0-back and 1-back to the 2-back task would be of interest in relation to the role of the pre-frontal cortex in fatigue (Roelke et al., 1997). However, the study by Roelke et al (1997) examined the relationship between the symptoms of fatigue (FSS) with cortical activity. There is no existing evidence to link the signs of fatigue, specifically fatigability (Iriarte et al., 2000) with cortical structure or activity. It is possible that specific cognitive tasks lead to specific metabolic changes, which may then lead to cognitive fatigue. By comparing the effects of working memory load on prefrontal cortex activity and fatigue, using imaging techniques such as PET or fMRI, future studies may clarify the aetiology of cognitive fatigue in people with MS. This may in turn have a significant influence on symptom management and treatment.

4.55 The HADS

The HADS was selected as a measure of depression in the present study for a number of reasons. It is brief and easy to administer, well validated on hospital samples (Zigmond and

Snaith, 1983) and has been used in a number of other studies with people with MS (e.g. Foong et al., 1997; Giovannoni et al., 2002), including advanced MS (Kenealy et al., 1999). Also, the HADS does not contain items directly relating to fatigue, unlike other measures of depression such as the BDI (Beck and Steer, 1987). However, two items on the HADS were endorsed by some of the MS sample, who felt that the items related more to their physical disability than their mood. The items in question were, "I feel as if I am slowed down", and, "I can sit at ease and feel relaxed". Some members of the MS sample said that they felt slowed down because they were in a wheelchair and had additional motor slowing due to MS. In addition, several participants in the MS group said that they could not sit at ease because of their wheelchair seating system. In future studies it may be appropriate to either remove these two items from the HADS, compare the MS sample with people with similar physical disabilities, or to use an alternative measure of depression. A measure that is commonly used in MS samples (e.g. Krupp and Elkins, 2000) is the Centre for Epidemiological Studies Depression scale.

4.6 Clinical implications

The present study failed to support the hypothesis that people with MS show evidence of a decline in cognitive performance across a testing session, although in the MS group there was a trend towards poorer n-back accuracy across the session. The inconclusive findings of this and other studies (Johnson et al., 1997; Krupp and Elkins, 2000; and Paul et al., 1998a) suggest that there may be significant individual differences in the effects of cognitive fatigue across a single testing session. This may have important implications for clinicians who are conducting neuropsychological assessments with people with MS. It is suggested that they should be aware of the possible effects of cognitive fatigue. However, given the limited association between subjective and cognitive fatigue, it is argued that assessment should

incorporate multiple sources of information to determine if fatigue is affecting cognitive performance. Clinicians should be sensitive to the qualitative aspects of test performance, such as increased distractibility as the session progresses.

One of the most striking findings in the present study was the poor association between subjective and cognitive fatigue. This has also been reported in a number of other studies on fatigue in MS (Johnson et al., 1997; Parmenter et al., 2003; Schwid et al., 2000). It has been suggested that people with MS overestimate the impact of subjective fatigue and restrict their activities for fear of the consequences of mental or physical exhaustion. Johnson et al (1997) propose that people with MS should be encouraged to continue to accept mental challenges rather than risk developing avoidant behaviours. However, it is also possible that people with MS experience subjective fatigue and compensate by increasing effort on the task. Alternatively, existing measures of fatigue may be poorly related to the subjective experience of fatigue and lack behavioural specificity. These different hypotheses have significant clinical implications and could be explored in future research.

If an individual with MS overestimates their level of fatigue it would then seem sensible to follow the advice of Johnson et al (1997) and encourage the person with subjective fatigue to approach challenges rather than avoid them. The evidence base on behavioural therapy for fatigue in MS would support this conjecture (Di Fabio et al., 1998).

Where someone is compensating for the effects of cognitive fatigue by increasing their effort, clinical assessment should investigate the situations when increased effort is not sufficient to maintain task performance. An individual with MS may be able to sustain attention when the

task demands are minimal by increasing effort, but when additional demands are placed on them, task performance may decline. In this situation, self-management strategies such as pacing may be particularly helpful in reducing the impact of cognitive fatigue. The person with MS could be encouraged to monitor their level of fatigue and take regular breaks when they rate themselves with higher levels of fatigue or reduced attention (Sohlberg and Mateer, 2001).

In addition, there are significant clinical implications from the hypothesis that existing scales of fatigue may not adequately measure the subjective experiences of cognitive fatigue. It is argued that when assessing fatigue clinicians should be aware of the limitations of rating scales such as the FSS. Krupp (1997) emphasises the importance of a thorough interview and medical investigations where appropriate. It would seem sensible to combine methods in the clinical assessment of fatigue. Clinicians should also be aware of the advice of Hertzog et al (2000) and be specific when asking about what they want to know. For example, asking an individual if they are easily fatigued may not be as informative as a question about specific symptoms of fatigue in a particular context (e.g. concentration difficulties at work).

This study found a significant association between depression and subjective fatigue. The literature on fatigue and depression has put forward two main hypotheses to account for this finding, both of which have important treatment implications. The first hypothesis is that there is a similar underlying mechanism for both depression and fatigue in MS (Bakshi et al., 2000). The second hypothesis contends that the measurement of fatigue may be confounded in measures of depression. If there are similar mechanisms underlying fatigue and depression in MS then we may expect medication for one symptom to also help the other symptom.

Although amantadine (Krupp et al., 1995) has been found to reduce symptoms of fatigue, it appears to have little effect on depression in MS. It is of significant clinical interest to investigate the therapeutic effects of anti-depressants in fatigue. Reingold (1990) suggests that anti-depressants are a useful first-line treatment when depression and fatigue are co-morbid. However the effectiveness of anti-depressants with fatigue without co-morbid depression has yet to be demonstrated. In the meantime it is argued that clinicians treating depression or fatigue in MS (psychological and pharmacological methods) should be mindful of the effect their intervention has on the other condition. For example, behavioural therapy may be useful for fatigue (Comi et al., 2001) and depression (Lewinsohn, 1974). However, the assessment and treatment of fatigue and depression in MS is complicated by the measurement difficulties highlighted above. For instance, a number of measures of depression include items that relate to fatigue (e.g. the BDI). So, when assessing depression in MS, clinicians should be aware of the potential limitations of questionnaires with items that ask about fatigue. Conversely, when assessing fatigue, clinicians should be aware of the potential fatiguing effects of depression. The lack of adequate measures suggests that clinical assessment should use multiple methods such as questionnaire, structured interview and wherever appropriate medical investigations.

4.7 Conclusions

This study investigated the relationship between fatigue and cognitive function in MS. The MS group in the present study were in the advanced stages of the disease and were severely cognitively impaired relative to a matched control group. This population is poorly represented in the existing literature on cognitive function and fatigue in MS.

The results of this study found equivocal evidence to support the notion that people with MS show objective signs of cognitive fatigue during a continuous cognitive task or across a neuropsychological testing session. However, people with MS did report greater subjective changes in their level of fatigue across a testing session compared to the control group, particularly when the task had a working memory load. In addition, ratings of the symptoms of fatigue were associated with depression, and there was a poor association between subjective and objective indices of fatigue.

These findings indicate that across a testing session, people with MS may feel fatigued, although this does not have an observable effect on cognitive performance. It is therefore possible that people with MS overestimate their level of fatigue. They may believe that they are exhausted whilst there is no objective evidence for their subjective experiences. This may be due to the effects of depression or beliefs about fatigue in MS. An alternative hypothesis is that existing measures of subjective fatigue have limited sensitivity in detecting the changes that occur when people with MS become fatigued. This suggests that there is a need for improved methods of detecting the symptoms and signs of fatigue in MS. However, it is also possible that when engaged in a neuropsychological testing session, individuals with MS experience subjective fatigue, but compensate for their difficulty by increasing effort. This effect may lead to a presentation of high subjective fatigue but low objective cognitive fatigue.

The association between depression and subjective fatigue suggests that the two symptoms may have similar mechanisms or that existing measures are not sensitive to differences between them. Both of these hypotheses have significant research and clinical implications.

The limited correspondence between changes in cognitive performance over time and self-reported fatigue suggests that when assessing fatigue in MS, clinicians should consider both subjective and objective evidence. This study also emphasises the need for further research into the effects of depression and specific cognitive tasks on subjective and cognitive fatigue in MS. It is argued that improved methods of identifying specific precipitants and components of fatigue in MS may facilitate the development of improved treatment methods. This is especially important given the prevalence and disabling effects of fatigue in MS.

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6.0 Appendices

Appendix 6.1: The Fatigue Severity Scale

The Fatigue Severity Scale

The subject is read each statement and asked to choose a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

During the past week, I have found that:	**Score**						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Appendix 6.2: The Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS)

- The EDSS is a classification scheme (Rating Scale) that insures all participants in clinical trials are in the same class, type, or phase of MS.
- It is also used to follow the progression of Multiple Sclerosis disability and evaluate treatment results, for similar groupings of people. The Functional System (FS) scale is incorporated within its overall framework.

0.0 - Normal Neurological Exam
1.0 - No disability, minimal signs on 1 Functional System (FS)
1.5 - No disability minimal signs on 2 of 7 FS
2.0 - Minimal disability in 1 of 7 FS
2.5 - Minimal disability in 2 FS
3.0 - Moderate disability in 1 FS; or mild disability in 3 - 4 FS, though fully ambulatory
3.5 - Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0 - Fully ambulatory without aid, up and about 12hrs a day despite relatively severe disability. Able to walk without aid 500 meters
4.5 - Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
5.0 - Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5 - Ambulatory for 100 meters, disability precludes full daily activities
6.0 - Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5 - Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
7.0 - Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5 - Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0 - Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
8.5 - Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
9.0 - Helpless bed patient, can communicate and eat
9.5 - Unable to communicate effectively or eat/swallow
10.0 – Death

Functional Systems

Pyramidal Functions
Cerebellar Functions
Brain Stem Functions
Sensory Functions
Bowel and Bladder Functions
Visual Functions
Cerebral (or Mental) Functions
Other Functions

Appendix 6.3: The Health Screening Interview

HEALTH SCREENING INTERVIEW

Name: _____
Address: _____
_____
_____
Phone number: _____
Sex? Male / Female Date of birth: _____ Right or left handed? _____
Is your first language English? Yes / No
If not, how fluent are you in English? _____
Do you have difficulty understanding conversations because of your hearing? Yes / No
Do you have trouble with your vision that prevents you from reading ordinary print, even with glasses on? Yes / No
Have you ever been diagnosed as having dyslexia? Yes / No
What type of school did you attend? _____
Did you have special schooling needs? _____
If yes, please give details _____
What age did you leave school? _____
What qualifications did you obtain at school? _____
_____
What qualifications, if any, did you obtain after leaving school? _____
_____
How long was the course of study? _____
Full time or part time? _____
What are the main types of work you have done (if any)? _____
_____
_____
Have you ever had a serious illness? Yes / No
If yes, please give details _____
_____
Have you ever had a serious accident? Yes / No
If yes, please give details _____
_____
Have you ever been unconscious? Yes / No
If yes, how many times have you been unconscious? _____
For how long each time? _____
Why? _____
_____
Have you ever had an operation under general anaesthetic? Yes / No
If yes, please give details _____
_____
Have you ever had: Meningitis Yes / No Encephalitis Yes / No
Tuberculosis Yes / No Diabetes Yes / No
Epilepsy / seizures / fits Yes / No
Have you ever had any other illness, disease, or injury that affected your brain? Yes / No
If yes, please give details _____
_____
Are you currently taking any prescribed medication? Yes / No
If yes, please give details _____
_____
How much alcohol do you drink each week? _____
Have you ever received treatment for mental or emotional problems? Yes / No
If yes, please give details _____
_____

Please return this form to Mr. Alastair Bailey, Department of Clinical Psychology, Royal Hospital for Neuro-disability, West Hill, Putney, SW15 3SW

Appendix 6.4: The Fatigue Rating Scale

Please choose a number from 0 to 8, depending on how tired / fatigued you feel right now

0	1	2	3	4	5	6	7	8
Not at all				Moderately				Extremely – the most tired / fatigued I have ever been

Appendix 6.5: Ethical approval letter (Royal Hospital for Neuro-disability Medical Research Advisory Committee)

Royal Hospital for
Neuro-disability

West Hill Putney London SW15 3SW
Switchboard 020 8780 4500
General Fax 020 8780 4501 Ext: 5141
Safe Haven Fax 020 8780 4511
Email info@neuro-disability.org.uk
Website www.neuro-disability.org.uk
Research Fax: 020 8780 4507

11th July 2002

Alastair Bailey
Trainee Clinical Psychologist
Department of Clinical Health Psychology
University College London
Gower Street
London WC1E 6BT

Dear Alastair

Title: Fatigue and Cognition Function in Advance Multiple Sclerosis (RHN/02/2)
Investigator(s): A. Bailey, Professor JG Beaumont, Dr S Channon

Thank you for submitting your revised proposal, which I am pleased to inform you has been approved by the Medical and Research Advisory Committee. The proposal can now be submitted to Riverside Research Ethics Committee and also to any funding body to seek support for the project.

Congratulations on your success and I look forward to watching the progress of the study.

Kind regards

Yours sincerely

Professor C Kennard
Chairman of the MRAC

Appendix 6.6: Ethical approval letter (Riverside Research Ethics Committee)

RIVERSIDE RESEARCH ETHICS COMMITTEE

Pharmacy Offices Lower Ground Floor
CHELSEA WESTMINSTER HOSPITAL
369 Fulham Road London SW10 9NH
Tel: 020 8846 6855 Fax: 020 8846 6860
Email: riverside.ethics@chelwest.nhs.uk

Thursday, September 19, 2002

Mr Alistair Bailey

Department of Clinical Health Psychology
University College London
Gower Street
London WC1E 6BT

Dear Mr Bailey,

RREC 3171 - Fatigue and Cognitive Function in Advanced Multiple Sclerosis
- -

Thank you for your application. The Chairman of the Riverside Research Ethics Committee, Dr Charles Mackworth-Young, has asked me to write to inform you that the above study has now been approved.

Please note the following conditions which form part of this approval:

[1] Your study has been assigned a unique reference number. This number must be quoted in any correspondence with the Committee concerning this study.

[2] This approval is for a limited period only. A letter from the principal investigator will be required in order to extend this period of approval.

[3] Any changes to the protocol or investigator team must be notified to the Committee. Such changes may not be implemented without the Committee's approval.

[4] Any revised study documents submitted must be given a new version number/date.

[5] For projects with an expected duration of more than one year, an annual report from the principal investigator will be required. This will enable the Committee to maintain a full record of research.

[6] The Committee must be advised when a project is concluded and should be sent one copy of any publication arising from your study, or a summary if there is to be no publication.

[7] The Committee should be notified immediately of any serious adverse events that are believed to be study drug related or if the entire study is terminated prematurely.

[8] Please note that research conducted on NHS Trust premises must receive the approval of the relevant Research and Development department. Approval by the Committee for your project does not remove your responsibility to obtain this approval.

[9] You are responsible for consulting with colleagues and/or other groups who may be involved or affected by the research, e.g., extra work for laboratories. Approval by the Committee for your project does not remove your responsibility to negotiate such factors with your colleagues.

[10] You must ensure that nursing and other staff are made aware that research in progress on patients with whom they are concerned has been approved by the Committee.

[11] Pharmacy must be told about any drugs and all drug trials, and must be given the responsibility of receiving and dispensing any trial drug.

[12] All documents relating to the study, including Consent Forms for each patient (if applicable), must be stored securely and in such a way that they are readily identifiable and accessible. The Committee will be conducting random checks on the conduct of studies, and these will include inspection of documents.

May I take this opportunity to wish you well in your research. If any doubts or problems of an unexpected nature arise, please feel free to contact me at any time.

Yours sincerely

Miss Katherine Bolton
Administrator
Riverside Research Ethics Committee
(On behalf of the Chairman, Dr C G Mackworth-Young MA MD FRCP)

The Riverside Research Ethics Committee has approved the following:

RREC 3171 - Fatigue and Cognitive Function in Advanced Multiple Sclerosis - -
Mr A Bailey, Professor J Graham, Dr S Channon, Dr A Sayer
This study was considered by the full Committee.
This study was first approved on the: 19/09/2002.
Approval for this study expires on the: 19/09/2003.

Study History:

	Comments
Application Form (16/09/02)	Approved 19/09/02
Patient Volunteer Information Sheet (Version 2: 16/09/02)	
Patient Volunteer Consent Form (Version 2: 16/09/02)	
Non-Patient Volunteer Information Sheet (undated)	
Non-Patient Volunteer Consent Form (undated)	
Recruitment Poster (undated)	
HADS	
Health Screening Interview	
Expanded Disability Status Scale	
Fatigue Severity Scale	

Appendix 6.7: Information sheet (MS group)

Resident volunteer

Department of Clinical Psychology
Royal Hospital for Neuro-disability, West Hill, Putney, London
SW15 3SW

Mr. Alastair Bailey
Lead Clinician
020 8 780 4500 ext. 5134
abailey@rhn.org.uk

Professor J Graham Beaumont
Project supervisor
020 8 780 4500 ext. 5013
gbeaumont@rhn.org.uk

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INFORMATION SHEET

ATTENTION AND FATIGUE IN MS STUDY

You are being invited to take part in a research study investigating attention and fatigue in people with Multiple Sclerosis (MS). Before you begin it is important to understand why the research is being done and what it will involve. Please take the time to read the following information carefully, and ask us 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 proposal was reviewed by the Riverside Research Ethics Committee.

What is the purpose of the study?

We are investigating the way that mental tiredness / fatigue affects the ability to pay attention and concentrate in people with MS. This has relevance for many people with MS, who report fatigue as a major

symptom of the disease. We also study people who do not have MS, so that we can compare the findings. This will not have an immediate impact on individuals, 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 various details of your medical condition, such as the medication you take. This will only be seen by members of the research team.

What will the study involve?

You will be asked to carry out a series of tasks involving attention, concentration, and problem solving. Some of these are presented on a computer screen and others will be pen and paper tests or puzzles. Some of the answers including giving spoken answers, and others involve pressing keys on the 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 questions about your educational, occupational and medical history, and any difficulties you may be having.

The testing will be arranged to suit your convenience. The date of the appointments, and the location will be arranged by Mr. Bailey.

You will be asked to complete the testing over two sessions that are separated by at least a week. Each testing session will take about one hour.

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 decide to take part.

Will I experience any discomfort or distress from the study?

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

After each testing session, you may feel tired. Therefore, you may want to plan an undemanding afternoon after each of the sessions.

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

You do not have to take part in the study if you do not want to do so. If you decide to take part, you are free to 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 more information?

If you want more information, please contact Mr. Alastair Bailey (020 8 780 4500 ext. 5134), or Professor Graham Beaumont (020 8 780 4500 ext. 5013) as shown at the top of the front page.

Appendix 6.8: Information sheet (control group)

Non-patient volunteer

Department of Clinical Psychology
Royal Hospital for Neuro-disability, West Hill, Putney, London SW15 3SW

Mr. Alastair Bailey
Lead Clinician
020 8 780 4500 ext. 5134
abailey@rhn.org.uk

Professor J Graham Beaumont
Project supervisor
020 8 780 4500 ext. 5013
gbeaumont@rhn.org.uk

CONFIDENTIAL

INFORMATION SHEET

ATTENTION AND FATIGUE IN MS STUDY

You are being invited to take part in a research study investigating attention and fatigue in people with Multiple Sclerosis (MS). Before you begin it is important to understand why the research is being done and what it will involve. Please take the time to read the following information carefully, and ask us 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 proposal was reviewed by the Riverside Research Ethics Committee.

What is the purpose of the study?

We are investigating the way that mental tiredness / fatigue affects the ability to pay attention and concentrate in people with MS. This has relevance for many people with MS, who report fatigue as a major symptom of the disease. We also study people who do not have MS, so that we can compare the findings. This will not have an immediate impact on individuals, 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.

What will the study involve?

You will be asked to carry out a series of tasks involving attention, concentration, and problem solving. Some of these are presented on a computer screen and others will be pen and paper tests or puzzles. Some of the answers including giving spoken answers, and others involve pressing keys on the 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 questions about your educational, occupational and medical history, and any difficulties you may be having.

The testing will be arranged to suit your convenience. The date of the appointments, and the location will be arranged by Mr. Bailey.

You will be asked to complete the testing over two sessions that are separated by at least a week. Each testing session will take about one hour.

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 decide to take part.

Will I experience any discomfort or distress from the study?

This research does NOT involve any blood tests or other medical procedures, and you will not be given any drugs. In fact, there are no physical investigations of any kind, and you will not be asked to do anything unpleasant or painful. However, it is possible that after each testing session you may feel a little tired.

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

You do not have to take part in the 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.

What should I do if I want more information?

If you want more information, please contact Mr. Alastair Bailey (020 8 780 4500 ext. 5134), or Professor Graham Beaumont (020 8 780 4500 ext. 5013) as shown at the top of the front page.

Appendix 6.9: Consent form (MS group)

Resident volunteer

Department of Clinical Psychology
Royal Hospital for Neuro-disability, West Hill, Putney, London
SW15 3SW

Mr. Alastair Bailey
Lead Clinician
020 8 780 4500 ext. 5134
abailey@rhn.org.uk

Professor J Graham Beaumont
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020 8 780 4500 ext. 5013
gbeaumont@rhn.org.uk

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CONSENT FORM

ATTENTION AND FATIGUE IN MS STUDY

Lead clinician: Mr. Alastair Bailey

(The subject should complete the whole of this sheet himself / herself. If they are unable to write, a member of staff should complete the form under instruction from the patient and in the presence of a witness)

Delete as necessary:

Have you read (or had read to you) the information sheet about this study?
Yes/No

Have you had an opportunity to ask questions and discuss this study?
Yes/No

Have you received satisfactory answers to all your questions?
Yes/No

Have you received enough information about this study?
Yes/No

Who have you spoken to? (write name)

_____

Do you understand that participation in this study is voluntary and that you are free to withdraw from this study:

- At any time
- Without a reason for withdrawing
- Without affecting your future medical care?

Yes/No

Do you understand that your medical notes may be looked at by Mr. Bailey, and do you give permission for him to have access to your records?
Yes/No

Do you agree to take part in this study?
Yes/No

Name of volunteer: _____

Signature: _____

Date: _____

Address:

_____

_____

If the person is unable to write, but has given verbal consent to take part in this study, a witness may sign the witness section below to indicate that he / she has witnessed verbal consent.

I have witnessed the verbal consent of _____
to take part in this study:

Yes / No

Name of Witness: _____

Signature: _____

Date: _____

Name of staff member who assisted the patient in completing the form: _____

Signature: _____

Date: _____

Name of researcher: _____

Signature: _____

Date: _____

Appendix 6.10: Consent form (control group)

Non-patient volunteer

Department of Clinical Psychology
Royal Hospital for Neuro-disability, West Hill, Putney, London SW15 3SW

Mr. Alastair Bailey
Lead Clinician
020 8 780 4500 ext. 5134
abailey@rhn.org.uk

Professor J Graham Beaumont
Project supervisor
020 8 780 4500 ext. 5013
gbeaumont@rhn.org.uk

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CONSENT FORM

ATTENTION AND FATIGUE IN MS STUDY

Lead clinician: Mr. Alastair Bailey

To be completed by the volunteer:	**Delete as necessary:**
Have you read (or had read to you) the information sheet about this study?	Yes/No
Have you had an opportunity to ask questions and discuss this study?	Yes/No
Have you received satisfactory answers to all your questions?	Yes/No
Have you received enough information about this study?	Yes/No
Who have you spoken to? (write name) _____	
Do you understand that participation in this study is voluntary and that you are free to withdraw from this study:	
• At any time	
• Without a reason for withdrawing?	Yes/No
Do you agree to take part in this study?	Yes/No

Name of volunteer: _____
Signature: _____
Date: _____
Address: _____
_____

Name of researcher: _____
Signature: _____
Date: _____