Self And Relative Reported Executive Dysfunction In Multiple Sclerosis: Prevalence And Relationship With Mood And Health Status

Thesis

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Self and relative reported executive dysfunction in multiple sclerosis: prevalence and relationship with mood and health status

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ABSTRACT

Introduction
Research indicates that cognitive impairment in multiple sclerosis (MS) may occur in approximately half of cases and may have detrimental effects on an individual’s general health status and mood. This study explores the usefulness of subjective measures of cognitive impairment in enhancing our knowledge of the relationships between these variables. Of particular interest was the self-reporting of executive dysfunction, an under-researched area in MS.

Method
One hundred and forty-seven individuals with MS completed a postal questionnaire survey measuring self-reported memory impairment, executive dysfunction, mood and health status. Eighty-two of their relatives completed a postal questionnaire survey, rating the patients’ memory impairment and executive dysfunction. Comparative samples were a traumatic brain injury (TBI) population and healthy controls.

Results
The amount of executive dysfunction reported by patients was lower than in a TBI population but not significantly different from that reported by healthy controls. Relatives reported lower levels of executive dysfunction than in a TBI population but significantly higher levels than healthy controls. There was no significant difference between patient and relatives’ reports of executive dysfunction in the group overall but detailed analyses highlighted sub-groups where significant differences were found. The sample was split into individuals who over-report and under-report executive
difficulties in comparison to their relatives. Over-reporters were found to be more likely
to have relapsing-remitting MS, report higher levels of anxiety, report higher levels of
memory impairment and have lower levels of relative-reported memory impairment,
compared to under-reporters. The discrepancy score (a tendency to over-report
executive dysfunction) was also found to be a predictor of depression. Subjective
reports of cognitive impairment were not found to predict health status (measured by
social functioning and employment status). However, self-reports of executive
dysfunction were found to be the strongest predictors of depression and anxiety.

Conclusions

These results are interpreted and possible implications for theory and clinical practice
suggested. The findings highlight relationships between subjective reports of cognitive
impairment and mood and health status that have not been investigated before in MS. A
number of hypotheses are proposed for the relationship between these variables, but
clarification of these relationships is not possible in the current design. Therefore,
avenues are suggested for future research.
1. INTRODUCTION

1.1 OVERVIEW

Over the last twenty years there has been an increasing awareness that cognitive impairment has a significant prevalence in multiple sclerosis (MS). This study aims to investigate the prevalence of self-reported executive and memory difficulties in a sample of individuals with MS and to explore the relationship between these subjective reports and health status and mood. The introduction details the clinical features of MS and describes the common effects of MS, focusing specifically on cognitive impairment. It introduces the concept of executive dysfunction and reviews the literature on executive dysfunction in MS. The literature describing the relationship between cognitive impairment and other MS disease factors is discussed, and the relationship between cognitive impairment and health status and mood is also described, highlighting gaps in the current research. The paradigms used to measure cognitive impairment are critically evaluated, focusing specifically on the use of subjective measures. The rationale and aims of the study are presented and a number of hypotheses specified for testing.

1.2 MULTIPLE SCLEROSIS: THE CLINICAL PICTURE

1.2.1 Prevalence

MS is the most common cause of severe neurological disability in young adults in the UK, occurring in approximately 0.1% of the population (British Society of Rehabilitation Medicine (BSRM), 1993). MS occurs mostly in individuals aged 15-50
years old, however the average age of occurrence of first symptoms is 30 years old (Sibley, 1990). It is twice as common in females (Sibley, 1990).

1.2.2 Pathology

MS is a progressive neurological disease of the central nervous system (CNS). An immunological response is thought to lead to multi-focal attacks on axons within the CNS, leading to the destruction of myelin and the death of oligodendrocytes (myelin-producing cells). This leads to the formation of lesions (sclerotic plaques) on the axons (Mohr and Cox, 2001), which disrupt the transmission of nerve impulses. The lesions ultimately lead to axonal loss and brain atrophy. Lesions are particularly common in the brainstem, spinal cord and optic nerves, although they can be scattered throughout the white matter (Zakzanis, 2000). As a result, the effects of MS are broad ranging and the clinical presentation can be very variable.

1.2.3 Clinical course

There are four clinical courses in MS: benign, relapsing-remitting, secondary-progressive and primary-progressive. These subtypes are characterised by distinct patterns of disability over time (see Figure 1).
Figure 1: Disease courses in MS (adapted from MS-Network, 2000)

- **a) BENIGN**: Approximately 10-15% of MS cases follow a benign course (Mohr and Cox, 2001) (see Figure 1a), characterised by relatively few periods of exacerbation with complete recovery and little or no disability.
- **b) RELAPSING-REMITTING**: The most common course is relapsing-remitting (see Figure 1b), which occurs in approximately 40% of cases (MS-Network, 2000). It is characterised by unpredictable episodes of relapse followed by remission, with or without complete recovery. A relapse lasts at least 24 hours and most commonly continues for 4-12 weeks (Sibley, 1990).
- **c) SECONDARY-PROGRESSIVE**: Approximately 85% of MS cases will begin with a relapsing-remitting course (Weinshenker, 1994). However, over time, recovery from the relapse may diminish, leading to an accumulation of disability. Within 10 years of diagnosis, approximately 30-40% of relapsing-remitting cases will develop a secondary-progressive course and after 10 years, approximately 50-60% will develop a
secondary-progressive course (Weinshenker, 1994). Secondary-progressive MS (see Figure 1c) follows a similar course, except that recovery is incomplete and disability usually progresses between relapses. Because relapsing-remitting MS frequently becomes secondary-progressive, Mohr and Cox (2001) describe both subtypes together as constituting 65-70% of all cases. Finally, approximately 10-15% of MS cases are primary-progressive (see Figure 1d), characterised by disease progression from the outset, with no or rare relapses (Sibley, 1990).

1.2.4 Diagnosis

Diagnosis of MS, especially in its early stages, is problematic since it requires evidence of signs and symptoms in multiple sites within the CNS, with changes over time (Brassington and Marsh, 1998). Magnetic Resonance Imaging (MRI) is the preferred method of imaging for the diagnosis of MS, highlighting gross axonal damage. Measurement of evoked potentials may provide evidence of abnormal axonal conduction, and examination of the cerebro-spinal fluid (CSF) via lumbar puncture may reveal elevated immunoglobulin-G in the CSF. These investigations are used in addition to neurological examination to provide evidence in support of an MS diagnosis. Poser et al (1983) detail diagnostic criteria for MS, with two groups of cases (definite and probable MS) and two subgroups within these (clinically or laboratory-supported). The diagnostic criteria were recently revised and the terms simplified (McDonald et al, 2001). The recommended terms are now either “MS”, “possible MS” or “not MS”.

1 Following BPS guidelines, where references contain more than five authors they are not included in the text.
1.2.5 Aetiology

The aetiology of MS is not clearly understood. However, proposed hypotheses include a slow-acting virus, a delayed reaction to a virus, or an autoimmune problem (Sibley, 1990). There is evidence for a genetic component, with first-degree relatives being 6-8 times more at risk than the general population and also evidence for the role for environmental factors, with MS prevalence rates being significantly lower near the equator (Thompson, 1996).

1.3 THE CONSEQUENCES OF MULTIPLE SCLEROSIS

Although there is considerable heterogeneity between individuals, the BSRM (1993) report that individuals with MS typically experience multiple severe physical, sensory, cognitive and emotional problems.

1.3.1 Physical effects

The BSRM state that 70% experience problems with loss of limb function and sensation; 35% experience problems with bladder or bowel functioning and 70% experience visual disturbance. Fatigue is also common, being reported in 90% of individuals with MS (Krupp, Alvarez, LaRocca, and Scheinberg, 1988). Other common symptoms include sexual dysfunction, loss of balance and pain (Mohr and Cox, 2001).

1.3.2 Psychological effects

"Having MS means living with uncertainty and adapting to changing situations" (MS Society, 2000, p1). An important feature of the disease from the patient’s perspective is its unpredictability. For an individual following diagnosis, it is not possible to predict
disease course. Aronson (1997) suggests that an unstable disease course is associated with poorer quality of life. Individuals with primary-progressive MS have been found to have better psychological functioning than those with other types (Vleugels et al, 1998) and one hypothesis for this is that the disease course is more predictable and, therefore, easier to adjust to.

Minden, Orav and Reich (1987) found that 54% of MS patients showed signs of psychopathology, including affective disturbances (principally depression and anxiety, but also bipolar disorders, manic episodes, euphoria and emotional lability), psychoses and personality changes. Depression is more common in MS compared to “normal” populations and other medical disorders (Minden et al, 1987). Lifetime prevalence of major depressive disorder following MS diagnosis is approximately 50% and the suicide rates are 7.5 times greater than the normal population (Sadovnick, Eisen, Ebers and Paty, 1991). The aetiology of depression is uncertain, with hypothesised contributions of neurological pathology, cognitive deficits and social stresses (Gilchrist and Creed, 1994). Anxiety is also common in MS (Stenager, Knudsen and Jensen, 1990), although it is relatively under-researched. Freed (1997) suggests that anxiety may be related to unpredictability, uncertainty about the future, dealing with new symptoms, the progressive nature of the disease and the lengthy diagnostic process. Euphoria is a well-recognized symptom of MS although it occurs rarely. Foong et al (1997) suggest it is likely to be a clinical expression of executive dysfunction.
1.3.3 Cognitive impairment in multiple sclerosis

1.3.3.1 Prevalence of cognitive impairment

Although MS has been recognised and described for over one hundred years (Charcot, 1877), recognition and investigation of related cognitive impairment has occurred only in the last 20 years. Controversy and disagreement exist regarding the exact nature of cognitive impairment and its implications. Despite this, the literature is fairly consistent in recognising that some individuals with MS do have difficulties with cognitive functioning.

Using neuropsychological assessment, Rao, Leo, Bernardin and Unverzagt (1991a) report the incidence of cognitive impairment in clinical samples of MS patients to be between 54 and 65% and within a community sample to be 43%. Ron, Callanan and Warrington (1991) report general cognitive difficulties with memory, attention, conceptual reasoning, verbal fluency and abstracting abilities, with relative sparing of language functions. Similarly, Rao et al (1991a) report significant differences between MS patients and controls on recent memory, sustained attention, verbal fluency, conceptual reasoning and visuospatial perception. The evidence for cognitive impairment within different cognitive domains will be reviewed individually within this section. In the following section, the discussion will focus particularly on the nature of executive dysfunction and evidence for executive dysfunction in MS.

1.3.3.2 Memory deficits

Memory deficits are the most frequently self-reported and neuropsychologically assessed problem in MS (Langdon and Thompson, 1996). MS seems to be particularly
associated with dysfunction in verbal memory ability and memory for complex material (Huber, Paulson, Shuttleworth and Chakeres, 1987). Kenealy, Beaumont, Lintern, and Murrell (2000) found deficits in autobiographical memory. Memory deficits have been described as problems with recall and working memory (Rao et al, 1993) and with inadequate initial learning/acquisition (DeLuca, Barbieri-Berger and Johnson, 1994). DeLuca et al (1994) suggested that multiple cognitive processes are likely to influence the memory impairment evident in MS.

1.3.3.3 Intellectual functioning deficits

Previous research has found small but consistent differences between MS patients and controls on intellectual functioning (Rao, 1986). MS patients perform significantly worse on performance IQ, although this is likely to be related to sensori-motor impairment.

1.3.3.4 Speed of information processing deficits

Rao, Aubin-Faubert and Leo (1989) found that MS patients had a significantly slower reaction time on a memory-scanning test. Litvan, Grafman, Vendrell, and Martinez (1988) found reduced performance on the Paced Auditory Serial Addition Task. Speed of information processing deficits may underlie the cognitive difficulties evident in MS, such as performance on memory tasks. D'Esposito et al (1996) found that in MS patients, the ability to coordinate two concurrent memory tasks was significantly poorer than controls and concluded that speed of information processing deficits might be associated with this difficulty.
1.3.3.5 Visuospatial deficits

Most studies have observed a dysfunction in visuospatial and visuoperceptual functions (Fennell and Smith, 1990), however, the tests used often require multiple brain functions, motor speed and dexterity, and so the implications of these results are unclear. On tests of pure visuospatial processing, problems seem to be related to deficits in planning and execution rather than visuospatial difficulties (Fennell and Smith, 1990).

1.3.3.6 Executive dysfunction

Individuals with MS have also been found to have difficulties with executive functions. These are described in more detail, as they are an important focus of the current study.

1.4 EXECUTIVE DYSFUNCTION

1.4.1 Theoretical framework

Executive functions are the higher-level cognitive processes required in situations involving decision making, planning, adapting to novel sequences, correcting errors and inhibiting strong habitual responses (Shallice and Burgess, 1991). These functions are commonly termed frontal lobe functions, given their basis in the frontal lobes and connected regions. Based on models of executive functioning (e.g. Lezak, 1995 and Stuss and Benson, 1987), executive functions are hypothesised to be fractionated into a number of areas:

- **Initiative and drive**: motivation, impulse control, drive, emotional responsiveness and capacity for pleasure.
• **Attention:** sustained attention, coping with interference, purposeful action, working memory, handling simultaneous sources of information, relating or integrating isolated detail and responding to the whole, switching attention and cognitive flexibility.

• **Memory:** voluntary recall of information, organisation of memory strategies, following instructions and temporally discriminating items in memory.

• **Planning, strategy and execution of sequences of action:** translating knowledge of facts into appropriate action, planning, comparing the results with the original intention, sequencing, decision making, anticipation, goal selection, shifting from one concept to another and changing a specific behaviour once started, looking ahead from present circumstances, viewing the environment objectively, conceiving alternatives and using external cues to guide behaviour.

• **Self-regulation in response to environmental contingencies:** self-regulation, self-monitoring, self-correction, self-awareness, meta-cognition, dealing with oneself in relation to the environment, effective performance and using information to influence behaviour.

1.4.2 **Clinical manifestations of executive dysfunction**

Executive dysfunction is a common problem following traumatic brain injury (TBI) because TBI is particularly associated with damage to the frontal lobes (Prigatano and Schacter, 1991). Consequently, the majority of research has therefore been conducted in TBI populations. However, these findings will have relevance to the study of other populations who may experience frontal lobe damage, such as MS patients. The findings
of this research are described, followed by some limited research in other populations and, finally, the evidence for executive dysfunction in MS.

1.4.2.1 Common symptoms of executive dysfunction

Executive functions encompass a broad range of cognitive functions and the behavioural consequences of any impairment will vary between individuals. However, common behavioural consequences include "personality change" resulting from disinhibition, lability, irritability, egocentricity and impulsivity, as well as resulting anger and frustration. Common symptoms also include poor planning and sequencing, poor self-monitoring, organizational problems, concrete thinking, stereotyped actions and poor judgement. Alderman and Ward (1991) describe individuals with executive dysfunction as being impulsive, distractible, having problems utilizing feedback and behaving inappropriately in social situations. Such difficulties will have a direct impact on their ability to maintain independent living and previous vocational and social activities.

A common element of executive dysfunction is reduced insight and self-awareness (Lezak, 1995). Individuals with TBI consistently underestimate cognitive (Tyerman, 1987), personality (Tyerman, Booth and Young, 1994) and family and lifestyle difficulties (Young, 1994) post-injury, in comparison to their relatives' ratings. Individuals with TBI are commonly unable to accurately judge their own behaviour, for example in vocational or social situations. This may lead to confusion, social isolation and sometimes delusional ideas (Prigatano and Schacter, 1991). This has an impact on rehabilitation outcome and successful independent living, because individuals with
Reduced insight is likely to be related to damage in the frontal and temporal lobes. Prigatano and Altman (1990) found that the group of patients with the greatest lack of insight had a greater number of lesions and a higher incidence of bilateral cerebral lesions. Stuss (1991) suggests that frontal lobe damage results in a breakdown of a multiple-domain awareness system, and leads to reduced access to the knowledge contained in specific domains (as lack of insight is rarely complete). However, apparent lack of insight is not always due to organic damage. Kihlstrom and Tobias (1991) discuss the differences between lack of awareness (due to neurological damage), denial (where the individual represses or is unable to accept difficulties due to psychological factors), and indifference (where the individual is aware but appears to be disinterested).

Although these symptoms of executive dysfunction are more common in those with extensive frontal lobe damage, such as TBI populations, they are also relevant to other populations who may experience more diffuse damage.

1.4.3 Evidence for executive dysfunction in other disorders

Symptoms associated with executive dysfunction have been noted in other disorders, such as dementia and schizophrenia. For example, McPherson, Fairbanks, Tiken, Cummings and Back (2002) investigated apathy (a common behavioural disturbance in Alzheimer's disease) and linked it to impaired performance on tests of executive functioning. Castellon, Hinkin and Myers (2000) found evidence of executive
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dysfunction (difficulties with dual tasks and inhibition of responses) in individuals with HIV and found impaired test performance to be related to apathy and irritability. Common symptoms of schizophrenia, such as impaired motivation and poor insight have also been found to be related to frontal lobe dysfunction (McGlynn and Schacter, 1997) and to impaired performance on tests of executive functions (Young, Davila and Scher, 1993). In their review paper, McGlynn and Schacter (1997) conclude that unawareness of deficits in schizophrenia and dementia depends on patterns of brain impairment involving the frontal lobes. This is relevant to the study of MS, in which lesions may present in the frontal lobes or connecting regions. The investigation of executive dysfunction in MS is, therefore, an important issue.

1.4.4 Evidence for executive dysfunction in multiple sclerosis

It is only recently that executive functions in MS have been investigated in neuropsychological studies (Foong et al, 1997). Such research has consistently found deficits in some elements of executive functioning. Some of the research described in the previous sections on cognitive impairment in MS, such as difficulties with planning and execution of visuospatial tasks and difficulties with attention and working memory can be related to difficulties with executive functions. More specific evidence is detailed below.

There is extensive research indicating difficulties with attentional processes in MS. Foong et al (1997) report deficits in spatial working memory, cognitive flexibility and switching attention. Fennell and Smith (1990) also report deficits in focal and sustained
attention. There is also evidence for impaired verbal working memory (digit span) (Huber et al 1987).

There is evidence for the role of executive dysfunction in MS memory impairment. Beatty, Goodkin, Beatty, and Monson (1989) suggest that, although MS patients do have mild deficits in retrieval of information, the extent of memory impairment seen in MS is related to inefficiency in the use of semantic encoding and a failure to use effective memory strategies - elements of executive function. Similarly, Scarrabelotti and Carroll (1999) suggest that MS memory deficits primarily involve an impaired ability to apply intentionally directed thinking processes to a memory task.

Studies of individuals with MS have found deficits in abstract concept formation, (Brassington and Marsh, 1998). Beatty, Hames, Blanco, Paul, and Wilbanks (1995) found that individuals with MS performed more poorly on tests of verbal abstract reasoning than controls, although Rao (1986) found no difference. Foong et al (1997) found reduced planning ability on the Tower of London task. Beatty et al (1989) used the Wisconsin Card Sorting Test (WCST) with MS patients. They found that MS patients did not have problems with non-perseverative errors, trials to first category or failures to maintain set, but they did have more perseverative errors, i.e. the MS patients had difficulties where problems involved abandoning formerly correct hypotheses. However, in a further study, Beatty and Monson (1996) compared performance on the WCST and the Californian Card Sorting Test (which allows more specific analysis of perseverative performance), and concluded that MS patients did not have a problem with perseveration, but had specific difficulties with concept formation. Beatty and
Monson (1994) also found that MS patients were impaired on picture sequencing tasks, but performed normally on a purely motor-sequencing test, indicating sequencing as a cognitive deficit. Reduced verbal fluency is also a commonly reported cognitive deficit (Brassington and Marsh, 1998).

No specific investigations of self-regulation, self-monitoring and self-awareness were found in the literature regarding individuals with MS. There is limited research on the metacognitive abilities of MS patients. Meta-memory refers to an individual’s knowledge about his or her memory, and is a function that seems to require both memory and conceptual abilities (Beatty et al, 1989). Beatty and Monson (1991) found that MS patients impaired in recognition memory or on the WCST had mild deficits in meta-memory and that those with deficits on both memory and WCST had extensive impairments in meta-memory. No specific studies of insight were found for individuals with MS, although anecdotal evidence would suggest lack of insight regarding cognitive and physical functioning to be a common phenomenon presented to clinicians (Langdon and Thompson, 1996).

1.5 RELATIONSHIP BETWEEN DISEASE VARIABLES AND COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

Only a subgroup of individuals with MS experience cognitive impairment, and research has attempted to understand this by investigating the relationship between cognitive impairment and disease variables. Most studies have investigated general cognitive impairment, but where executive functioning has been specifically examined, this will be discussed.
1.5.1 Disease course

There is evidence that individuals with primary-progressive MS experience significantly more general cognitive impairment than other subtypes. Heaton, Nelson, Thompson, Burks and Franklin (1985) found that 72% of patients with primary-progressive MS showed cognitive impairment, compared to 46% of those with relapsing-remitting MS. Other studies have found no influence of clinical course on cognitive functioning (Möller, Wiederman, Rohde, Backmund and Sonntag, 1994; Rao, Leo, Bernardin and Unverzagt, 1991b). There is also evidence that the prevalence of executive dysfunction may differ between subtypes. Mahler (1992) found that individuals with primary-progressive MS performed more poorly than those with relapsing-remitting MS on tasks involving abstract concept formation and set shifting. Foong et al (1997) found trends for differences between subtypes on neuropsychological tests of executive dysfunction, but found that individual differences lead to considerable group overlaps and overall non-significant results. Zakzanis (2000) reviewed evidence to date and concluded that individuals with primary-progressive MS experience more executive functioning impairments and individuals with relapsing-remitting MS experience more memory impairment. There is a consistent finding in the literature of a relationship between disease course and cognitive functioning, although the relationship may only be weak (Brassington and Marsh, 1998).

1.5.2 Disease duration

Although cognitive impairment has been reported in the early stages of MS, it is generally thought to be more prevalent in individuals with longer disease duration
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(Klonoff, Clark, Oger, Paty and Li, 1991). However, research findings are inconsistent. Some studies have found a significant positive relationship between general cognitive impairment and disease duration (e.g. Heaton et al, 1985) and others not (Rao et al, 1991b). In a review, Zakzanis (2000) report higher levels of cognitive difficulties, especially increased prevalence of executive dysfunction in patients with longer disease duration. This relationship appears to be significant, but weak.

1.5.3 Physical disability

McIntosh-Michaelis et al (1991) found evidence for a weak relationship between physical disability and general cognitive impairment, but Rao et al (1991b) found no significant difference in physical disability between individuals who were cognitively impaired and those who were cognitively intact. Foong et al (1997) found no correlation between physical disability and tests of executive function.

1.5.4 Pathology

Feinstein, Ron and Thompson (1993) found number of cerebral lesions to be strongly correlated with general cognitive impairment, as measured by neuropsychological functioning. Arnett et al (1994) found a relationship between frontal lobe lesions and impaired conceptual reasoning. Nocentini et al (2001) and Foong et al (1997) found cognitive deficits to be correlated with frontal lobe lesion. However, both were unable to find relationships between pathology and specific cognitive deficits and Beatty (1993) suggests that the extent of diffuse brain damage may be more important than the specific site of damage. The relationship between pathology and cognitive impairment is far
from clear and there is limited evidence that MRI lesion load predicts cognitive performance (Foong et al, 1997).

1.5.5 Conclusions

Research generally provides some support for the hypothesis that there may be a relationship between cognitive impairment and disease course, disease duration and pathology. However, this relationship is weak at best and cognitive dysfunction cannot be predicted precisely from any other aspect of the disease for any individual (Langdon and Thompson, 1996). Currently, it is also not possible to predict which patients will deteriorate cognitively and the rate at which this might occur (Beatty, Scott and James, 1993).

1.5.6 Methodological issues in this research

The severity and pattern of cognitive impairment varies greatly from patient to patient (Ryan et al, 1996). Due to the distribution of pathology, within a group of MS patients, one would expect wide variation in symptoms, with some individuals experiencing predominantly physical symptoms and others predominantly cognitive symptoms. This natural heterogeneity brings into question the validity of homogeneous samples in research studies. The use of heterogeneous groups of MS patients in research studies is likely to be an important factor in the lack of clear relationships found between disease variables and cognitive impairment.
1.6 THE IMPACT OF COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

Brassington and Marsh (1988) suggest that the most critical question from the patients' perspective is the impact of MS on an individual's general health status/quality of life. Vinck, Put, Arickx and Medaer (1997) found that MS patients reported poorer quality of life than individuals with rheumatoid arthritis or cancer. One of the differences between these diseases and MS is the presence of cognitive impairment in MS, suggesting cognitive impairment might be an important factor. Evidence for the relationship between cognitive impairment and health status and mood will be reviewed.

1.6.1 Health status

The majority of research has used objective measures of cognitive impairment, i.e. neuropsychological assessment. Rao et al (1991b) found that cognitively impaired MS patients were less likely to be working and engaged in fewer social or vocational activities than cognitively intact individuals. They were more dependent, reported more sexual dysfunction and experienced greater difficulty in performing household tasks. Such difficulties were irrespective of physical disability. Stenager, Knudsen and Jensen (1994) found that, although cognitive deficits do not correlate consistently with physical impairment, they do correlate with disability and handicap, particularly unemployment.

Some studies have examined the relationship between self-reported cognitive impairment and functional status. Edgley, Sullivan and Dehoux (1991) found that perceived cognitive impairment was a significant determinant of unemployment. Vinck et al (1997) examined the role of self-reported cognitive impairment in predicting
quality of life. They found that quality of life was low in those with both objective and self-reported cognitive dysfunction. However, Higginson, Arnett and Voss (2000) found that, whilst only relatives’ reports of memory impairment correlated with performance on the Rivermead Behavioural Memory Test, neither self nor relative reports were predictive of functional status.

1.6.2 Mood

The relationship between cognitive impairment and mood in MS has received relatively little research attention. Gilchrist and Creed (1994) found cognitive impairment to be more frequent in subjects diagnosed with depression and that depressed patients experienced significantly more stress in occupation and family relationships. However, it is not possible to infer causality in these findings, due to the cross-sectional design. Vinck et al (1997) suggest that cognitive deficits add to the emotional problems associated with MS. However, Möller et al (1994) found no relationship between cognitive impairment and depression. Both these studies used neuropsychological assessment to measure cognitive impairment and there are no studies of the relationship between mood and self-reported cognitive impairment in MS.

1.6.3 Impaired insight

Some studies suggest that impaired insight may have an impact on the reporting of mood and quality of life. Kenealy et al (2000) found that patients with impaired autobiographical memory reported significantly better quality of life and lower levels of depression than those with normal autobiographical memory. They concluded that patients with deficits in autobiographical memory had impaired knowledge about their
past and may be unable to make valid comparative judgements about the quality of their present life. Individuals with primary-progressive MS have been found to experience less distress and to experience greater executive dysfunction. One hypothesis for their reduced distress is a lack of insight into any difficulties. Support for this hypothesis is that physical disability has been found to cause increased distress and strain on carers, but not increased distress in patients (Nicholl, Lincoln, Francis and Stephan, 2001). Rao, Huber and Bornstein (1992) found depression scores were higher in MS patients with mild cognitive dysfunction compared with those with no cognitive dysfunction or severe deficits, suggesting that those with more severe deficits had reduced insight and therefore, less psychological distress.

1.7 SUMMARY

The following important factors have been highlighted:

- MS is a common neurological disease with an unpredictable and usually progressive course. The diagnostic process is often lengthy, the aetiology is unknown and there is currently no treatment. These elements make MS a particularly distressing chronic condition.

- The effects of MS are far-reaching and include physical symptoms (sensory and motor), fatigue and mood disorders (especially depression and anxiety). Cognitive impairment is also found and symptoms include impairments in memory, attention, conceptual reasoning, verbal fluency and abstracting abilities.

- There is evidence for impairment in executive functioning in MS, especially attentional processes, working memory, planning and strategy and concept
formation. The prevalence and clinical presentation of executive dysfunction in MS has not been investigated.

- Individual variability in lesion site means that different individuals with MS may experience very different patterns of symptoms.

- The link between disease variables and cognitive impairment is unclear. This means that disease variables are currently not very useful for predicting cognitive impairment in individuals.

- There is some evidence that objective cognitive impairment in MS is related to health status and mixed evidence that subjective cognitive impairment is related to health status. In other clinical conditions, such as TBI, executive dysfunction has an impact on health status, although the specific effects of executive dysfunction have not been investigated in MS.

- There is mixed evidence that objective cognitive impairment in MS has a negative impact on mood. However, there is also some preliminary evidence to suggest that poor memory and lack of insight may reduce awareness of symptoms and, therefore, reduce self-reported distress. The relationship between subjective cognitive impairment and mood in MS has not been examined.

The next section will discuss the methodological issues relevant to the assessment of executive dysfunction in MS patients.
1.8 PARADIGMS FOR MEASURING COGNITIVE IMPAIRMENT

1.8.1 Neuropsychological assessment in multiple sclerosis

Neuropsychological assessment provides an invaluable tool for the objective assessment of cognitive impairment. However, Langdon and Thompson (1996) suggest there are a number of problems with the use of neuropsychological assessment with MS patients. Physical impairments are likely to compromise sensori-motor functions on which many of the tests rely. Foong et al. (1997) suggest that the disseminated nature of the disease pathology leads to general intellectual deterioration and, given the general effect of cerebral involvement in neuropsychological tasks, it is difficult to isolate a specific dysfunction. Also, fatigue, which is a common feature of MS, is likely to affect test performance (Krupp and Elkins, 2000).

1.8.2 Limitations of neuropsychological assessment of executive dysfunction

There are also potential problems with measuring executive dysfunction using neuropsychological assessment (Lezak, 1995). The test situation provides a much more structured environment than normal, where the individual is required to follow direct instructions. Such factors make it difficult to assess such skills as initiation, planning and sequencing. Also the testing situation may provide increased motivation, compared to the natural environment.

1.8.3 Ecological validity of neuropsychological assessment

The use of neuropsychological tests in general has also been examined in terms of their ability to predict real-life abilities, i.e. their ecological validity. Research described earlier provides support for a link between cognitive impairment, as measured by
neuropsychological assessment, and health status in MS. However, the ecological validity of many neuropsychological tests has generally been assumed and not tested (Higginson et al., 2000) and some research has found that neuropsychological assessment is not able to adequately predict difficulties in everyday life (Richardson, 1996). Wilson (1993) concludes that neuropsychological assessments alone "do not give us sufficient detail to be able to predict what kinds of everyday problems are likely to be faced, nor do they tell us much about the nature and frequency of the problems" (p209).

A number of reasons have been suggested for why neuropsychological tests may not be predictive of functional status (Higginson et al., 2000). Tests may be too abstract or general, they may not sample the correct skills on which everyday tasks depend, they may pay insufficient attention to the role of the environment, and the testing situation may be an unrealistic environment, for example, by increasing motivation. Patients may also use ameliorative strategies and environmental cues in real life situations. Higginson et al (2000) suggest the use of tests designed to be more ecologically valid (such as the Test of Everyday Attention and the Rivermead Behavioural Memory Test) and the use of subjective measures of cognitive impairment.

1.8.4 Subjective reports of cognitive impairment

An alternative method for assessing extent of cognitive impairment is to gather the self-reports of individuals or informants. It has been argued that subjective reports of cognitive impairment from patients and their family members provide a rich source of additional information regarding cognitive dysfunction (Vinck et al, 1997).
1.8.4.1 Memory impairment

By far the majority of research on self-reported cognitive impairment in MS has been in the domain of memory impairment. There is evidence that MS patients under-report memory impairment in comparison to their relatives and to objective tests. McIntosh-Michaelis et al (1991) found that 44% reported memory impairment compared to 54% of relatives, indicating a discrepancy between self and other report. Beatty and Monson (1991) found that patients underestimated their memory difficulties compared to neuropsychological assessment. Taylor (1990) found that test performance correlated with relative-reported memory but not self-reported memory.

However, other researchers, such as Randolph, Arnett and Higginson (2001) found that patients' self-reported memory was as accurate as relatives' reports. Richardson (1996) investigated self-reported memory difficulties and found significant correlations between self and relative reports and no significant differences between the scores. This was found for the most serious problems identified, the frequency of learning and memory failures and overall functional level.

A number of questionnaire measures of memory have been developed. Memory questionnaires are generally considered to possess good test-retest reliability and internal reliability (Wade, 1992). However, the validity of questionnaires is more questionable. Sunderland et al (1983) describe two main problems that may invalidate patients' own reports of their memory failures. The first is that the reporting will require a memory of that memory failure (i.e. meta-memory) which, by definition, will be impaired in those with memory difficulties. The second is that individuals with
neurological damage may have impaired insight into their cognitive functioning. Taylor (1990) found support for the second hypothesis in a sample of MS patients, where the discrepancy between patient and relative’s scores was correlated with performance on tests of executive dysfunction and not correlated with performance on tests of memory functioning. Issues such as mood and social desirability factors are also likely to impact on subjective reports.

The Everyday Memory Questionnaire (EMQ) (Sunderland, Harris and Baddeley, 1983) is a commonly used self-report measure of memory impairment that has been used in a number of MS studies (e.g. Richardson, 1996; Lincoln et al, 2002). Lincoln et al (2002) used the EMQ in a neuro-rehabilitation MS population. These patients required specialist rehabilitation services and are likely to be more severely physically or cognitively disabled than a community MS population.

1.8.4.2 Executive dysfunction

The literature does not contain studies examining self-reported executive dysfunction in MS. However, given its prevalence in neuropsychological studies of MS, this is an important area for investigation. Self-reported executive dysfunction has, however, been investigated in other neurological samples. Research using self-report methodology has found that TBI patients commonly underestimate their problems compared to relatives, especially more complex skills, such as social abilities (Prigatano et al, 1990). Burgess, Alderman, Evans, Emslie and Wilson (1998) examined the relationship between neuropsychological assessment and self and relative-reported executive dysfunction in a mixed neurological population (predominantly TBI), using the Dysexecutive
Questionnaire (DEX) (Wilson, Alderman, Burgess, Emslie and Evans, 1996). They found that relative-reported problems significantly correlated with neuropsychological assessment, whereas self-reported problems did not. They used the discrepancy between self and relative-reports as a measure of insight and found that the discrepancy scores were significantly related to neuropsychological tests of executive dysfunction. They also found that in the predominantly TBI population, self-reported executive dysfunction was significantly less than relative-reported executive dysfunction, whereas in normal controls, self-reported executive dysfunction was significantly greater than relative-reported executive dysfunction. However, they did not investigate the variables that might explain these differences. One might expect that a sample of individuals with MS would experience less executive dysfunction than TBI patients due to the greater variation in lesion site and lower rates of cognitive impairment. One might also expect that a sample of MS patients would experience more executive dysfunction than normal controls. The DEX questionnaire has only been used with MS patients in one recently published study (Lincoln et al, 2002), but not investigated in detail.

1.8.5 Conclusions

Neuropsychological assessment has an invaluable role in assessing cognitive function and has been used extensively in MS research. However, there may be some potential limitations with the ecological validity of neuropsychological assessment and with the neuropsychological assessment of both MS patients and of executive functioning. The use of more ecologically based assessments and patient and family reports may provide important additional and converging evidence of any cognitive impairment and its possible effects. Lincoln and Tinson (1989) conclude, "the ability of a particular form
of measurement depends on the purpose of the assessment. Objective tests are needed to identify the nature of cognitive deficits in patients with neurological damage. Subjective assessments are useful for identifying problems which affect daily life and planning treatment programmes." (p61).

1.9 SUMMARY AND RATIONALE FOR RESEARCH

As discussed, there is evidence that a large number of individuals with MS experience some form of cognitive impairment, including executive dysfunction. However, while neuropsychological studies have shown deficits in aspects of executive functioning, the psychological/behavioural manifestation of any executive dysfunction in MS has not been examined. Neuropsychological studies have also found that general cognitive impairment has an impact on health status in MS. Neuropsychological assessment is a valuable tool for the assessment of cognitive impairment. However, there are methodological concerns regarding the ecological validity of neuropsychological assessment and its usefulness in predicting health status and psychological variables.

The usefulness of self-reported data on cognitive functioning, particularly in relation to problems experienced by patients in everyday lives, is now increasingly recognized. Valuable information can also be obtained from the discrepancies between relatives' and patients' reports of cognitive impairment. However, research is limited, especially within MS populations. Stenager et al (1990) highlight the paucity of investigations into MS patients' subjective reports of cognitive impairment. Some research has been conducted, but this has concentrated solely on memory impairment. While the role of
self-report data in executive dysfunction has been examined in TBI populations, it has not been examined within MS populations. The DEX questionnaire has been developed as a measure of executive dysfunction in a predominantly TBI population, but the properties have not been assessed in an MS population. Research has also only briefly examined the usefulness of self-reported memory impairment in the prediction of health status in MS and has not yet examined the usefulness of self-reported executive dysfunction in MS. Research has also not examined the relationship between self-reported cognitive impairment and mood in MS.

This study, therefore, proposes to investigate the prevalence and pattern of self-reported executive dysfunction in a sample of MS patients and to conduct preliminary investigations of the properties of the DEX questionnaire in an MS population. The study also proposes to examine the relationship between these variables and mood and health status. This may have important implications for predicting patients’ health status and psychological distress.

1.10 RESEARCH QUESTIONS AND HYPOTHESES

1. In a community sample of MS patients is the frequency and pattern of anxiety and depression significantly different from a normal healthy population?

Hypothesis 1.1

i) There will be significantly higher levels of anxiety and ii) depression compared to a normal healthy population.
2. In a community sample of MS patients:

- Is the frequency and pattern of self and relative-reported executive dysfunction significantly different from a predominantly TBI population and normal controls?
- Is the frequency and pattern of reduced insight significantly different from a predominantly TBI population and normal controls?
- Is the frequency and pattern of self and relative-reported memory impairment significantly different from a neuro-rehabilitation MS population?

Hypothesis 2.1

i) Self-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population and ii) significantly higher than that reported in normal populations; iii) relative-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population and iv) significantly higher than that reported in normal populations.

Hypothesis 2.2

The discrepancy between self and relative-reported executive dysfunction will be significantly different from that found in i) a predominantly TBI population and ii) normal controls.
Hypothesis 2.3

i) Self-reported memory impairment and ii) relative-reported memory impairment will be significantly lower than that reported in a neuro-rehabilitation MS population.

3. Does self-reported cognitive impairment predict health status and mood in a community sample of MS patients?

Hypothesis 3.1

Subjective reports of executive dysfunction and subjective reports of memory impairment will account for a significant proportion of the variance in health status (employment status, social functioning and physical role limitations).

Hypothesis 3.2

Subjective reports of executive dysfunction and subjective reports of memory impairment will account for a significant proportion of the variance in mood (anxiety and depression).
2. METHOD

2.1 DESIGN

The study was an exploratory survey in which both quantitative and qualitative data were collected. The design was two-staged, involving:

1. A cross-sectional postal survey of self-reported cognitive difficulties, mood and health status in individuals with MS attending neurology clinics in Aylesbury and Milton Keynes.

2. A cross-sectional postal survey of the cognitive difficulties of individuals with MS as perceived by a close relative or friend, allowing a matched pairs comparison.

2.2 PARTICIPANTS

2.2.1 Patients

Patients were selected from the NHS clinical registers of three consultant neurologists in two geographical areas (Aylesbury and Milton Keynes).

Inclusion criteria were:

- Individuals with a definite diagnosis of MS, including those who fulfilled the criteria of “clinically definite MS” (Poser et al, 1983) and those who fulfilled the new criteria of “MS” (McDonald et al, 2001). Individuals fulfilling the old criteria of “probable MS” were excluded to increase comparability with the new criteria.
- Individuals who had attended an NHS clinic of one of the neurologists involved.
- Individuals aged over 16 years old.

Exclusion criteria were:

- Where a clinician involved considered that the individual’s participation in the research would be clinically inappropriate.
- Where a clinician involved informed the researcher about a co-morbid psychiatric condition.
- Individuals attending the neurology clinics as a private patient.
- Individuals under 16 years old.

2.2.2 Relatives

Patients were invited to name a relative or friend who knew them well. These individuals were invited to participate in a parallel survey.

2.3 MEASURES

2.3.1 Patient questionnaires

2.3.1.1 Background information

The questionnaire contained questions to gather information on disease variables, such as type of MS, duration of illness, demographics and employment status.

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2 The term "patients" is used to refer to individuals with MS.
3 The term "relatives" is used to describe the relative, friend or other identified by the patient as knowing them well.
2.3.1.2 The Everyday Memory Questionnaire (EMQ) (Sunderland et al, 1983)

This is a questionnaire to measure self-reported memory difficulties. The EMQ comprises 28 questions on aspects of individuals’ everyday memory. Individuals rate their answers on a five-point scale, ranging from “once or less in the last month” to “once or more in a day”. Scores are summed to give a total score, used as a measure of the general extent of everyday memory impairment. The EMQ has been used in a number of previous studies using TBI patients (Sunderland et al, 1983), stroke patients (Lincoln and Tinson, 1989) and MS patients (Richardson, 1996). For this study the original data from a neuro-rehabilitation sample of MS patients (Lincoln et al, 2002) was available for comparison.

The psychometric properties of the EMQ have been found to be variable. In a TBI sample, Sunderland et al (1983) found poor correlations between self and other reported memory impairment and poor correlations between self-reported memory impairment and objective test scores, although they found significant correlations between relative’s responses and scores on six out of fourteen objective tests. However, Richardson (1996) found a high degree of correlation between patient and relative’s reported memory difficulties in a sample of MS patients. Lincoln and Tinson (1989) also found self-reports to be consistent with relatives’ reports and found significant correlations with an objective measure (the Rivermead Behavioural Memory Test). Wade (1992) concludes that, overall, the EMQ has acceptable validity and reliability as a measure of subjective everyday memory difficulties. Although the psychometric properties of the measure are questionable, there are limited other measures available and the EMQ has been widely used.
2.3.1.3 Hospital Anxiety and Depression Scales (HADS) (Zigmond and Snaith, 1983)

This is a self-completion measure of subjective symptoms of depression and anxiety over the past week. It consists of 14 items, each on a four-point scale, divided into two sub-scales (anxiety and depression). A higher score indicates a greater degree of distress. The questionnaire was designed to measure anxiety and depression in individuals with medical problems and, therefore, excludes items related to both emotional and physical disorders (e.g. dizziness). The HADS has been found to have acceptable validity, correlating well with psychiatric assessment (0.70 for depression and 0.74 for anxiety) (Zigmond and Snaith, 1983), and also correlating well with other measures of depression and anxiety (0.76 to 0.77) (Aylard, Gooding, McKenna and Snaith, 1987). It has been found to be easily understood and acceptable to patients (Bowling, 1998) and has been used extensively in previous research. Normative data are available for a non-clinical sample of 1792 adults (Crawford, Henry, Crombie and Taylor, 2001). Zigmond and Snaith (1983) recommend the following classification: 0-7 (normal), 8-10 (mild), 11-15 (moderate), 16+ (severe). In the present study, a score of 11+ is used as the cut-off for “caseness”, as advocated by Crawford et al (2001). This identifies individuals with moderate/severe anxiety or depression.

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

This is a questionnaire measure of executive dysfunction, and forms a part of the Behavioural Assessment of the Dysexecutive Syndrome. The questionnaire covers four areas of likely change (emotion/personality, motivation, behaviour and cognition), based on Stuss and Benson’s (1984) model of executive functioning. The questionnaire
contains 20 items with five-point scales from 0 (never) to 4 (very often). Item scores are totalled, with a higher score indicating greater executive dysfunction. Correlation coefficients show good internal reliability between the items (Burgess et al, 1998) and factor analysis revealed five underlying factors: Inhibition, Intentionality, Executive Memory, Positive Affect and Negative Affect. Burgess et al (1998) found that relatives' scores and the discrepancy between patient and relatives' scores were related to tests of executive dysfunction, providing support for its validity as a measure of executive dysfunction. Normative data are available for 92 patients from a mixed neurological (predominantly TBI) population. The original data were also available for 82 MS patients from a neuro-rehabilitation sample (Lincoln et al, 2002).

2.3.1.5 Short Form 36 (SF-36) (Ware, Snow, Kosinski and Gandek, 1993)

This is a self-completion measure of general health status/quality of life. The SF-36 contains 36 items which measure health status across 8 dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain and general health perception. There is also a single item about perceptions of health changes over the past 12 months. The questionnaire contains a number of response formats, including yes/no responses, five-point scales and six-point scales. Item scores for each of the dimensions are transformed into a scale from 0 (poor health) to 100 (good health). The SF-36 has been found to have higher sensitivity than other measures of health status (Brazier et al, 1992), and good responsiveness to change (Garratt, Ruta and Abdalla, 1992).

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4 A mixed neurological population comprising 59% TBI, 13% dementia, 8.5% cerebrovascular accidents, 6.5% encephalitis and 13% miscellaneous. Described as predominantly TBI throughout the text.
1993). Brazier et al (1992) report good internal reliability (0.60 to 0.81) and Ware et al (1993) report acceptable test-retest reliability (0.43 to 0.90). Ware et al (1993) report significant and consistent associations between the scale scores and work ability, utilization of care and various mental health criteria. UK normative data are available from a community sample (Jenkinson, Coulter and Wright, 1993).

Vickrey, Hays, Harooni, Myers and Ellison (1995) have supplemented the SF-36 with 18 additional items specifically for MS groups, relating to health distress (4 items), sexual function (4 items), satisfaction with sexual function (1 item), overall quality of life (2 items), cognitive function (4 items), energy (1 item), pain (1 item) and social function (1 item) to produce the Multiple Sclerosis Quality of Life Instrument (MSQOL-54). In the current study the SF-36 was chosen because of its wide use in research, its good psychometric properties and the availability of normative data. Elements of the MSQOL-54 were added to the SF-36. These included the extra question on the energy scale, the cognitive function scale and the overall quality of life scale. However the MSQOL-54 was not used in its entirety, because of its limited use in previous research and to reduce the length of the overall questionnaire.

2.3.1.6 Additional qualitative data

A space was included in the questionnaire for individuals to add any additional comments.
2.3.2 Piloting the patient questionnaire

Four patients attending a support group at a local rehabilitation service piloted the questionnaires. They completed the questionnaires and provided feedback over the telephone, providing an opportunity for discussion of any difficulties. The piloted questionnaires originally included the Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald, and Parkes, 1982) as a measure of general self-reported cognitive difficulties. However, feedback indicated that this made the total questionnaire battery too lengthy, so this measure was removed from the final battery. The approximate time for completing the final battery was 30 minutes.

2.3.3 Relatives’ questionnaire

The following measures were used:

- The DEX questionnaire for other completion. This allows a comparison to be made between self and other responses, providing a measure of patients’ insight into executive dysfunction.
- The EMQ for other completion. This allows a comparison to be made between self and other responses, providing a measure of insight into memory difficulties.
- Additional questions regarding demographics.

A space for additional qualitative comments.

2.4 ETHICAL ISSUES

Ethical approval was granted from the Aylesbury Vale Local Research Ethics Committee and from the Milton Keynes Local Research Ethics Committee following
minor amendments. Copies of letters confirming ethical approval are included in Appendix A.

The questionnaires were identified with a personal number to link them to the appropriate patient and to preserve confidentiality. The information sheet contained sources of support for participants should any issues be raised and included a telephone number should they wish to contact the researcher. If a completed questionnaire contained data raising concern for the welfare of that individual (for example, suicidal ideation), the researcher would discuss this with their supervisors and take appropriate action.

2.5 PROCEDURE

There were slight differences in procedure between regions based on the resources available and preference of the clinicians involved. In the Aylesbury sample, no electronic database existed for the MS patients. Therefore, the consultant neurologist gave the researcher a list of all patients with MS and access to the patients’ neurology files. The neurologist reviewed the list for any inappropriate participants. The files were examined to obtain demographic information, MS information (whether they had clinically definite MS, subtype, date of diagnosis) and GP details, and the researcher inputted this information to a database. For some patients, the neurology files were unobtainable and the patient’s medical notes were accessed for information. In the Milton Keynes sample, the researcher was given a printout of the demographic information of all individuals with clinically definite MS. The MS Clinical Specialist reviewed the list for appropriate participants and the researcher inputted details to a
database. From these databases, personalised letters were sent to all individuals fulfilling the criteria, and an information sheet, a consent form and the questionnaires were enclosed. These are shown in Appendix B.

Participants were invited to complete the questionnaires and return them to the researcher. Participants were advised that they could ask for help completing the questionnaires from a family member, or could contact the researcher and complete the questionnaires over the telephone. Individuals who wished to participate were asked to return their completed questionnaires along with the signed consent form. If they did not want to participate they were asked to return the blank questionnaires. A reminder letter was sent (see Appendix C) if individuals did not respond after three weeks.

They were also asked to supply the name and address of someone who knew them well, who they consented to being contacted to complete the relatives’ survey. If patients had provided details of a relative, personalised letters were sent to that person with an information sheet, a consent form and the questionnaires (see Appendix D). A reminder letter was sent (see Appendix E) if individuals had not responded after three weeks. However, due to delay in access to the Milton Keynes sample, time constraints did not allow for reminder letters to be sent for this sample.
3. RESULTS

3.1 OVERVIEW

This section includes:

- the demographics of the two samples;
- the properties of the DEX questionnaire;
- the investigation of proposed hypotheses, and
- the investigation of additional exploratory hypotheses.

3.2 PREPARATION FOR DATA ANALYSIS

Statistical testing was guided by whether the data fulfilled the assumptions for parametric analysis, and following statistical advice from a consultant statistician. Kolmogorov-Smirnov tests and histograms were used to test for normal distribution of the data. Levene's test was used to assess homogeneity of variance. In cases where the assumptions were not met, non-parametric tests were used. If no suitable non-parametric alternatives were available, data were appropriately transformed. Where existing literature allowed a directional hypothesis (hypotheses 1.1, 2.1 and 2.3), one-tailed probabilities were used. For non-directional hypotheses (2.2, 3.1, 3.2 and additional exploratory hypotheses), two-tailed probabilities were used.
3.3 DEMOGRAPHIC DATA

3.3.1 Sample characteristics: patients

3.3.1.1 Sample size

In the Aylesbury sample, 109 patients fulfilled the inclusion criteria and were invited to participate. Sixty-seven completed the questionnaire, 11 returned a blank questionnaire, 3 were unobtainable at the known address and 28 did not respond. This was an overall response rate of 74.3% and a completed response rate of 61.5%. In the Milton Keynes sample, 154 met the inclusion criteria and were invited to participate. Eight-two completed the questionnaire, 17 returned a blank questionnaire, 3 were unobtainable at the known address and 53 did not respond. Two were excluded from the analysis because their questionnaire responses were obviously from their relative’s viewpoint and not their own. This was an overall response rate of 64.6% and a completed response rate of 53.3%. For the total sample there was an overall response rate of 67.3% and a completed response rate of 56.7%. This was a good response rate, compared to an expected response rate from a postal survey of approximately 30% (Goyder, 1985) and particularly good for a neurological population. The total sample size for which the results are presented was 147.

3.3.1.2 Age

The age range of the participants was 20 to 73 years, with a mean of 47.4 (standard deviation (SD) =10.8). A Mann-Whitney test revealed no significant difference in age between regions. Previous research on MS patients has found similar ages, such as Rao et al (1991a) who found a mean age of 46.3 (SD=11.0).
3.3.1.3 Gender

Of the 147 participants, 41 were male and 106 were female (a ratio of 1:2.6). There were slightly more females than expected compared to known prevalence rates (1:1.5-2, Sibley, 1990). However, this did not represent a significant difference as tested by chi-square.

3.3.1.4 Marital status

Of the 147 participants, 102 were married, 18 were divorced, 12 were single, 8 were cohabiting, 5 were widowed and 2 were engaged.

3.3.1.5 Occupation and qualifications

Sixty-three (57.1%) participants were not working and 61 (72.6%) of these participants reported a change in their working situation because of MS. Fifty-seven (55.9%) reported having taken early retirement, 22 (21.6%) reported having changed tasks within the job, 22 (21.6%) reported having reduced working hours, 22 (21.6%) reported having taken sick leave and 9 (8.8%) reported having gone part-time.

3.3.1.6 MS subtype

Seventy-five (51.0%) participants knew their MS subtype, 25 (17.0%) did not know and 47 (32.0%) were unsure. Of the 75 who knew their subtype, 43 (47.3%) reported having relapsing-remitting MS, 23 (25.3%) reported having secondary-progressive MS, 22 (24.2%) reported having primary-progressive MS and 3 (2%) reported having benign MS. There were differences in incidence of the different subtypes between regions. In the Milton Keynes sample there were fewer individuals with relapsing-remitting MS and
more with secondary-progressive MS. The percentages of each subtype are illustrated in Table 1 with comparative normative data. Chi-square analyses revealed that the frequency of each subtype in the current total sample was significantly different from that reported in the general population ($\chi^2=13.53$, df=3, $p=0.004$), with fewer patients with benign MS and more with primary progressive MS. The current sample was also significantly different from that found in a neuro-rehabilitation population (Foong et al, 1997) ($\chi^2=28.69$, df=2, $p<0.0001$), comprising more patients with primary-progressive MS and fewer patients with relapsing-remitting MS.

Table 1: Subtypes in current study and comparative populations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Current study % (n=76)</th>
<th>Aylesbury sample % (n=34)</th>
<th>Milton Keynes sample % (n=43)</th>
<th>General population % (BSRM, 1993)</th>
<th>Neuro-rehab population % (Foong et al, 1997) (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting</td>
<td>47.3</td>
<td>53.8</td>
<td>42.3</td>
<td>40</td>
<td>66.7</td>
</tr>
<tr>
<td>Primary-progressive</td>
<td>24.2</td>
<td>20.5</td>
<td>26.9</td>
<td>10-15</td>
<td>7</td>
</tr>
<tr>
<td>Secondary-progressive</td>
<td>25.3</td>
<td>17.9</td>
<td>30.8</td>
<td>30</td>
<td>23.8</td>
</tr>
<tr>
<td>Benign</td>
<td>3.3</td>
<td>7.7</td>
<td>0</td>
<td>10-15</td>
<td>2.4</td>
</tr>
</tbody>
</table>

To provide a rudimentary validation of patients’ self-reported subtype, clinician ratings were gathered from the neurology files for a sub-sample of 20 random Aylesbury patients. A cross-tabulation was calculated on these values. There was 70% agreement between ratings. The Kappa value was .60, $p<0.001$, indicating a significant, moderate-to-substantial relationship (Landis and Koch, 1977) between patient-reported subtype and subtype in the neurology file.
3.3.1.7 Disease duration

The time since diagnosis reported by participants ranged from 6 months to 43 years, with a mean of 10.19 (SD=8.82) years. This is similar to the disease duration reported by Rao et al (1991), who found a range of 1-43 years, with a mean 9.5 (SD=9.0). The median time since diagnosis was 7.5 years, and the sample was positively skewed.

A Mann-Whitney test indicated a significantly longer time since diagnosis in the Milton Keynes sample than the Aylesbury sample (U=2081.0, p=0.026). A Kruskal Wallis test also indicated significant differences between each subgroup on time since diagnosis ($\chi^2=15.01$, df=3, p=0.002). The mean ranks indicated differences in the expected direction (secondary-progressive (53.79), primary-progressive (40.44), relapsing-remitting (31.36) and benign (18.83). This provided support for the hypothesis that the greater number of individuals who had progressed on to secondary-progressive MS in the Milton Keynes sample was related to a significantly greater time since diagnosis in this group.

3.3.1.8 Relapses

One hundred and seven (72.3%) of the sample reported having relapses as a part of their MS and 36 (24.3%) reported currently experiencing a relapse.
3.2.1.9 Other illnesses

Forty-eight (32.4%) reported experiencing other illnesses. These are shown in Table 2.

Table 2: Illnesses reported by the patients

<table>
<thead>
<tr>
<th>Reported illness</th>
<th>Number of responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>10</td>
</tr>
<tr>
<td>Thyroid difficulties</td>
<td>6</td>
</tr>
<tr>
<td>Circulation difficulties</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
</tr>
<tr>
<td>Asthma</td>
<td>4</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>3</td>
</tr>
<tr>
<td>Digestive problems</td>
<td>3</td>
</tr>
<tr>
<td>Back problems</td>
<td>2</td>
</tr>
<tr>
<td>Manic depression</td>
<td>2</td>
</tr>
<tr>
<td>Schizophrenic tendencies</td>
<td>1</td>
</tr>
<tr>
<td>Oedema</td>
<td>1</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Angina</td>
<td>1</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
</tr>
</tbody>
</table>

3.3.2 Sample characteristics: relatives

3.3.2.1 Sample size

In the Aylesbury sample, 59 patients provided details of a relative to contact. Of these, 44 returned completed questionnaires and 3 returned blank questionnaires. This was an overall response rate of 79.7% and a completed response rate of 74.6%. In the Milton Keynes sample, 74 patients provided details of a relative. Of these, 39 returned completed questionnaires and none returned blank questionnaires. This was a completed response rate of 52.7%. For the total sample of relatives there was a completed response rate of 62.4%. This was also a good response rate for a postal survey (Goyder, 1985). One relative’s questionnaire was omitted because it related to an omitted patient
questionnaire. The total sample size of relatives for which the results are presented is 82.

3.3.2.2 Age

Relative’s ages ranged from 20-84 (4 missing), with a mean of 46.6 (SD=13.28) years.

3.3.2.3 Gender

There were 45 (56.3%) females and 35 (43.8%) males (2 missing).

3.3.2.4 Relationship

Twenty-seven (32.9%) relatives described their relationship as husband, 16 (19.5%) as wife, 5 (6.09%) as partner, 7 (8.54%) as mother, 6 (7.31%) as sister, 2 (2.44%) as son, 6 (7.31%) as friend, 2 (2.44%) as carer and 2 (2.44%) as other. Fifty-four (65.9%) lived with the patients and 28 (34.1%) did not. Sixty-four relatives (79%) saw the patient daily, 15 (18.5%) saw them once a week and 2 (2.5%) saw them less than once a month.

The relatives had known the patients for a mean of 24.05 years (SD=12.94) with a range of 1-63 years and 88.9% of the relatives had known them before they were diagnosed with MS.
3.4 PROPERTIES OF THE DYSEXECUTIVE QUESTIONNAIRE (DEX)

Data were examined to indicate the properties of the DEX questionnaire in this sample.

3.4.1 Pattern of responses

The pattern of responses for the patients and relatives is shown in Table 3.

Table 3: Responses on the DEX

<table>
<thead>
<tr>
<th>Item</th>
<th>Patient Responses</th>
<th>Relative Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td>Mean (sd)</td>
<td>Median</td>
</tr>
<tr>
<td>1</td>
<td>1.18 (1.07)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.21 (1.03)</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>.29 (.69)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.14 (1.24)</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>.81 (1.07)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.03 (1.05)</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>1.02 (1.16)</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1.70 (1.23)</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>.76 (.94)</td>
<td>.5</td>
</tr>
<tr>
<td>10</td>
<td>1.16 (1.25)</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1.08 (1.30)</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1.35 (1.22)</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>.71 (.92)</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>.71 (1.02)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1.37 (1.27)</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>1.21 (1.25)</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>.95 (1.04)</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>1.67 (1.28)</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>1.71 (1.31)</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>.97 (1.15)</td>
<td>1</td>
</tr>
</tbody>
</table>

The patient and relative’s responses were very similar. For all except one question, both groups used the maximum range, however, the mean and median values were low for all items. The highest items scored by patients and relatives were DEX8 (I am lethargic, or unenthusiastic about things) and DEX19 (I have trouble making decisions, or deciding what I want to do). The lowest item scored by patients and relatives was DEX3 (I sometimes talk about events or details that never actually happened, but I believe did
happen). DEX7 (I have difficulty realizing the extent of my problems and am unrealistic about the future) had a comparatively large number of missing data for the patient sample.

### 3.4.2 Internal reliability

Cronbach’s alpha values were calculated to determine the internal consistency of the DEX. The alpha values for the total scales were 0.92 (patient questionnaire) and 0.95 (relative questionnaire). Individual alpha values if items were deleted ranged from 0.91 to 0.95. Nunally (1978) suggests that 0.7 is the minimally acceptable level for internal consistency. These alpha levels indicate that over 90% of the measured variance is reliable, indicating good internal consistency and that no individual items reduce the reliability of the scale.

Item-total correlations were also calculated to measure the extent to which each item correlated with the total score. These values ranged from 0.42 to 0.75 for the patient questionnaire and from 0.35 to 0.81 for the relative questionnaire. Kline (1986) suggests that item-total correlations should be above 0.20, therefore, these results show good internal consistency for both versions of the questionnaire. There were four questions with low coefficients. For the patients’ questionnaire, these were DEX5 (I sometimes get over-excited about things), DEX11 (I have difficulty showing emotion), DEX15 (I tend to be very restless) and DEX16 (I find it difficult to stop myself from doing something). For the relatives’ questionnaire, it was DEX11.
3.5 INVESTIGATION OF HYPOTHESES

3.5.1 Hypothesis 1.1

i) There will be significantly higher levels of anxiety and ii) depression compared to a normal healthy population.

The descriptive statistics from the Hospital Anxiety and Depression Scales (HADS) are shown in Table 4.

Table 4: Descriptive statistics from the HADS

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>144</td>
<td>8.55</td>
<td>4.40</td>
<td>0-19</td>
</tr>
<tr>
<td>Depression</td>
<td>144</td>
<td>5.91</td>
<td>3.53</td>
<td>0-16</td>
</tr>
</tbody>
</table>

The responses on the anxiety and depression scales were positively skewed. However, with a large sample size, it is reasonable to assume a normal distribution for the sample mean (Kirkwood, 1988). Therefore, in this instance statistical advice was that a t-test was suitable.

i) The mean score on the anxiety scale was 8.58 (SD=4.4) and the mean score in the normal population was 6.14 (SD=3.76) (Crawford et al, 2001). This represented a significant difference (t=6.603, df=144, p<0.0001, one-tailed). There were 47 participants (32.4%) scoring above caseness for anxiety, who were above the 88th percentile for the normal population.
ii) The mean score on the depression scale was 5.94 (SD=3.53) and the mean score in the normal population was 3.68 (SD=3.07). This represented a significant difference (t=7.576, df=143, p<0.0001, one-tailed). There were 18 participants (12.5%) scoring above caseness for depression, who were above the 96th percentile for the normal population.

3.5.2 Hypothesis 2.1

i) Self-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population and ii) significantly higher than that reported in normal populations; iii) relative-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population and iv) significantly higher than that reported in normal populations.

Table 5 shows the mean values used for these analyses

Table 5: Descriptive data from the DEX for the current and normative samples

<table>
<thead>
<tr>
<th>Score on Dysexecutive Questionnaire (DEX)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current sample</td>
<td>137</td>
<td>22.01</td>
<td>14.33</td>
<td>0-80</td>
</tr>
<tr>
<td>TBI population (Burgess et al)</td>
<td>92</td>
<td>27.20</td>
<td>13.96</td>
<td>-</td>
</tr>
<tr>
<td>Normal controls (Burgess et al)</td>
<td>216</td>
<td>21.04</td>
<td>9.69</td>
<td>-</td>
</tr>
<tr>
<td><strong>Relative-ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatives scores</td>
<td>80</td>
<td>21.71</td>
<td>16.91</td>
<td>0-71</td>
</tr>
<tr>
<td>TBI population (Burgess et al)</td>
<td>92</td>
<td>33.52</td>
<td>16.15</td>
<td>-</td>
</tr>
<tr>
<td>Normal controls (Burgess et al)</td>
<td>216</td>
<td>16.97</td>
<td>11.72</td>
<td>-</td>
</tr>
</tbody>
</table>

i) The responses on the DEX were positively skewed. However, the non-parametric alternative to the t-test (sign test) requires a median value, which was not
obtainable for the TBI population. Also, with a large sample size, it is reasonable to assume a normal distribution for the sample mean (Kirkwood, 1988). Therefore, in this instance statistical advice was that a t-test was suitable. For these analyses, the normative data reported by Burgess et al (1998) were used. The mean self-rating on the DEX in the study sample was 22.01 (SD=14.33), and the mean self-rating from the predominantly TBI sample was 27.20 (SD=13.96). This represented a significant difference ($t=-4.235$, df=136, p<0.0001, one-tailed), providing support for the hypothesis that self-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population.

ii) The mean self-rating from a sample of normal controls was 21.04 (SD=9.69). A t-test indicated no significant difference, indicating that self-rated DEX scores from the current sample of MS patients were not significantly different from normal controls. This did not provide support for the hypothesis that self-reported executive dysfunction will be significantly higher than that reported in normal controls.

iii) The relatives' ratings on the DEX questionnaire were also positively skewed, however the t-test was deemed suitable for the same reasons given above. The mean other-rating was 21.71 (SD=16.91) and the mean other-rating from the predominantly TBI population was 33.52 (SD=16.15). This represented a significant difference ($t=-6.245$, df=79, p<0.0001, one-tailed), providing support for the hypothesis that relative-reported executive dysfunction will be significantly lower than that reported in a predominantly TBI population.
iv) The mean other-rating on the DEX was 21.71 (SD=16.91) and the mean other-rating from a sample of normal controls was 16.97 (SD=11.72). This represented a significant difference (t=2.508, df=79, p=0.007, one-tailed), providing support for the hypothesis that relative-reported executive dysfunction will be significantly higher than that reported in normal controls.

3.5.3 Hypothesis 2.2

The discrepancy between self and relative-reported executive dysfunction will be significantly different from that found in i) a predominantly TBI population and ii) normal controls.

The discrepancy score was calculated by subtracting the patient score from the relative score, following Burgess et al (1998). Table 6 shows the mean values used for the analysis.

<table>
<thead>
<tr>
<th>Discrepancy between relative and patient scores</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current sample</td>
<td>75</td>
<td>-1.71</td>
<td>13.76</td>
<td>-33 - +47</td>
</tr>
<tr>
<td>TBI population (Burgess et al)</td>
<td>92</td>
<td>6.32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Normal controls (Burgess et al)</td>
<td>216</td>
<td>-4.07</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

i) The mean DEX discrepancy score was -1.71 (SD=13.76) with a range of -33 to 47 and the mean discrepancy score in a predominantly TBI population was 6.32 (SD=unavailable). A one-sample t-test revealed a significant difference (t=2.903, df=74, p=0.005, two-tailed). The discrepancy between scores was significantly less than that reported in a predominantly TBI population.
ii) The mean DEX discrepancy score in comparative normal controls was -4.07 (SD=unavailable). A one-sample t-test revealed a significant difference (t=-3.636, df=74, p=0.0001, two-tailed). The discrepancy between scores in the sample was significantly higher than that found in normal controls.

A Wilcoxon test indicated no significant difference between paired self and relative reports of executive dysfunction in the current sample. In a predominantly TBI population, relatives reported significantly more executive dysfunction than the patients reported of themselves, leading to a positive discrepancy (relative minus patient score). In normal controls, relatives reported significantly less executive dysfunction than the controls did of themselves, leading to a negative discrepancy. In the current sample, there was no significant discrepancy in either direction, indicating that the MS population lay in between the TBI population and normal controls. This is indicated in Figure 2.
Figure 2: Comparison of DEX scores between sample type

<table>
<thead>
<tr>
<th>Sample</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current patient scores</td>
<td>138</td>
<td>22.25</td>
<td>21.75</td>
<td>0-62</td>
</tr>
<tr>
<td>Neuro-rehabilitation MS sample patient scores (Lincoln et al)</td>
<td>76</td>
<td>26.11</td>
<td>24.02</td>
<td>0-96</td>
</tr>
<tr>
<td>Current relative scores</td>
<td>74</td>
<td>19.54</td>
<td>22.11</td>
<td>0-110</td>
</tr>
<tr>
<td>Neuro-rehabilitation MS sample relative scores (Lincoln et al)</td>
<td>64</td>
<td>21.06</td>
<td>23.57</td>
<td>0-104</td>
</tr>
</tbody>
</table>
i) Self-reported EMQ scores were also positively skewed, which, following statistical advice, was rectified using a square root transformation. This produced a normal distribution \((z=0.853, p=0.461)\). For these analyses, the original data reported by Lincoln et al. (2002) were used, allowing these data to be transformed using square root for comparability and a one-sample t-test to be conducted on the mean value. The mean self-reported EMQ score for the study sample was 22.25 (SD=21.75), transformed to a mean of 4.04 (SD=2.44). The mean self-reported EMQ score from the neuro-rehabilitation MS sample was 26.11 (SD=24.02) transformed to a mean of 4.55 (SD=2.35). This represented a significant difference \((t=-2.439, df=137, p=0.008, \text{ one-tailed})\), providing support for the hypothesis that self-reported memory impairment will be lower than in a neuro-rehabilitation MS sample.

ii) Relative-reported EMQ scores were also positively skewed, which was rectified using a square root transformation. This produced a normal distribution \((z=0.844, p=0.474)\). The original data reported by Lincoln et al. (2001) was also transformed using square root and a one-sample t-test was conducted on the mean value. The mean relative-rating for the study sample was 19.54 (SD=22.11), transformed to a mean of 3.62 (SD=4.55) and the mean relative-rating in a neuro-rehabilitation MS sample was 21.06 (SD=23.57), transformed to a mean of 3.71 (SD=2.72). No significant difference was found.
3.5.5 Section summary

- The current sample reported higher levels of depression and anxiety than the normal population.

- MS patients reported themselves as experiencing lower levels of executive dysfunction than the predominantly TBI population, but the same levels as normal controls. Their relatives reported lower levels of executive dysfunction than the predominantly TBI population, but more than normal controls.

- There was no significant discrepancy between patient and relatives reports of executive dysfunction. However, the extent of the discrepancy was less than that found in the predominantly TBI population and more than that found in normal controls.

- The patients reported lower levels of memory impairment than that reported in a neuro-rehabilitation MS sample. Their relatives reported the same level of memory impairment as in a neuro-rehabilitation MS sample.

3.6 PREDICTION OF HEALTH STATUS AND MOOD

3.6.1 Hypothesis 3.1

Subjective reports of executive dysfunction and subjective reports of memory impairment will account for a significant proportion of the variance in health status.

Three measures of health status were used (physical role limitations, employment status and social functioning); therefore, three separate analyses were conducted. Missing data were dealt with by listwise deletion. The number of valid cases was 44, and the ratio of
cases to independent variables was satisfied according to Tabachnik and Fidell (1989). Correlations between applicable variables were examined. Several correlations were significant and so regression analysis was deemed appropriate. Also, none of the correlation coefficients were more than 0.8, indicating low risk of multicollinearity. In each analysis, the tolerance values were also examined to assess risk of multicollinearity. The distribution of residuals was examined for normality. Given the exploratory nature of the hypothesis, all variables were entered together and stepwise regressions were requested, to provide the "best fit" model.

3.6.1.1 Prediction of physical role limitations

For this analysis the residuals were not normally distributed, therefore regression was not appropriate. However, examination of the Spearman’s $\rho$ correlation coefficients indicated that those with poorer physical role limitations had higher levels of self-reported memory impairment ($\rho=-.234$, $p=0.006$, $n=134$) and executive dysfunction ($\rho=-.173$, $p=0.047$, $n=133$) and higher levels of relative-reported memory impairment ($\rho=-.299$, $p=0.011$, $n=72$).

3.6.1.2 Prediction of social functioning

Independent variables were age and gender, duration of disease and type of MS (dummy-coded$^5$), physical functioning, anxiety and depression, self-reported EMQ and DEX scores, relative-reported EMQ and DEX scores and discrepancy between self and other EMQ and DEX scores. The regression equation was significant ($F_{(1,42)}=40.19$).

$^5$ Dummy coding allowed the subtype variable with 3 categories (RR-MS, PP-MS and SP-MS) to be converted to 2 dichotomous variables. Subtype I indicated PP-MS or not, Subtype II indicated SP-MS or not and RR-MS was, therefore, indicated by a zero on either variable.
Depression was the only predictor of social functioning \((t = -6.339, \ p < 0.0001)\), explaining 47.7% of the variance \((R^2 = 0.477, \ df = 1,42, \ p < 0.0001)\). See Table 8 for the regression equation.

### Table 8: Regression Equation: social functioning

<table>
<thead>
<tr>
<th></th>
<th>Adjusted R^2</th>
<th>Unstandardized coefficients</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>98.705</td>
<td>5.444</td>
<td>18.130</td>
<td>.000</td>
</tr>
<tr>
<td>Depression</td>
<td>0.477</td>
<td>-5.080</td>
<td>-6.339</td>
<td>.000</td>
</tr>
</tbody>
</table>

Since subtype was not predictive and reduced the sample size, the analysis was repeated with a larger sample size by excluding subtype. The regression equation was significant \((F(1,67) = 83.057, \ p < 0.0001)\). Depression was the only predictor of social functioning \((t = -9.114, \ df = 1,67, \ p < 0.0001)\), predicting 55.7% of the variance \((R^2 = 0.557, \ df = 1,67, \ p < 0.0001)\).

### 3.6.1.3 Prediction of employment status

Since the variable “employment status” was dichotomous, a logistic regression was conducted using the same independent variables. The overall model was significant \((\chi^2 = 30.10, \ df = 12, \ p = 0.003)\). The two significant coefficients were physical functioning \((Wald = 3.989, \ p = 0.046)\) and subtype I \((Wald = 5.164, \ p = 0.023)\). MS patients with primary-progressive MS and poorer physical functioning were less likely to be working. Conversely, those with relapsing-remitting MS and better physical functioning were more likely to be working. The model predicted 84.1% of the responses correctly. The significant results of this regression are presented in Table 9.
Table 9: Logistic regression: employment status

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype I</td>
<td>-4.253</td>
<td>5.164</td>
<td>.023*</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.072</td>
<td>3.989</td>
<td>.046*</td>
</tr>
<tr>
<td>Constant</td>
<td>-7.621</td>
<td>3.848</td>
<td>.050</td>
</tr>
</tbody>
</table>

3.6.2 Hypothesis 3.2: Subjective reports of executive dysfunction and subjective reports of memory impairment will account for a significant proportion of the variance in mood.

3.6.1.4 Prediction of depression

The same independent variables were entered. The regression equation was significant ($F(1,40)=10.558$, $p<0.0001$). Altogether, 40.0% of the variance ($R^2=.400$, $df=1,40$, $p<0.0001$) was predicted by patient DEX score, DEX discrepancy score and age. Patient DEX score ($t=5.241$, $p<0.0001$) was the strongest predictor of depression, followed by DEX discrepancy score ($t=-2.244$, $p<0.030$) and age ($t=2.052$, $p=0.047$). Table 10 shows the regression equation.

Table 10: Regression equation: depression

<table>
<thead>
<tr>
<th></th>
<th>Adjusted R²</th>
<th>Unstandardized coefficients</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>-</td>
<td>-1.204</td>
<td>2.173</td>
<td>-.554</td>
</tr>
<tr>
<td>Patient DEX</td>
<td>.300</td>
<td>.121</td>
<td>.031</td>
<td>3.918</td>
</tr>
<tr>
<td>DEX discrepancy</td>
<td>.353</td>
<td>-8.045E-02</td>
<td>.036</td>
<td>-2.244</td>
</tr>
<tr>
<td>Patient age</td>
<td>.400</td>
<td>8.601E-02</td>
<td>.042</td>
<td>2.052</td>
</tr>
</tbody>
</table>
Since subtype was not a significant predictor, the analysis was repeated with a larger sample size by excluding subtype data. The regression equation was significant \( F(1,67)=30.554, \ p<0.0001 \). Altogether, 30.3% of the variance \( R^2=0.303, \ df=1,67, \ p<0.0001 \) was predicted by patient DEX score \( t=5.528, \ p<0.0001 \).

3.6.1.5 Prediction of anxiety

Using the same independent variables, the regression equation was significant \( F(1,42)=30.450, \ p<0.0001 \). Altogether, 57.8% of the variance \( R^2=0.578, \ df=1,42, \ p<0.0001 \) was predicted by patient total DEX score and subtype I. Patient DEX score \( t=7.340, \ p<0.0001 \) was the strongest predictor of anxiety, followed by the subtype I \( t=-2.382, \ p=0.022 \). Table 11 shows regression equation.

<table>
<thead>
<tr>
<th>Adjusted R²</th>
<th>Unstandardized coefficients</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
<td>Standard Error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>4.143</td>
<td>.803</td>
<td>5.158</td>
</tr>
<tr>
<td>Patient DEX</td>
<td>.531</td>
<td>.209</td>
<td>7.340</td>
</tr>
<tr>
<td>Subtype I</td>
<td>.578</td>
<td>-2.398</td>
<td>1.007</td>
</tr>
</tbody>
</table>

Given the dummy-coded nature of the variables these results could suggest either that those with primary-progressive MS report lower levels of anxiety or that individuals with relapsing-remitting MS report greater levels of anxiety. Kruskall-Wallis analyses indicated that individuals with relapsing-remitting MS report significantly higher levels of anxiety than those with primary-progressive \( 7.217, \ df=1, \ p=0.007 \) and secondary-progressive MS \( 7.226, \ df=2, \ p=0.027 \). The conclusion was that a higher DEX score and relapsing-remitting-MS was predictive of higher levels of anxiety.
3.7 COMPARISON OF TWO GROUPS: UNDER-REPORTERS AND OVER-REPORTERS

3.7.1 Creation of two sub-groups

There was a concern that examination of the mean values of the group may be masking significant relationships between variables. It was felt appropriate to explore for the existence of separate subgroups within the overall sample. This was attempted by examination of the discrepancy between patient and relative DEX scores. Some individuals reported few executive problems compared to their relatives, some reported more executive problems compared to their relatives and others reported the same level. The discrepancy values were interesting because of the differences seen in TBI (high negative discrepancy) and the differences seen in a normal population (high positive discrepancy). A clearer indication of discrepancies in DEX scores is indicated in the scatter-plot in Figure 3. There were some individuals who had close agreement with their relatives. This would be indicated by a discrepancy score of approximately 0, and a range of -5 to 5 was chosen to indicate close agreement (indicated between the parallel lines on the graph). Those above and below this range were divided into two groups, producing a group of patients who over-report executive dysfunction (N=25) and a group who under-report executive dysfunction (N=18). These two groups were then used for analyses to investigate possible differences between those who over-report and under-report.
Figure 3: Scatter-plot showing discrepancies between self and relative-reported executive dysfunction and division into three groups

- Individuals who under-report executive dysfunction
- Individuals who report the same as relatives
- Individuals who over-report executive dysfunction
3.7.2 Differences between groups

Descriptive statistics for the two groups were examined and appropriate analyses were conducted. These findings are indicated in table 12.

Table 12: Descriptive data and significant differences between over-reporters and under-reporters (*=p<0.05, **=p<0.01).

<table>
<thead>
<tr>
<th></th>
<th>Over-reporters (n=25)</th>
<th>Under-reporters (n=18)</th>
<th>Analysis of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>Mean: 45.44</td>
<td>Mean: 51.50</td>
<td>t=-2.076, df=41, p=0.044</td>
</tr>
<tr>
<td>Disease duration</td>
<td>8.68</td>
<td>10.17</td>
<td>n.s</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9.60</td>
<td>7.56</td>
<td>n.s</td>
</tr>
<tr>
<td>Depression</td>
<td>7.16</td>
<td>6.22</td>
<td>n.s</td>
</tr>
<tr>
<td>Patient EMQ</td>
<td>26.08</td>
<td>21.83</td>
<td>n.s</td>
</tr>
<tr>
<td>Relatives EMQ**</td>
<td>12.35</td>
<td>36.73</td>
<td>U = 72.0, p=0.003</td>
</tr>
<tr>
<td>EMQ discrepancy**</td>
<td>-13.09</td>
<td>13.47</td>
<td>t=-4.57, df=36, p&lt;0.0001</td>
</tr>
<tr>
<td>Health status scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>29.4</td>
<td>30.56</td>
<td>n.s</td>
</tr>
<tr>
<td>Physical role limitations</td>
<td>33.33</td>
<td>27.78</td>
<td>n.s</td>
</tr>
<tr>
<td>Mental role limitations</td>
<td>62.50</td>
<td>66.67</td>
<td>n.s</td>
</tr>
<tr>
<td>Social function</td>
<td>57.50</td>
<td>64.58</td>
<td>n.s</td>
</tr>
<tr>
<td>Mental Health</td>
<td>64.00</td>
<td>72.67</td>
<td>n.s</td>
</tr>
<tr>
<td>Energy/vitality</td>
<td>29.40</td>
<td>32.65</td>
<td>n.s</td>
</tr>
<tr>
<td>Pain</td>
<td>53.78</td>
<td>56.79</td>
<td>n.s</td>
</tr>
<tr>
<td>Health perceptions</td>
<td>41.80</td>
<td>48.53</td>
<td>n.s</td>
</tr>
<tr>
<td>Change in health</td>
<td>34.00</td>
<td>38.89</td>
<td>n.s</td>
</tr>
<tr>
<td>Quality of life</td>
<td>55.21</td>
<td>56.94</td>
<td>n.s</td>
</tr>
<tr>
<td>Extended energy/vitality scale</td>
<td>30.08</td>
<td>34.59</td>
<td>n.s</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>57.20</td>
<td>69.17</td>
<td>n.s</td>
</tr>
<tr>
<td>Categorical variables</td>
<td>N</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>16</td>
<td>8</td>
<td>44.4</td>
</tr>
<tr>
<td>Subtype (RR)</td>
<td>11</td>
<td>4</td>
<td>44.0%</td>
</tr>
<tr>
<td>Subtype (PP)</td>
<td>11</td>
<td>4</td>
<td>16.0%</td>
</tr>
<tr>
<td>Subtype (SP)</td>
<td>2</td>
<td>2</td>
<td>8.0%</td>
</tr>
<tr>
<td>Subtype (Benign)</td>
<td>1</td>
<td>1</td>
<td>4.0%</td>
</tr>
<tr>
<td>Work status (working)</td>
<td>52.0%</td>
<td>38.9%</td>
<td>n.s</td>
</tr>
</tbody>
</table>

* Not significant
Patients who over-report executive difficulties compared to their relatives were significantly older and also reported significantly more memory impairment than their relatives.

3.7.3 Discriminant function analysis

A discriminant function analysis was conducted to determine which combination of variables best discriminated between those who over-report (score of 1) and those who under-report (score of 2) executive dysfunction. The following variables were included as potential discriminating variables: age, gender, time since diagnosis, MS subtype (dummy-coded), relative’s gender, anxiety, depression, patient EMQ, relative EMQ and physical functioning. A step-wise analysis was requested using Wilk’s Lambda as the criteria for power of separation between groups. Inclusion of the data of MS subtype reduced the total sample size to 23, with 16 over-reporters and 7 under-reporters. This fulfilled the criteria for minimum sample size (that the number of the smallest group should be greater than the number of predictors) (Tabachnik and Fidell, 1989).

The four extracted variables are shown in Table 13.

Table 13: Discriminant function analysis summary

<table>
<thead>
<tr>
<th>Step</th>
<th>Entered</th>
<th>Wilks’ Lambda</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxiety</td>
<td>.791</td>
<td>.028</td>
</tr>
<tr>
<td>2</td>
<td>Relative EMQ score</td>
<td>.661</td>
<td>.016</td>
</tr>
<tr>
<td>3</td>
<td>Patient EMQ score</td>
<td>.505</td>
<td>.004</td>
</tr>
<tr>
<td>4</td>
<td>Subtype</td>
<td>.372</td>
<td>.001</td>
</tr>
</tbody>
</table>

The unstandardised canonical discriminant function coefficients and groups means are shown in Table 14.
Table 14: Unstandardised canonical discriminant function coefficients and group means

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Group means</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype II</td>
<td>1.956</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>-.169</td>
<td>Over-report</td>
<td>-.822</td>
</tr>
<tr>
<td>Patient EMQ</td>
<td>-.048</td>
<td>Under-report</td>
<td>1.878</td>
</tr>
<tr>
<td>Relative EMQ</td>
<td>.054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>1.305</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Over-reporters were more likely to have relapsing-remitting MS, report higher levels of anxiety, report higher levels of memory impairment and have lower levels of relative-reported memory impairment. The discriminant function correctly classified 87.0% of cases (see Table 15).

Table 15: Classification of cases into groups

<table>
<thead>
<tr>
<th>Actual group</th>
<th>N</th>
<th>Predicted over-reporters</th>
<th>Predicted under-reporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-reporters</td>
<td>16</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Under-reporters</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28.6%</td>
<td>71.4%</td>
</tr>
</tbody>
</table>

3.8 QUALITATIVE DATA

The patients and relatives were invited to provide additional comments. Some of these comments provide interesting support for a higher rate of distress in the “over-reporters” Two “over-reporters” commented, “I find it difficult to come to terms with feeling that I have very little control over how the disease is affecting me”; and “I lack confidence because I am not in control of my physical and mental abilities”. These comments were not as apparent in the “under-reporters”.
Comments covered a number of other topics. Numbers indicate number of comments. Patients commented on fatigue (10), pain (7), visual problems (4), mobility problems (4), incontinence (3), other sensations (3) and sleep problems (2). Some commented that their problems were mostly physical (3) and life very limited (5). Others mentioned memory (7), wording finding (2) and concentration (2) difficulties. Patients also mentioned emotional difficulties such as irritability (2), frustration (3) and depression (3). Patients commented on disease variability (3), relapses (1), and a lack of control over the disease (3). Others mentioned a difficulty in adjusting to the disease (3), trying to take a positive outlook (5), the importance of support (2) and of faith (1). One patient commented on the positive effect of MS on their life.
4. DISCUSSION

4.1 OVERVIEW

This section begins with a summary of the results, followed by a summary detailing the findings of the investigated hypotheses. Methodological issues are discussed and the results are interpreted. Implications are discussed for theory and clinical practice, recommendations suggested for future research and conclusions drawn from the study.

4.2 SUMMARY OF FINDINGS

4.2.1 Sample characteristics

The gender proportions, age range and disease duration were representative of other study populations (e.g. Rao et al., 1991a). The majority of the sample were not working and the majority of these reported MS to be the reason. The prevalence of MS subtypes was significantly different from that found in community populations and neuro-rehabilitation populations and also significantly differed between regions. The implications of this are discussed later. The majority of informants chosen by the patients for the study were family members and 79% saw the patient daily.

4.2.2 Investigation of hypotheses

The findings were as follows:

- The sample reported significantly higher levels of anxiety and depression than the normal population.
• The amount of executive dysfunction reported by patients was lower than in a predominantly TBI population and not significantly different from that reported by normal controls.

• The amount of executive dysfunction reported by relatives was lower than that reported in a predominantly TBI population, but significantly higher than normal controls.

• In the group overall, there was no significant difference between patient and relatives' reports of executive dysfunction. However, the amount of discrepancy was lower than that found in a predominantly TBI population and higher than found in normal controls, indicating a deviation from the normal population.

• The amount of memory impairment reported by patients was lower than in a neuro-rehabilitation sample, but the amount reported by relatives was not significantly different.

• Individuals with poorer physical role limitations had higher levels of self-reported memory impairment and executive dysfunction and higher levels of relative-reported memory impairment.

• Depression was the only predictor of social functioning, with those reporting higher levels of depression having poorer social functioning. This finding was robust in both the small and larger sample.

• Having primary-progressive MS and poorer physical functioning was predictive of being out of work.

• A high rating of patient reported executive dysfunction was the strongest predictor of depression, followed by a low discrepancy between patient and
relative reported executive dysfunction (a tendency to over-report executive dysfunction) and higher age. When subtype data were excluded to increase the sample size, patient reported executive dysfunction was the only predictor of depression.

- Patient reported executive dysfunction was the strongest predictor of anxiety, followed by having relapsing-remitting-MS.
- The sample was split into individuals who over-report and under-report executive difficulties in comparison to their relatives. Over-reporters were more likely to have relapsing-remitting MS, have lower age, report higher levels of anxiety, report higher levels of memory impairment and have lower levels of relative-reported memory impairment, compared to under-reporters.

4.3 METHODOLOGICAL CONSIDERATIONS

4.3.1 Sample size

There was a good response rate, resulting in a large patient sample size, which is a strength of the study. There was a smaller response rate for the patients in the Milton Keynes sample, which may represent the greater level of disability and longer disease duration. There was also a reasonable response rate from the relatives, but the relatives’ sample size was smaller because they were selected by a subgroup of patients. There was a smaller response rate for the relatives in the Milton Keynes sample, which is likely to be due to the fact that reminder letters were not sent for this region.
The matched pairs comparison of patient and relatives score to produce a discrepancy score reduced the sample size. Also the use of subtype data, which was not available for 44% of the sample, reduced the sample size further. Therefore, the sample size used in some of the regression analyses was significantly reduced. This limitation was partially rectified by repeating the regression analyses with the subtype data excluded. It was felt appropriate to include results using both sample sizes given the slight differences in results. The sample was split into two groups: over-reporters and under-reporters. These two groups had very small sample sizes (25 and 18). The findings from analyses using such small sample sizes need to be interpreted with caution, as the results may not be generalisable to the wider MS population.

4.3.2 Sample characteristics

The good response rate increases the likelihood that the sample was representative of the MS population as a whole. However, it is not possible to know the characteristics of those who did not respond. There may be a response bias in the sample, given that they were self-selecting. For example, the responders may be individuals for whom cognitive impairment is particularly relevant. Alternatively, those who are severely cognitively impaired may be less likely to respond. Two cases were excluded because it was obvious that the responses were from their relative’s point of view. In a questionnaire sample it is difficult to ensure that all responses are from the participant’s own point of view. Unfortunately, this may be more of a problem for those patients who are more severely cognitively or physically impaired.
One difference in this sample was the prevalence of each MS subtype compared to other MS populations. There are a number of reasons why the proportions of subtypes may differ from other samples. The current sample contained only individuals with clinically definite MS, excluding those with probable MS, which some studies (e.g. Foong et al, 1997) have used. The main difference is that the subtype data in the current study is self-reported and, unfortunately, neurological validation of this data was not possible for the majority of the sample. It is not possible to verify whether the differences represent true differences in the prevalence of subtype, a bias in response or a lack of knowledge on the patients' behalf. It is also possible, however, that in previous studies, neurological subtype data was incorrect and that patients themselves may be well-informed of the MS subtype they experience. A difference may also lie in the use of terminology; for example, the term "benign" is not universally used.

4.3.3 Possible confounding variables

Some patients reported experiencing other illness, which provided some useful data on the co-morbidity of other illnesses with MS. However, those other illnesses may affect mobility, cognition, health status and mood and this is a possible confounding factor in the study. There were also a number of patients experiencing a relapse when they completed the questionnaire. Foong et al (1997) reports that cognitive impairment may increase during a relapse and return to baseline following exacerbation, and this may have affected the reports of cognitive impairment. However, excluding those patients reporting a relapse would have significantly reduced the sample size. It is also valuable to include these participants, as relapses are a fundamental aspect of the disease. A final confounding factor was that no data were collected on the medications or treatments
patients received. In the comments, some patients referred to physiotherapy, psychology and occupational therapy input, or medications, such as anti-depressants, Interferon and being on a medical trial for cannabis. Including such data in the analysis would not have been feasible. However, it is important to note that they may be factors affecting mood, cognitive impairment and health status.

4.3.4 Measures

4.3.4.1 Everyday Memory Questionnaire

This measure was criticised by participants for its lack of a category to indicate “never occurs” for the memory lapses (although there is a category for “once a month or less”), and some participants added their own category to indicate a particular memory lapse had never occurred. Unfortunately, no comparative data are available from a normal sample. However, one might expect it to be unusual for individuals to have no lapses in some types of memory tasks. This may indicate that the patients have an overly positive view of their memory ability, or find it difficult to admit memory difficulties. These factors indicate that the measure may lack face validity for this sample.

4.3.4.2 Dysexecutive Questionnaire

The DEX questionnaire was found to have good internal consistency. There were four questions that had slightly lower correlation coefficients, although they were still above the accepted value. These were “I sometimes get over-excited about things”, “I have difficulty showing emotion”, “I tend to be very restless” and “I find it difficult to stop myself from doing something”. These questions did not relate as well to a total score representing executive dysfunction. The patients and relatives used the maximum range
on all except one question. However, the mean and median values were very low, indicating low levels of reported executive dysfunction in the overall sample. This may suggest a restricted variance in DEX scores in the sample. The highest rated questions were “I am lethargic and unenthusiastic”, which may relate to fatigue in MS and “I have trouble making decisions”, which may reflect anxiety. Also a number of patients did not respond to the question, “I have difficulty realizing the extent of my problems and am unrealistic about the future”. Given the unpredictability of disease course in MS, this question may pose particular difficulty for MS patients.

It was not possible in the current study to investigate whether the five-factor structure was replicable for MS patients. Burgess et al (1998) used relatives’ data for their factor analysis and the relatives’ sample was not large enough in the current study. Further investigation would provide additional information on whether the DEX questionnaire is valid for MS samples and whether it has the same structure.

4.3.5 Design

The cross-sectional nature of the study poses some difficulties for interpretation of the findings and does not allow questions of causality to be addressed. The questionnaire survey only provides a snap-shot picture of the cognitive impairment, mood and health status reported by patients and their relatives. This does not provide information on how these variables change over time, which, given the progressive and unpredictable nature of MS, is likely to be an important factor.
4.3.6 Biases in self-report data

There are a number of factors that are likely to bias subjective reports. Richardson (1996) notes that subjective reports of cognitive impairment are vulnerable to observational biases. Self-reports will be biased by how easily different types of memory failure can be remembered and those that suffer memory failures are likely to forget such failures (Sunderland *et al.*, 1983). Relatives’ reports of cognitive impairment will be biased by how easily the memory failure can be observed. The environment is also likely to play an important factor. For example, patients may have limited lives as a result of MS and, therefore, be exposed to less demanding situations. This was noted in some of the questionnaire responses. For example, some patients were unable to rate whether they lost the thread of a story in a book because they were unable to read due to visual problems. Some patients made comments regarding the use of strategies, such as planning events and the use of diaries. This is also likely to affect the reports of themselves and others.

MS patients and their relatives may also be reluctant to admit to cognitive impairment in the face of progressive physical deterioration (Taylor, 1990). This may lead both to under-report the occurrence of cognitive impairment. Relatives may also overlook cognitive impairment or attribute it to emotional problems, such as depression (Rao *et al.*, 1992). Vinck *et al* (1997) emphasise that a patient’s mood and an expectation of cognitive impairment may have a strong influence on the perception and reporting of cognitive impairment. Responses on questionnaires may also be confounded by fatigue in MS patients and negative responses may reflect indifference or loss of motivation.
4.4 INTERPRETATION OF THE FINDINGS

Despite these methodological limitations, a number of interesting findings were revealed.

4.4.1 Prevalence of subjective cognitive impairment

MS patients and their relatives reported them as experiencing less executive dysfunction than a predominantly TBI population. This is as predicted since MS patients would be expected to experience less severe frontal lobe impairment. Levels were low in the sample as a whole, but the scores indicated that some individuals reported very low levels of executive dysfunction and some reported very high levels of executive dysfunction. This is also as expected in a mixed MS sample, given that some individuals would be expected to be cognitively impaired and others cognitively intact.

MS patients reported themselves as experiencing similar levels of executive dysfunction as that reported in a normal population. This is not as predicted since some MS patients would be expected to experience more executive dysfunction than healthy controls. Their relatives reported them as experiencing more than in a normal population, which is as predicted.

The amount of memory impairment reported by patients was lower than in a neuro-rehabilitation sample. This finding is as predicted since the neuro-rehabilitation sample are more likely to have more severe cognitive difficulties. The amount of memory impairment reported by relatives was not significantly different, suggesting that the
relatives perceive patients as exhibiting the same level of memory difficulties as a more severely disabled population.

Both these results indicate that patients report less cognitive impairment compared to their relatives. One hypothesis is that these findings indicate a lack of insight or awareness for some patients, whereby those with executive dysfunction are less aware of their own difficulties and/or those with memory impairment cannot remember their memory difficulties. This would fit with the known effects of executive dysfunction, which include a lack of insight or denial of problems (Prigatano and Schacter, 1991) and the difficulties with memory reporting highlighted by Sunderland et al (1983).

However, there was no significant discrepancy between patients and relatives reports of executive dysfunction in the overall sample. This reflects the similar findings of Richardson (1996) in relation to reports of memory impairment. This might seem to suggest that lack of insight or denial was not an issue in this sample and it is certainly not possible to conclude a lack of insight in the sample as a whole. However, the amount of discrepancy between patient and relative scores was significantly lower than that found in a predominantly TBI population and higher than found in normal controls. TBI patients commonly under-report symptoms of executive dysfunction, usually attributed to a lack of insight and normal controls have been found to over-report executive dysfunction. The reasons for this have not been investigated, although it is possible that emotional factors such as anxiety, or social desirability contribute. The current group of MS patients as a whole differed from both of these populations.
These results seem to indicate a mixed population with a range of cognitive impairment reported by patients and relatives with some patients experiencing high levels of cognitive impairment and others not, and some patients lacking awareness of these difficulties and others not. This is as expected given the mixed community sample of MS patients. Overall, the pattern seems to indicate a greater similarity to the normal population, with non-significant discrepancies overall and low mean values on the two measures. However, conclusions regarding the relationship between the patient and relatives’ reports of cognitive impairment and actual underlying impairment are not possible in the absence of objective assessments.

4.4.2 Differences within the overall group

Using the DEX discrepancy scores, the sample was split into two groups – individuals who over-report and those who under-report executive difficulties in comparison to their relatives. Over-reporters were more likely to have relapsing-remitting MS, report higher levels of anxiety, report higher levels of memory impairment and have lower levels of relative-reported memory impairment. It is possible that the under-reporters are those patients who experience executive dysfunction and lack insight into their difficulties, although it is not possible to test this out in the current design. There appear to be two possible explanations for the second group of over-reporters. This group was characterized by high levels of anxiety, by relapsing-remitting MS (more unpredictable) and also over-reported memory impairment in comparison to their relatives. It is possible that this group comprises more distressed individuals, who find it difficult to adjust to the unpredictable course of their disease and are more anxious, leading them to over-report symptoms. These patients appear similar to those described by Gervasio and
Blusewicz (1988) as maintaining a "sick role". It is also possible that this group resembles more the group of normal controls in Burgess et al.'s study, who also over-reported symptoms compared to their relatives. The comments made by some patients would seem to tentatively support the former hypothesis, although this requires further investigation.

4.4.3 Does subjective cognitive impairment predict health status?

Physical role limitations were found to be correlated with higher levels of self-reported memory impairment and executive dysfunction and relative-reported memory impairment. These findings suggest a correlation between physical disability and perceived and observed cognitive impairment. However, the regression analyses were not appropriate, so it is not possible to draw conclusions regarding the predictive power of these variables.

Self-reported cognitive impairment was not predictive of social functioning. Depression was the only predictor of social functioning, with those reporting higher levels of depression having poorer social functioning. Depression is likely to be a disabling condition, which will limit an individual's social functioning. Individuals with depression are also more likely to be more withdrawn and lethargic and find it difficult to be socially active. However, Smith and Young (2000) found that MS patients who were depressed were also more likely to negatively rate their disability. This finding may, therefore, reflect those who are depressed perceiving their social functioning as low.
Self-reported cognitive impairment was also not found to be predictive of employment status. Individuals with poorer physical functioning and primary-progressive MS were more likely to be no longer working. This finding would seem to indicate the primary importance of physical functioning in remaining in work. However, one would also expect those with primary-progressive MS to have more severe cognitive impairment. Therefore, perhaps cognitive impairment is a predictive factor, but the measures are not sufficient.

Overall, in the current study, it can be concluded that subjective cognitive impairment is not predictive of health status, as measured by social functioning and employment status. This supports the findings of Higginson et al (2000), who found that neither self or relatives reports of memory impairment were predictive of functional status. In previous studies, neuropsychological measures of cognitive impairment have been found to be predictive of health status. It is possible, therefore, that subjective measures are not adequate in this respect, although further investigation is required to understand these differences.

4.4.4 Does subjective cognitive impairment predict mood?

The sample reported significantly higher levels of anxiety and depression than the normal population and reported particularly high levels of anxiety. This finding is important especially given the wealth of literature on depression in MS and the lack of research on anxiety.
Self-reported executive dysfunction was found to be predictive of depression and anxiety. The discrepancy between patient and relative reports was also found to predict depression, with a lower discrepancy score being predictive of higher levels of depression. This finding may suggest that those who report lower levels of executive dysfunction and whose relatives report them as experiencing high levels of executive dysfunction (i.e. those who lack insight or deny difficulties) report lower levels of depression. This supports the finding of Rao et al (1992), who suggest that lack of awareness of symptoms may lead to less distress in some MS patients. These different results require further investigation. The results may also indicate that those with cognitive impairment have higher levels of depression. An alternative explanation for these findings is that depression has an adverse effect on the perception and reporting of cognitive impairment (Vinck et al, 1997). When subtype data were excluded to increase the sample size, patient reported executive dysfunction was the only predictor of depression. This results brings into question the role of insight in predicting mood and supports the finding that either those who experience higher levels of executive dysfunction experience higher levels of depression and *vice versa*, or that those with higher levels of depression perceive greater cognitive difficulties. In the current design it is not possible to clarify these hypotheses.

Anxiety was predicted by higher levels of patient reported executive dysfunction and by relapsing-remitting-MS. This suggests that those with relapsing-remitting MS experience greater levels of anxiety, as would be expected. Seligman (1975) suggests that unpredictable stress (such as would be experienced in a relapsing-remitting disease course) leads to a sense of helplessness and has a negative impact on behaviour. The
role of self-reported executive dysfunction in the prediction of anxiety is less clearly understood, in the absence of relative-reported executive dysfunction. It is possible that those individuals who experience executive dysfunction experience anxiety as a result. However, it is also possible that anxiety leads to an over-reporting of symptoms of executive dysfunction.

4.5 THEORETICAL AND CLINICAL IMPLICATIONS

In the current study, self-reported cognitive impairment was found to be related to perceived physical limitations, depression, and anxiety. These findings highlight relationships between subjective reports of cognitive impairment and mood and health status that have not been investigated before in MS. A number of hypotheses have been proposed to understand these relationships, but further studies are needed to clarify these hypotheses.

One theory which may provide a useful framework for understanding the current findings is that of illness representations (Nerenz and Leventhal, 1983), which places an importance on the beliefs an individual holds about their illness. An individual can conceptualise an illness in terms of identity, causes, consequences, timeline and controllability (Weinman, Petrie, Moss-Morriss and Horne, 1996) and representations of these dimensions are thought to affect the individual’s beliefs, illness behaviour and adjustment to the illness. Illness representation theory may be a useful model for understanding some of the current findings. For example, certain beliefs, such as the expectation, presence, extent or impact of any cognitive impairment or physical
limitations may affect the perception and reporting of cognitive impairment, health status and mood.

In the current design it is not possible to conclude to what extent these subjective reports relate to actual cognitive impairment. However, the implications of subjective cognitive impairment, irrespective of actual cognitive impairment should be considered. Vinck et al (1997) suggest that it is not important whether subjective reports of cognitive impairment reflect actual cognitive impairment or perceived cognitive impairment. They suggest that if patients are reporting cognitive impairment then this should be addressed in any rehabilitation program and that the emotional and social variables associated with these reports should be examined and addressed if possible.

The findings indicate that patient and relative responses on the DEX questionnaire are internally reliable. The measure potentially provides a useful structured and informal measure of executive dysfunction, although at present the self-reports of patients and their relatives need to be used in the context of additional neuropsychological assessment. In TBI populations, relatives' reports are considered to be the more valid measure of executive dysfunction. In the current study, relative scores were not found to be related to health status or mood, however, patient scores on the DEX were found to be related to mood. Self-reported DEX scores, therefore, appear to be a useful indicator of a patient's distress. These findings indicate a clinical use for this measure in an MS population, but further investigations are required to fully understand its use.
The findings indicate that some MS patients underestimate their level of cognitive impairment (both executive dysfunction and memory impairment) in comparison to their relatives whilst others may overestimate their level of cognitive impairment in comparison to their relatives. The clinician would be advised to gain reports both from the patient and another informant to provide additional information for the clinical assessment. This supports the findings of Hermann (1982) who recommends the use of relatives’ reports in conjunction with patient reports in the assessment of cognitive impairment. The use of both patient and relatives scores in MS may help to clarify any problems with insight or misattribution of cognitive symptoms. The findings suggest a possible role for a lack of insight and/or anxiety in the reporting of cognitive impairment and the discrepancy between patient and relatives reports, which may be useful in informing clinical assessment and intervention.

The findings support previous studies, indicating high prevalence rates of anxiety and depression in this patient population. This highlights a need for interventions aimed at addressing the psychological distress associated with MS. The study also found a link between depression and social functioning, which indicates that depressed MS patients are likely to experience reduced social functioning. This could be addressed in psychological intervention.

4.6 SUGGESTIONS FOR FUTURE RESEARCH

From the results, a number of further hypotheses have been raised which cannot be elucidated in the current design, but which require further investigation. In the current findings self-reported cognitive impairment was related to other variables, such as
physical role limitations, depression and anxiety. However, it is not clear whether the self-reported cognitive impairment represents actual underlying cognitive impairment, or reflects a more negative perception of cognitive ability due to distress. These findings need to be investigated further using neuropsychological assessment, which would allow a comparison with objective measures of cognitive impairment. The role of lack of insight or denial of difficulties also requires further investigation with the use of more objective measures.

Future research would also benefit from improved data on subtype, and a larger sample size for relatives' reports. A longitudinal design would be ideal, allowing any changes with the progression of the disease to be investigated and causal relationships to be explored. Given the complexity of the area and individual differences, future research may also benefit from more detailed analysis of qualitative data.

The current study investigated the presence of subgroups within the MS sample of individuals who report cognitive impairment in different patterns and can be distinguished on certain characteristics. These findings partly address the criticisms of previous research, which has used homogenous groups of MS patients and therefore, potentially masked relationships between factors. The current study found the apparent existence of two groups – those who over-report and those who under-report executive dysfunction compared to their relatives. This finding requires further exploration. It needs to be replicated using a larger sample size and the differences between the groups explored further. Further investigation would be useful to help understand whether those who under-report are experiencing executive dysfunction and lack insight into their
difficulties, and whether those who over-report are particularly distressed, or similar to normal controls. It would be especially interesting to investigate the characteristics of the relatives in relation to over-reporters and under-reports to understand the discrepancy scores more fully.

An interesting avenue for further research might be to investigate the effects of these variables on an individual’s self-concept. Taylor (1996) suggests that in the context of progressive disability, patients may lower their levels of aspiration and the reference groups with whom they compare their performance. Such factors may affect self-reported cognitive impairment and would be a useful adjunct to future research.

Finally, further investigation of the measures is required. The DEX questionnaire would benefit from additional psychometric analysis, especially factor analysis to understand whether the same factor structure applies in MS as exists in TBI populations. The EMQ would also benefit from additional psychometric analysis and improvements to its face validity, especially in this patient population.

4.7 CONCLUSIONS

In the context of a heterogeneous patient population with a range of cognitive, physical and emotional difficulties, this study aimed to investigate the usefulness of self-reported cognitive impairment as an additional tool in clinical assessment. Relationships were found between self-reported cognitive impairment and physical limitations, and between self-reported executive dysfunction and depression and anxiety. The discrepancy
between patient and relatives scores was also found to be a potentially useful source of information.

In the current design it is not possible to clarify the relationship between the subjective reports and actual cognitive impairment. The amount of cognitive impairment reported by patients and relatives is likely to be subject to a number of biases and to emotional factors and overall, it is probable that several factors are operating in the self-report of cognitive impairment by patients and their relatives. However, the self-reports of patients and their relatives seem to be potentially useful clinical tools for the assessment of MS patients. Further research is required to understand the potential role of self-reported cognitive impairment and its usefulness in understanding MS patients' difficulties.
REFERENCES


Self-reported executive dysfunction in multiple sclerosis


APPENDICES

Appendix A: Ethics Committee letters

Appendix B: Patients’ letter and questionnaires

Appendix C: Patients’ reminder letter

Appendix D: Relatives’ letter and questionnaires

Appendix E: Relatives’ reminder letter
Dear Ms Atkins,

Re: NC1074 – The Pattern and Significance of Self-Reported Executive Dysfunction in Individuals with Multiple Sclerosis

I refer to your application to the Local Research Ethics Committee for consideration of the above project. I am pleased to inform you that the Committee approves the project on ethical grounds on the understanding that:

i. Any ethical problem, arising in the course of the project, will be reported to the Committee.

ii. Any change in the protocol will be reported to the Committee.

iii. The Data Protection Act 1998 be adhered to.

iv. There is compliance, throughout the conduct of the study, with good clinical research practice.

v. The Committee be informed if the research is discontinued for any reason.

vi. A report be submitted after completion.

vii. Ethical approval is for three years from the date of this letter

Ethical approval by the Committee is not an authority to proceed. You are advised to discuss your proposal with all heads of departments and others who might be affected, particularly if there are financial and/or staffing implications.

31st August 2001

Ms L Atkins
Trainee Clinical Psychologist
Oxford Doctorate Course in Clinical Psychology
Isis Education Centre
Warneford Hospital
Oxford OX3 7JX
Dear Ms Atkins,

28/01 The pattern and significance of self-reported executive dysfunction in MS

Thank you for attending the meeting on 25th July 2001 to speak on the above protocol. Please accept my apology for the delay in responding formally to you.

The protocol was reviewed under LREC procedures and approved. However, the Committee did make the following suggestions and recommendations. The introductory letter should advise patients that selection for the follow up element of the study will be on a random basis and contact details on the questionnaire should be clearer. In addition the element of GP involvement should be removed from the study.

I attach a list of the Committee members present for your retention. The Committee complies with the ICH GCP guidelines on the composition, functions and operations of Independent Ethics Committees. The Committee is accountable to Buckinghamshire Health Authority. A copy of the constitution of the Committee is available on request.

If you have any queries or require further assistance, please do not hesitate to contact me.

Once again thank you for taking the time to attend the meeting.

Yours sincerely,

Ann Frew,
Acting Secretary,
Milton Keynes Local Research Ethics Committee.
Dear

We are currently undertaking a study about some of the physical and psychological effects of multiple sclerosis. You are being invited to take part in this research study. If you are interested in filling out the questionnaire please read the enclosed information sheet. After having read the information sheet, if you would like to take part in the study, please sign the enclosed consent form and complete the questionnaires.

If you have find any difficulty, you may fill in the questionnaire with help from a friend or relative or contact Elisabeth Atkins on the above number to complete the questions over the telephone.

Please return the completed consent form and questionnaires in the envelope provided. If you do not wish to participate please return the blank questionnaire in the envelope provided.

We would also like to hear the views of a family member or friend who knows you well. If you are happy for us to send questionnaires to a relative or friend, please write their name and address on the questionnaire and we will contact them. Any information supplied by you or them will be completely confidential to the researchers.

We look forward to hearing from you and many thanks for your time. Please do not hesitate to get in touch with us at the above number if you have any query.

Yours sincerely
INFORMATION SHEET

Study Title
The pattern of cognitive difficulties reported in multiple sclerosis.

Introduction
You are being invited to take part in a research study about multiple sclerosis. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
People with multiple sclerosis report difficulties in many different areas of their life, such as physical symptoms, cognitive (thinking) problems, emotional changes and social difficulties. This research aims to investigate the types of difficulties people with multiple sclerosis report and the relationship between these difficulties. This will further our understanding of the effects of multiple sclerosis.

Why have you been chosen?
Individuals have been selected through the clinics of Dr Briley, Consultant Neurologist at Stoke Mandeville Hospital and Dr Hilton-Jones, Consultant Neurologist at Milton Keynes General Hospital (names changed for Milton Keynes sample). Individuals who have been diagnosed with multiple sclerosis have been contacted for this study.

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

What would happen to you if you take part?
If you agree to take part you would be asked to complete a number of questions about your physical and psychological health and how multiple sclerosis affects you in your everyday life. You will also be asked to name someone who knows you well, who could also answer similar questions from their point of view.

At a later date, a small number of people may be randomly selected and invited to take part in a second stage of the study, which would involve an assessment of cognitive functioning or an interview. Further information would be provided at the time and people would be able to decide whether they wished to take part or not.
Would my taking part in this study be kept confidential?
All information will remain completely confidential.

What would happen to the results of the research study?
The results of the study will be written up in the form of a thesis and the intention is to also produce academic papers. Although no individual feedback will be available, a summary of the results will be sent to all participants who would like to receive one.

Who is organising and funding the research?
The study is being carried out by Elisabeth Atkins (Trainee Clinical Psychologist) as part of the research requirements of the Oxford Doctoral Course in Clinical Psychology.

Who has reviewed the study?
This study has been reviewed and approved by the following ethics committees:
- Aylesbury Vale Local Research Ethics Committee
- Milton Keynes Local Research Ethics Committee

Contact for Further Information
For more details, please contact:
Elisabeth Atkins
Rayners Hedge
Croft Road
Aylesbury
Bucks, HP21 7RD
Tel: 01296 393319

Please also remember that should the questionnaire raise any personal issues for you, you may discuss these concerns with the researcher, or your Consultant.

Thank you for your time.

Please keep this front sheet for your information.
CONSENT FORM

Title of Project:
The pattern of cognitive difficulties reported in multiple sclerosis.

Name of Researchers:
Elisabeth Atkins, Trainee Clinical Psychologist
Mr John Pimm, Consultant Clinical Psychologist
Dr Gavin Newby, Principal Clinical Psychologist

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I agree to take part in the above study.

Name of participant __________________________ Date ___________ Signature ___________

Would you like to receive a summary of the results of this study? Yes/ No

PLEASE RETURN THIS FORM WITH YOUR QUESTIONNAIRES
BACKGROUND INFORMATION

I would be grateful if you would answer the following questions:

Age: ______________________

Gender: Male/Female

Marital status:  
> Single  □
> Married  □
> Divorced  □
> Widowed  □
> Co-habiting  □
> Other: _____________________________

Number of family members in household: __________

In what year were you diagnosed with multiple sclerosis? ______________

When did you first notice any symptoms of multiple sclerosis? ______________

Do you know what type of multiple sclerosis you have? Yes/ No/ Not sure.

If yes, what diagnosis do you have? (please tick)
  > Relapsing-remitting  □
  > Primary-progressive  □
  > Secondary-progressive  □
  > Other: _____________________________

Current or most recent occupation: _____________________________

Are you working at the moment: Yes/ No

If yes, are you working part-time/ full-time

What are your job details? _____________________________

Has your work situation changed as a result of multiple sclerosis? Yes/ No

If yes, in what way (please tick any appropriate boxes)
  > Changed job  □
  > Changed work tasks within same job  □
  > Reduced hours  □
  > Gone part-time  □
  > Taken sick leave  □
  > How many days in the last year? _______
  > Taken early retirement through illness  □
What are your highest qualifications: ______________________________________________

Do you drive a car? Yes/ No

Has your ability to drive a car changed as a result of multiple sclerosis? Yes/ No

If yes, in what way? ____________________________________________________________

Do you ever experience a relapse or “flare up” of symptoms of MS? Yes/ No

If yes, are you currently experiencing a relapse or “flare up” of symptoms? Yes/ No

Do you have any other illness? Yes/ No

If yes, please describe: _________________________________________________________

Please provide a name and address of a relative or friend who knows you well, who would be able to complete questionnaires on their view of how multiple sclerosis has affected you.

Name: __________________________________________________________
Relationship to you: ____________________________________________
Address: ________________________________________________________

Please provide a telephone number so that the researcher can contact you should there be any queries: ________________________________

Thank you.
Please turn over to the questionnaires.
MEMORY QUESTIONNAIRE

Below are listed some examples of things that happen to people in everyday life. Some of them may happen frequently and some may happen very rarely. We should like to know how often on average you think each one has happened to you over the past month. We realise that people vary from day to day depending on their mood and the exact circumstances they are in. However, we would like you to try and give us an OVERALL impression of how often these things happen to you. Circle the appropriate number beside each item.

<table>
<thead>
<tr>
<th></th>
<th>Once or less in the last month</th>
<th>More than once a month but less than once a week</th>
<th>About once a week</th>
<th>More than once a week but less than once a day</th>
<th>Once or more in a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Forgetting where you have put something. Losing things around the house.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>2. Failing to recognise places that you have often been to before.</td>
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<td>3. Finding a television story difficult to follow.</td>
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<td>4. Not remembering a change in your daily routine, such as a change in the place where something is kept, or a change in the time something happens. Following your old routine by mistake.</td>
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<td>5. Having to check whether you have done something that you should have done.</td>
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<td>6. Forgetting when it was that something happened; for example, whether it was yesterday or last week.</td>
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<td>7. Completely forgetting to take things with you or leaving things behind and having to go back and fetch them.</td>
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<td>8. Forgetting that you were told something yesterday or a few days ago, and maybe having to be reminded about it.</td>
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<td>9.</td>
<td>Starting to read something (a book or an article in a newspaper, or a magazine) without realising you have already read it before.</td>
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<td>10.</td>
<td>Letting yourself ramble on to speak about unimportant or irrelevant things.</td>
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<tr>
<td>11.</td>
<td>Failing to recognise, by sight, close relatives or friends that you meet frequently.</td>
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<tr>
<td>12.</td>
<td>Having difficulty picking up a new skill. For example, finding it hard to learn a new game or to work some new gadget after you have practised it once or twice.</td>
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<tr>
<td>13.</td>
<td>Finding that a word is “on the tip of your tongue”. You know what it is but cannot quite find it.</td>
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<tr>
<td>14.</td>
<td>Completely forgetting to do things you said you would do, and things you planned to do.</td>
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<tr>
<td>15.</td>
<td>Forgetting important details of what you did or what happened to you the day before.</td>
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<tr>
<td>16.</td>
<td>When talking to someone, forgetting what you have just said. Maybe saying “What was I talking about?”</td>
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<tr>
<td>17.</td>
<td>When reading a newspaper or magazine being unable to follow the thread of a story; losing track of what it is about.</td>
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<tr>
<td>18.</td>
<td>Forgetting to tell somebody something important. Perhaps forgetting to pass on a message or remind someone of something.</td>
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<td><strong>Same scale as previous page</strong></td>
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<tr>
<td>19. Forgetting important details about yourself, e.g. your birth date or where you live.</td>
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<tr>
<td>20. Getting the details of what someone has told you mixed up and confused.</td>
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<tr>
<td>21. Telling somebody a story or joke that you have told them once already.</td>
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<tr>
<td>22. Forgetting details of things you do regularly, whether at home or at work. For example, forgetting details of what to do, or forgetting at what time to do it.</td>
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<tr>
<td>23. Finding that the faces of famous people seen on the television, or in photographs, look unfamiliar.</td>
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<tr>
<td>24. Forgetting where things are normally kept or looking for them in the wrong place.</td>
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<tr>
<td>25. Getting lost or turning in the wrong direction on a journey, on a walk, or in a building where you have OFTEN been before.</td>
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<tr>
<td>26. Getting lost or turning in the wrong direction on a journey, on a walk, or in a building where you have ONLY BEEN ONCE OR TWICE before.</td>
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<tr>
<td>27. Doing some routine thing twice by mistake. For example, putting two lots of tea in the teapot, or going to brush/comb your hair when you have just done so.</td>
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<tr>
<td>28. Repeating to someone what you have just told them or asking someone the same question twice.</td>
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</tbody>
</table>
HOSPITAL ANXIETY AND DEPRESSION SCALE

Read each item below and underline the reply which comes closest to how you have been feeling in the past week. Don’t take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or “wound up”
Most of the time
A lot of the time
From time to time, occasionally
Not at all

I still enjoy the things I used to enjoy
Definitely as much
Not quite so much
Only a little
Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
Very definitely and quite badly
Yes, but not too badly
A little, but it doesn’t worry me
Not at all

I can laugh and see the funny side of things
As much as I always could
Not quite so much now
Definitely not so much now
Not at all

Worrying thoughts go through my mind
A great deal of the time
A lot of the time
Not too often
Very little

I feel cheerful
Never
Not often
Sometimes
Most of the time

I can sit at ease and feel relaxed
Definitely
Usually
Not often
Not at all

I feel as if I am slowed down
Nearly all the time
Very often
Sometimes
Not at all

I get a sort of frightened feeling like “butterflies” in the stomach
Not at all
Occasionally
Quite often
Very often

I have lost interest in my appearance
Definitely
I don’t take as much care as I should
I may not take quite as much care
I take just as much care as ever

I feel restless as if I have to be on the move
Very much indeed
Quite a lot
Not very much
Not at all

I look forward with enjoyment to things
As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all

I get sudden feelings of panic
Very often indeed
Quite often
Not very often
Not at all

I can enjoy a good book or radio or television programme
Often
Sometimes
Not often
Very seldom
This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your own experience:

1. I have problems understanding what other people mean unless they keep things simple and straightforward
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

2. I act without thinking, doing the first thing that comes to mind
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

3. I sometimes talk about events or details that never actually happened, but I believe did happen
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

4. I have difficulty thinking ahead or planning for the future
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

5. I sometimes get over-excited about things and can be a bit ‘over the top’ at these times
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

6. I get events mixed up with each other, and get confused about the correct order of events
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

7. I have difficulty realizing the extent of my problems and am unrealistic about the future
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

8. I am lethargic, or unenthusiastic about things
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

9. I do or say embarrassing things when in the company of others
   - Never
   - Occasionally
   - Sometimes
   - Fairly often
   - Very often

10. I really want to do something one minute, but couldn’t care less about it the next
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

11. I have difficulty showing emotion
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

12. I lose my temper at the slightest thing
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

13. I am unconcerned about how I should behave in certain situations
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

14. I find it hard to stop repeating saying or doing things once I’ve started
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

15. I tend to be very restless, and ‘can’t sit still’ for any length of time
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

16. I find it difficult to stop myself from doing something even if I know I shouldn’t
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

17. I will say one thing, but will do something different
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

18. I find it difficult to keep my mind on something, and am easily distracted
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

19. I have trouble making decisions, or deciding what I want to do
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often

20. I am unaware of, or unconcerned about, how others feel about my behaviour
    - Never
    - Occasionally
    - Sometimes
    - Fairly often
    - Very often
HEALTH STATUS QUESTIONNAIRE

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities.

General Health

Please tick one box for each question.

1. In general would you say your health is:
   - Excellent □
   - Very good □
   - Good □
   - Fair □
   - Poor □

2. Compared to one year ago, how would you rate your general health now?
   - Much better now than one year ago □
   - Somewhat better now than one year ago □
   - About the same □
   - Somewhat worse now than one year ago □
   - Much worse now than one year ago □

Health and Daily Activities

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much? Please tick one box on each line.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes limited a lot</th>
<th>Yes limited a little</th>
<th>No not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.</td>
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<tr>
<td>Lifting or carrying groceries</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td></td>
<td></td>
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<tr>
<td>Bending, kneeling or stooping</td>
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<tr>
<td>Walking more than a mile</td>
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<tr>
<td>Walking half a mile</td>
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<tr>
<td>Walking 100 yards</td>
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<tr>
<td>Bathing and dressing yourself</td>
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</tbody>
</table>
4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? Answer Yes or No to each question.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had to cut down on the <strong>amount of time</strong> you spent on work or other activities</td>
<td></td>
</tr>
<tr>
<td>Accomplished <strong>less</strong> than you would like</td>
<td></td>
</tr>
<tr>
<td>Were limited in the <strong>kind</strong> of work or other activities you could do</td>
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</tr>
<tr>
<td>Had any <strong>difficulty</strong> performing the work or other activities (e.g. it took extra effort)</td>
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</tbody>
</table>

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Answer Yes or No to each question.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had to cut down on the <strong>amount of time</strong> you spent on work or other activities</td>
<td></td>
</tr>
<tr>
<td>Accomplished <strong>less</strong> than you would like</td>
<td></td>
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<tr>
<td>Didn’t do work or other activities as <strong>carefully</strong> as usual</td>
<td></td>
</tr>
</tbody>
</table>

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? Please tick one.

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?

- None
- Very mild
- Mild
- Moderate
- Severe
- Very severe
8. During the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework)? Please tick one

- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

**Your Feelings**

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please indicate the answer that comes closest to the way you have been feeling. Please tick one box on each line

<table>
<thead>
<tr>
<th>How much time during the past 4 weeks ....</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel full of life?</td>
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<td>Have you been a very nervous person?</td>
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<td>Have you felt so down in the dumps that nothing could cheer you up?</td>
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<td>Have you felt calm and peaceful?</td>
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<td>Did you have a lot of energy?</td>
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<tr>
<td>Have you felt downhearted and low?</td>
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<td>Did you feel worn out?</td>
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<td>Have you been a happy person?</td>
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<td>Did you feel tired?</td>
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<td>Did you feel rested on waking in the morning?</td>
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</tbody>
</table>

During the past 4 weeks how much has your physical health or emotional problems interfered with your social activities (like visiting friends/relatives)? Please tick one.

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time
- Extremely
Health in General

10. Please choose the answer that best describes how true or false each of the following statements is for you. Please tick one box on each line.

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Not sure</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get ill more easily than other people.</td>
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<tr>
<td>I am as healthy as anybody I know.</td>
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<tr>
<td>I expect my health to get worse.</td>
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<tr>
<td>My health is excellent</td>
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</table>

Cognitive Function

11. The following questions are about problems you may have experienced with your 'cognitive functions'. That is, problems with tasks involving memory, concentration or problem solving. Please tick one box on each line.

<table>
<thead>
<tr>
<th>How much time during the past 4 weeks ....</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had difficulty concentrating and thinking?</td>
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<tr>
<td>Did you have trouble keeping your attention on an activity for long?</td>
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<tr>
<td>Have you had trouble with your memory?</td>
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<tr>
<td>Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?</td>
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</tbody>
</table>
Quality of Life

Overall, how would you rate your own quality of life? Please circle one number on the scale below.

Which best describes how you feel about your life as a whole? Please tick one.

- Terrible
- Unhappy
- Mostly dissatisfied
- Mixed-about equally satisfied and dissatisfied
- Mostly satisfied
- Pleased
- Delighted

Please write down any other comments you would like to make. For example, you may wish to expand on some of your answers or comment on another aspect of MS.

THIS IS THE END OF THE QUESTIONNAIRE. THANK YOU VERY MUCH FOR TAKING THE TIME TO COMPLETE IT. PLEASE POST IT IN THE ENCLOSED ENVELOPE WITH YOUR SIGNED CONSENT FORM.
APPENDIX C

Dear

We wrote to you recently, as a friend/relative of someone with multiple sclerosis, inviting you to participate in the above research project on the physical and psychological effects of multiple sclerosis. To date we have not received a response from you. Your views would be invaluable in helping us understand how we can help people with MS.

If you would like to participate in the study we would be grateful if you could return the completed questionnaire in the envelope provided as soon as possible. If you would like another set of questionnaires, please contact us on the above telephone number. If you would not like to participate we would be grateful if you would return the blank questionnaire in the envelope provided.

We look forward to hearing from you and many thanks for your time. Please do not hesitate to get in touch with us at the above number if you have any query.

Yours sincerely
Dear

We are currently undertaking a study about some of the physical and psychological effects of multiple sclerosis. "Patient name" has taken part in this study and agreed for us to contact you to gain your views on how multiple sclerosis affects them.

If you are interested in taking part, please read the enclosed information sheet. After having read the information sheet, if you would like to take part in the study, please sign the enclosed consent form and complete the questionnaires. Return them both in the envelope provided. If you do not wish to participate please return the blank questionnaire in the envelope provided.

Any information you provide will be completely confidential to the researchers. We look forward to hearing from you and many thanks for your time. Please do not hesitate to get in touch with us at the above number if you have any query.

Yours sincerely
INFORMATION SHEET
Same as patients’ information sheet with minor amendments.

CONSENT FORM
Same as patients’ consent form
BACKGROUND INFORMATION

I would be grateful if you would answer the following questions:

Age: ___________________________

Gender: Male/ Female

What is your relationship to the individual in the study? (Please tick)
- Husband □
- Wife □
- Partner □
- Mother □
- Father □
- Sister □
- Brother □
- Son □
- Daughter □
- Friend □
- Carer □
- Other □ (please specify) ______________________

Do you live with them? Yes/ No

If no, how often do you see them?
- Daily □
- Once a week □
- Once a month □
- Less than once a month □

How many years have you known them?

___________________________

Did you know them before they were diagnosed with MS? Yes/ No

Thank you.
Please turn over to the questionnaires.
MEMORY QUESTIONNAIRE

DEX QUESTIONNAIRE

Same questionnaires as patients with the amended wording for informant completion
APPENDIX E

Dear

We wrote to you in December inviting you to participate in the above research project on the physical and psychological effects of multiple sclerosis. To date we have not received a response from you. Your views would be invaluable in helping us understand how we can help people with MS.

If you would like to participate in the study we would be grateful if you could return the completed questionnaire in the envelope provided as soon as possible. If you would like another set of questionnaires, please contact us on the above telephone number. If you would not like to participate we would be grateful if you would return the blank questionnaire in the envelope provided.

We look forward to hearing from you and many thanks for your time. Please do not hesitate to get in touch with us at the above number if you have any query.

Yours sincerely