THE IMPACT OF DYSEXECUTIVE AND METACOGNITIVE IMPAIRMENTS ON NEUROREHABILITATION OUTCOME IN MULTIPLE SCLEROSIS

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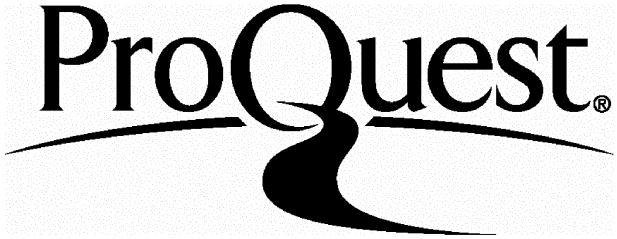
A thesis submitted in partial
fulfilment of the requirements for
the degree of

Doctor of Clinical Psychology
(D.Clin.Psy)

Vol. 1

University College London

2000



Abstract

The impact of dysexecutive and metacognition impairments on neurorehabilitation outcome in multiple sclerosis

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One of the most important aims of rehabilitation for patients with multiple sclerosis (MS) is to reduce their levels of disability and handicap. Despite clinical awareness that cognitive impairments are a common feature in the clinical presentation of MS and that specific deficits (especially dysexecutive syndrome) can impede rehabilitation success, there has been a dearth of empirical research into the impact of these cognitive impairments on rehabilitation outcome. This thesis set out to further characterise findings of both dysexecutive and metacognitive impairments in MS and how they might impact on neurorehabilitation outcome in MS.

22 participants with clinically probable MS were assessed on a cognitive battery, which included tests of executive function. In addition, to assess participants' insight into their executive test abilities, they were asked to rate their performance on each of the executive tests on a five-point scale. MS participants also completed a questionnaire about their dysexecutive problems in everyday life. Thirty matched healthy controls also completed the cognitive battery and the dysexecutive questionnaire. Relatives of both patients and controls rated participants' dysexecutive performance, which was used to

assess participants' degree of insight into everyday executive function. Rehabilitation outcome was monitored using the Functional Independence Measure (FIM) (motor and cognitive) and the Expanded Disability Status Scale (EDSS).

The MS participants were found to be weaker on the majority of dysexecutive tests, particularly on measures of rule learning and response suppression, compared to controls. Significant correlations were observed for the MS group's evaluations of recent executive test performance but not for the control group. Only one measure (Hayling Test A, a sentence completion task) predicted rehabilitation outcome (FIM cognitive gain).

The findings highlight the subtlety of insight and dysexecutive difficulties to the cognitive profile in MS and confirm previous findings of the importance of verbal skills to neurorehabilitation outcome.

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ACKNOWLEDGMENTS

I wish to thank my supervisors Drs' Dawn Langdon Paul Burgess. In particular Dawn, who gave me the opportunity, her invaluable guidance and experience and without whom, this work would not have been possible.

I am also grateful to Professor Thompson for firstly giving me the opportunity to be part of his team and for his continued support of the project.

I am most thankful to the therapy and nursing staff of the neurorehabilitation unit of the National Hospital, not just for their help in rating the MS participants on the outcome measures, but also for their kindness and warmth and making me feel part of a very hard working and skilled team.

I would like to extend my gratitude to all the participants who gave their valuable time and energy to help me with this work. Particularly the MS suffers who have also taught me a great deal about the experience of living with a progressive disease. Their enduring strength has been a humbling experience.

Thanks also to Pasco Fearon for statistical advice and Dr. Nancy Pistrang for her continued support.

Finally, a big thank you to my family Hazel, Sian and Miles, for once again putting up with my need for isolation and giving me the space to 'close the deal'.

CHAPTER 1

The nature of multiple sclerosis

Many chapters and papers on multiple sclerosis (MS) begin with the observation that MS is the commonest disabling neurological disease affecting young and middle-aged adults. From the first clinical description of the disease in the late 1830's, the attention has largely focused on neurological manifestations and it is only over the past decade that researchers, clinicians and perhaps the patients themselves, have really accepted the cognitive changes that accompany this disease. However, a burgeoning literature on the neuropsychology of MS attests to this new interest, although those with knowledge of the medical history of MS may find themselves somewhat perplexed as to why it has taken so long for this interest to ignite.

Before describing the cognitive changes associated with MS, reference will be made to the neurology and pathology of the disease. This chapter therefore begins with a summary of the pathogenesis, pathology, diagnosis, differential diagnosis and signs and symptoms of multiple sclerosis. With the focus of this thesis being on cognition, this introduction will by design be brief and those seeking more detailed explanations are encouraged to consult the many texts specifically devoted to these aspects. This chapter will however, discuss in depth the research guidelines for diagnosing MS and furnish clear definitions for terms that relate directly to the disease. These points are important, for they will clarify from the outset, many descriptive terms that appear throughout this thesis.

EPIDEMIOLOGY

Multiple sclerosis is a degenerative disease of the central nervous system (CNS), which causes destruction of the myelin sheath around the axons of the nerves fibres (Brassington & Marsh, 1998). This pathological process leads to defective nerve conduction. The disease has a predilection for certain areas such as the periventricular white matter, optic nerves, cerebellum, brain stem and the spinal cord.

In the United Kingdom, the lifetime risk is 1:800, which equates to about 60,000 people with the disease (Compston, 1990). The figure is considerably higher in the USA. There is a recognition that some cases of MS go undetected in life and appear as a chance finding at postmortem (Gilbert & Sadler, 1983). Estimates that up to 20% of cases fall into this category (e.g. Mackay & Hirano, 1967), does introduce a cautionary note in interpreting the epidemiological data.

It is well recognised that there is a greater prevalence of MS in the Northern Hemisphere, Europe and Australia compared to Asian, African and West Indian countries. Thus, MS is seen with greater frequency as the distance from the equator increases in either hemisphere (Gonzalez-Scarano et al. 1986; Skegg et al. 1987). There is also a greater incidence in females, twice as many in fact, with the common age of onset between the ages of 20-40.

ETIOLOGY

The etiology of MS remains unknown. However, genetic, environmental and immunologic influences are considered important. Contemporary immunologic explanations for MS include a delayed reaction to a common virus, a slow-acting virus and an autoimmune reaction in which the body

attacks its own tissues. On the other hand, figures such as a 25% concordance rate among monozygotic twins (e.g. Ebers and Bulman, 1986; White et al. 1992) provide reasonable evidence for a genetic component to this disease and suggest a relatively straightforward mechanism for the observed signs and symptoms. Evidence of environmental influences however, present a rather more complex picture, which comes from three main sources. Migration studies (Knight, 1992) have argued that people who move from a 'high-risk' latitude (e.g. Europe) to a 'low-risk' latitude (e.g. Africa) carry with them the same risk from their place of origin, but only if they move after the age of 15. If the move occurs in childhood, people assume the risk of the country of adoption (Dean, 1967). Disease epidemics have been reported in isolated communities like the Faroe Islands (Kurtzke and Hyllested, 1979) and striking variations in prevalence have been found in genetically homogeneous populations (Miller et al. 1990).

CLINICAL FEATURES (symptoms)

The disorder may present with diverse neurological signs that vary considerably between patients. Initial symptoms, which reflect the presence and distribution of the plaques, commonly involve numbness or tingling in the limbs or weakness affecting one or more limbs, loss of vision or impaired visual acuity, facial numbness, vertigo, dysathria, ataxia and urinary frequency or urgency and fatigue and optic neuritis (Knight, 1992). The broad term optic neuritis represents degeneration, inflammation or demyelinisation of the optic nerve, resulting in temporary partial or total loss of vision usually occurring over a number of hours or days.

There are a number of other symptoms that may occur singly or in combination, which may signify the onset of MS. These include nystagmus (involuntary rhythmic oscillation of one or both eyes), deafness, gait

disturbances, auditory hallucinations and emotional changes (White et al., 1992). However, it is not uncommon for initial episodes to be disregarded or not investigated because of their mildness or remission.

A common presenting problem in patients with MS is bladder dysfunction. However, many more experience urinary difficulties during the course of the disease. The common symptoms include urinary frequency, urgency, nocturia, dysuria (difficulty or pain in passing urine) and incontinence.

A dominating feature of MS is spasticity. Clinically, it presents as increased resistance to passive lengthening of the muscles, more often in the lower limbs. Its cause is overactive nerve cells located along the spinal cord. It has been reported (e.g. Cervera-Deval et al. 1994) that spasticity and weakness were the neurological symptoms that exerted the most disadvantageous influence on patients' vocational and social lives.

Among the most common and debilitating complaints associated with MS is fatigue. Figures suggest that as many as 90% of patients are affected and 40% consider fatigue to be their most serious symptom (Krupp et al. 1988). Fisk et al. (1994) not only found that almost half of their sample reported fatigue to be at least one of their worst symptoms, but that the severity of fatigue was not predictable from routine clinical assessment. More recently Coulthard-Morris and Zeng (1996) examined the relationship between fatigue psychosocial, neurological and cognitive functioning in a sample of 139 patients with MS and found that only patients' perceived control over their own environment and depression were associated with fatigue. It was observed that patients interpreted fatigue as impacting on their cognitive performance and was a limiting factor to work, social and overall role performance, but not physical performance. Despite the robustness of this finding, not all studies are in agreement with all its findings. For example, Moller et al. (1994) and Vercoulen et al. (1996) failed to find any association

between subjective ratings of fatigue severity and depression. However, in the latter study, a low sense of control over symptoms and focusing on bodily symptoms were reported to have a significant influence on the experience of fatigue.

Brassington & Marsh (1998) have argued that the evidence as to whether the fatigue experienced by people with MS is different from healthy adults is uncertain. To support this, they site the work of Kersten & McLellan (1996) amongst others who found that the causes of fatigue identified by people with MS, namely heat or humidity, manual work and household activities were the same as for healthy people. With the use of a quadriceps test, Kersten & McLellan found that whilst the muscle fatigability was similar for both groups, the perceived fatigue levels were disproportionately higher in patients with MS. Taken collectively, these studies suggests that the psychological factors associated with fatigue in patients with MS are at least as important as the actual physical fatigue experienced.

The progression of MS brings with it more widespread subcortical white matter involvement, which makes it more likely that diffuse cognitive changes will emerge. However, it should be pointed out that cognitive impairment has been reported in the early stages of the disease, even in cases where the physical disability is not yet advanced and a diagnosis of MS has not been made (e.g. Hotopf et al. 1994). In general the most commonly reported cognitive deficits in multiple sclerosis by clinicians are memory, conceptual reasoning, attention, executive functions and abstract reasoning, with a relative sparing of language functions (Ron et al. 1991). The reported frequency of cognitive impairment is variable, but Rao et al. (1991) found that the frequency in a community-based sample of 100 patients with MS was 43%.

It is well known that emotional symptoms and psychiatric problems can accompany multiple sclerosis. Moreover, these can compound the cognitive difficulties that MS suffers experience. Psychiatric problems readily seen in MS include psychosis, affective disturbances and even personality changes (Peterson & Kokmen, 1989). Bipolar affective disorders, euphoria, emotional lability (pathological laughing and crying) have been reported in concurrence with MS ever since Charcot, the French Neurologist first described the disease (Knight, 1992). However, depression in various forms is by far the commonest of all the mental state changes in MS (Feinstein, 1999). In a recent review by Feinstein (1999) of 100 consecutive referrals to his neuropsychiatric clinic, 80% had mood disorders, the majority having 'major' depression.

The term depression is however often used loosely to describe either a symptom or syndromes of varying severity, with the spectrum including transient changes in mood, adjustment disorders to life events, dysthymia and major depression with or without psychotic features. Given the heterogeneous nature of depression, it difficult to interpret the nature of the depression observed in studies of patients with MS.

The impact of applying depression in a loose manner has added to the difficulty in establishing the prevalence of depression in MS, as task which has itself been confounded by the cohorts studied and the methods used. For example, some studies have looked at point and/or lifetime prevalence rates while others at prevalence figures since the onset of MS. A number of studies have used the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L), which allows for Research Diagnostic Criteria diagnosis to be made. Minden et al. (1987) reported a 54% lifetime prevalence, whereas Schiffer et al. (1983), in a sample of 30 cases, found a prevalence of 37%. More recently Sadovnik et al. (1996) have reported a lifetime prevalence of DSM–III-R major depression in 50% of MS patients. A

meta-analysis conducted by Schubert & Foliart (1993) confirms an increase prevalence of major depression in MS compared to other neurological disorders. These figures are in keeping with prevalence rates obtained from self-report questionnaires (Beatty et al. 1989; Ron & Logsdail, 1989), although it should be noted that this approach is not geared towards establishing a diagnosis.

In summary, from a pooling of figures from published reports, Minden & Schiffer (1990) have estimated the lifetime prevalence for major depression due to MS to vary from 25-50%. These figures equate to almost three times the lifetime prevalence reported in the general population by the National co-morbidity study (Kessler et al. 1994). These findings, together with the possibility of depression impacting on cognition, strongly suggests that the incidence and level of depression need to be taken into account in any of neuropsychological study of MS patients.

As MS is predominantly a white matter disease, symptoms referable to cortical (grey matter) involvement are considered rare. Thus, dementia, aphasia, seizures, abnormal and involuntary movement, muscle atrophy and fasciculations although possible, are so unusual as to cast doubt on the diagnosis (Rolak, 1996).

DIAGNOSIS

The diagnosis of multiple sclerosis inevitably holds major implications for patients and their families. Issues like uncertainly over the future, the ability to work or earn a living and live independently readily spring to mind. It is therefore imperative for the clinician to be clear about what symptoms and signs constitute a diagnosis of MS.

The diagnosis of MS is fundamentally a clinical one and requires that a patient of an appropriate age (typically between 10-59) has at least two episodes of neurological disturbance, implicating different sites in the central white matter (Feinstein, 1999). A number of investigations may help the clinician establish the presence and site of white matter lesions, thereby facilitating a diagnosis. It should be pointed out however that investigations like neuroimaging, cerebrospinal fluid electrophoresis and evoked potentials, are not specific to multiple sclerosis and thus should be seen as helpful adjuncts to the clinical presentation.

From the point of view of research in MS, making a correct diagnosis is equally important. Research across sites need to speak the same language and while well-defined clinical criteria are essential, they cannot stand apart from the advances in technology. A recognition of a need to bring coherence to what can often be widely divergent neurological presentations had incited researchers over the years to come up with a series of diagnostic guidelines. For a number of years, those of Schumacher (1965) sufficed, but in the light of advances in laboratory and clinical procedures, these have given way to revised criteria (Poser et al. 1983).

Poser's criteria designed specifically for research purposes, divides MS patients into two broad groups, *definite* and *probable*. Each group may be subdivided into *clinical* and *laboratory* supported.

The Poser Classification Criteria

To be diagnosed as having clinically definite MS (CDMS) the patient must have experienced either:

(i) Two attacks and clinical evidence of two separate lesions.

(ii) Two attacks; clinical evidence of one lesion and paraclinical evidence of another, separate lesion.

The two attacks must involve different parts of the central nervous system and each must last a minimum of 24hours and be separated by a period of a month. In some cases, symptoms if considered reliable and adequate to localise a lesion typical of MS, may in fact be accepted in lieu of clinical evidence, e.g. Lhermitte's sign in any person under 50 years of age who does not have radiological evidence of an independent cause. Symptoms on their own must however, only be considered with caution and where possible, corroboration from friend or relative should be sought if the attack was not recorded by a physician.

Paraclinical evidence that aids in the diagnosis of MS includes CT and MRI scans, evoked potentials, hyperthermia challenge and specialised urological studies. Of particular note for the present thesis is the recommendation that neuropsychological evidence of impairment in someone under 50 years of age, although suggestive of MS, was not specific enough to be considered diagnostic. The recommendation, which was made in 1983, predated the numerous studies later in the decade that unequivocally demonstrated the presence of clinically significant cognitive dysfunction in approximately 40% of community-based MS patients (Rao et al. 1991a). To date however, impaired cognition is not one of the accepted paraclinical signs used for diagnosing MS.

Laboratory-supported definite MS (LSDMS)

Appropriate laboratory support comes from increased production of immunoglobulin G (IgG) in the cerebral spinal fluid (CSF). IgG is a naturally occurring protein that acts as an antibody and therefore offers a protective function against diseases. The increased IgG in the CSF needs to occur in the context of normal levels in the serum or oligoclonal bands in the CSF, but not in the serum.

(i) Two attacks; either clinical or paraclinical evidence of one lesion and CSF IgG or oligoclonal bands.

(ii) One attack; clinical evidence of two separate lesions and CSF IgG or oligoclonal bands.

(iii) One attack; clinical evidence of one lesion and paraclinical evidence of another lesion; CSF IgG or oligoclonal bands.

The Poser committee criteria clearly states that the two attacks must involve different parts of the CNS and each must last at least 24 hours and be separated by a month. In addition, one of the episodes must involve a part of the CNS that is distinct from that demonstrated by the clinical or paraclinical evidence. Whether derived from clinical or paraclinical evidence, both lesions must not be have been present at the time of the first examination and must be separated by at least a month. The function of the time factor is to reduce the possibility of including a case of acute disseminated encephalomyelitis.

In patients with progressive MS from the onset of symptoms, clinical or paraclinical evidence of the second lesion should not have been present at the time of symptom onset. If this turns out to be the case, the patient can only be deemed to have had MS once symptom progression had taken place for 6 months.

Clinically probable multiple sclerosis (CPMS)

The criteria for clinically probable MS are:

(i) Two attacks and clinical evidence of one lesion.

(ii) One attack and clinical evidence of two separate lesions.

(iii) One attack; clinical evidence of one lesion and paraclinical evidence of another separate lesion.

The two attacks must involve separate parts of the CNS. Historical information however, cannot replace clinical evidence and the restrictions discussed under *laboratory supported definite multiple sclerosis* also apply.

Laboratory supported probable multiple sclerosis (LSPMS)

(i) Two attacks of CSF IgG or oligoclonal bands.

The two attacks must involve different parts of the CNS, must be separated by a minimum of a month and each must have lasted 24 hours.

In summary, the Poser committee acknowledge that there will always be patients who defy easy categorisation. The neurologist will have to rely on 'intuition' and accumulated clinical skill in arriving at diagnoses for this group. The criteria as outlined above are primarily for research purposes. Moreover, there is a recommendation that clinical trials and research protocols should be limited to patients in one of the two *definite* groups. The category of *probable* was designed for the purpose of prospectively evaluating new diagnostic methods.

THE CLINICAL COURSE OF MULTIPLE SCLEROSIS

A particularly stressful feature of MS is the unpredictable nature of the disease course. Indeed Aronson (1997) reported that an unstable disease course was significantly associated with poorer quality of life in people with MS. However, in trying to describe the clinical course of MS, difficulties have been noted with regards to terminology (Whitaker et al. 1995). Although there is general recognition that the course of MS shows individual variability and physical disability usually follows either a relapsing-remitting or a steady progressive course, what is meant precisely by these terms has been unclear.

From a research perspective, a tightening up of terminology is not only important where clear definitions of patient subgroups are essential for valid data interpretation, but also for correctly assigning patients to particular treatments.

It is fair to say that differences amongst researchers and clinicians in defining terms that describe the course and severity of MS have stemmed from a reliance on verbal descriptions rather than biological markers. Indeed, it was this recognition that led to an international survey of MS researchers, with the aim of establishing agreement of the various descriptive terms currently being used (Lublin & Reingold, 1996). The survey supplied definitions for the following disease courses and types: relapsing-remitting (RR), relapsing-progressive (RP), primary progressive (PP), secondary progressive (SP), benign and malignant. The results of this survey led to the National Multiple Sclerosis Society (USA) providing a set of consensus definitions. These are provided below.

Clinical course definitions

Relapsing-remitting (RR) MS

This term refers to clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. The periods between the disease relapses are characterised by a lack of disease progression. The defining characteristics of this particular course are acute episodes of neurological deterioration with variable recovery, but a stable course between attacks.

Primary-Progressive (PP) MS

The consensus definition refers to disease progression from symptom onset, with occasional plateaux and temporary (minor) improvements allowed. The cardinal feature here is a gradual, almost continuous worsening of

neurological function from the initial presentation with some minor fluctuations, but no discrete relapses.

Secondary-progressive (SP) MS

This term defines a course that is initially relapsing-remitting, but later, is followed by a progression, with or without occasional relapses, minor remissions and plateaux. SP-MS is viewed as the long-term outcome of patients who initially show a RR-MS course. The switch from one to the other is characterised by a worsening of the relapses relative to the baseline.

Progressive-relapsing (PR) MS

It is generally agreed that this term defines a progressive disease from symptom onset, with clear acute relapses, with or without full recovery. The periods between relapses are marked by continuing disease progression. PR-MS is considered an additional, but rare clinical course that warrants a separate definition.

Relapsing-progressive (RP) MS

Although this is a frequently used term, there was no consensus amongst those surveyed (Lublin & Reingold, 1996), which was largely due to the overlap between this term and some of the other categories. In view of this, it was recommended that the term be abandoned.

Benign MS

The was defined as a disease in which the patient remains fully functional in all neurologic systems at least 15 years after the disease onset.

Malignant MS

The consensus definition was of a disease with a rapidly progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

Currently there is no explanation as to the cause of the relapses or remissions, or what determines the progression of this disease. To date, there is no treatment on the market that is able to reverse the effects of MS or stop process of demyelination. However there has been a lot of research activity in the last few years for treatment to slow down the rate of demyelination, which seems promising.

CHAPTER 2

The neuropsychology of MS

Since the writings of Charcot (1877) it has been widely recognised that cognitive impairment occurs in MS. In recent years however, there has been a surge of interest in this area, which seems largely due to the use of extensive and standardised neuropsychological test batteries providing more accurate prevalence estimates. It is also now well established that severe cognitive impairment is usually a feature of the advanced stages of the disease (Feinstein, 1999). Clinically, the neuropsychological profile often observed in MS resembles fairly closely the prototype of subcortical dementia, although this concept remains somewhat controversial. Nevertheless, the typical picture of cognitive deficits includes memory retrieval failure, slowed information processing, impairment of abstraction and executive function (problem solving, planning, sequencing, self-monitoring and self-correcting) with a relative preservation of general intelligence and language functions. This pattern of impairment is associated with diffuse white-matter involvement and relative sparing of the cortical mantle (e.g. Huntington's disease, Parkinsonism and MS). Subcortical dementia is believed to be characterised by forgetfulness, reduced insight, impaired manipulation of learned information, depression and personality changes like apathy and lack of initiative (Peterson & Kokmen, 1989). Neuroanatomically, this pattern of cognitive deficits is characteristic of lesions in the frontal and subcortical structures (Foong et al. 1997).

The majority of research suggests that there does not appear to be any significant relationship between cognitive impairment and neurological disability status in MS, or indeed disease duration (Penman, 1991; Maurelli et al. 1992). This is felt to be largely due to the considerable variability in lesion sites. For example, patients with mostly spinal cord lesions may be profoundly physically disabled, but have little or no cerebral demyelination and thus demonstrate little cognitive change. By contrast, Feinstein et al. (1992) reported that although disease duration and severity were unrelated to cognitive impairment, disease course was a sensitive marker of cognitive decline. Moreover, the patients with a chronic-progressive disease demonstrated greater impairment in cognitive performance. These findings were confirmed by Heaton et al. (1985), although these authors like Beatty et al. (1990) also found a relationship between the degree of neuropsychological impairment and disease duration. On balance however, since it is more common not to find a relationship between physical and cognitive functioning in MS patients, it cannot be ascertained from neurological examination that a patient will have accompanying cognitive impairment. This speaks to the value and necessity of neuropsychological assessment. In the last decade, a lot of research has been carried out to clarify the precise nature of cognitive impairments in MS. The main findings will now be discussed in detail.

Intellectual functioning

Taken collectively, the results of cross-sectional studies of patients with MS have reported that their IQ's are within the normal range. However this broad overview risks overlooking significant, albeit mild degrees of deterioration. The largest differences are observed on the performance scales rather than the verbal scales, which may be more of a reflection of sensorimotor than visuospatial difficulties. This interpretation is likely to account for at least in part, the findings of longitudinal studies that have found a small but significant decline in intellectual functions over time, most

marked in performance IQ scores (Rao, 1986; Penman, 1991). In a study by Rao et al. (1991) patients averaged 6.3 points lower than control subjects on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Verbal IQ.

An alternative approach has been to assess premorbid IQ with the reading test The National Adult Reading Test (NART) (Nelson & Willison, 1991) and compare this estimate with current intellectual functioning as determined by the WAIS-R. By subtracting the WAIS-R from the NART score, one is able to derive a measure of change in intellect. Using this method, Ron et al. (1991) found a significant decline in MS patients compared with a group of disabled control subjects who had neurological disorders that spared the brain. The results of this study are somewhat negated by a number of contrary findings. For example, Jambor (1969) carried out a four-way comparison between MS patients, healthy controls, psychiatric patients (diagnoses unspecified) and disabled patients without CNS involvement (e.g. muscular dystrophy) and observed rather similar intergroup scores on a shortened version of the verbal subscale. Goldstein & Shelly (1974) were able to replicate this finding with respect to psychiatric patients (schizophrenia, depression), but also reported that non-brain-damaged patients had similar scores. They reported that the greatest difficulties experienced by MS patients were on tests reliant on motor performance. Reitan et al. (1971), although recognising this fact, also observed differences in verbal IQ between MS patients and age and education matched healthy controls. However, the mean verbal IQ in their MS group was still in the upper normal range and it was unclear whether this represented a decline from premorbid functioning.

Whilst it is relatively easy to conclude that decline in intelligence is primarily limited to performance IQ, it is perhaps useful to emphasise two points. Firstly, there is considerable individuality in the IQ score of MS patients, which is reflective of the variability that characterises their cognitive abilities

in general. Moreover, by focusing on group scores may obscure significant decline in individual patients. Secondly, there are more subtle indications of impairment on one of the verbal subscales. The digit-span is a composite score of recalling digits forwards and backwards and MS patients as a group perform normally on this test. However, when the forward and backwards components are analysed separately, impairments that are masked by the total score may become apparent on the backwards recall (Rao et al. 1991a; Feinstein et al. 1997).

Memory

It is perhaps fair to say that memory difficulties are the most frequently reported cognitive impairment in MS. Rao et al. (1993) have reported that between 40-60% of MS patients have memory problems of some kind. Generally speaking, patients with a chronic-progressive disease course perform more poorly on tests of memory than those with a relapsing-remitting course (Mahler, 1992). However what is clear from the literature is that memory difficulties do not follow a characteristic progression. For instance, Minden et al. (1990) observed from a study of 50 MS patients that 30% had a severe memory impairment, 30% a moderate impairment and 30% were either not impaired or only mildly so. In this study, significant associations were found between other cognitive functions, chronic-progressive disease course, lower socio-economic status and the use of anti-anxiety medication. Physical disability and the duration of MS symptoms were not found to be related to memory impairment.

In line with the variability of MS symptoms a number of studies have shown that MS patients are impaired on a wide variety of memory tasks (e.g. Beatty, 1993; DeLuca et al. 1994; Beatty et al. 1996). Rao et al. 1993, has argued that the memory impairment seen in patients with MS is characterised by poor free recall from long-term memory and to a lesser extent working/short-term memory relative to other aspects of memory such as encoding

information into long-term memory, implicit learning and recognition memory. This work has been supported and extended by Armstrong et al. (1996) and Coolidge et al. (1996), who have demonstrated that MS patients often recall information from long-term storage in a inconsistent way, but perform normally on assessments of recognition and have normal rates of forgetting and immediate recall. This pattern of memory impairment is quite different from that seen in patients with Alzheimer's disease, where short-term memory difficulties are a characteristic feature and is more like the pattern seen in Huntington's disease (though less severe) and closed head injuries (Rao et al. 1989).

Despite the fact that a number of authors have implicated an impaired retrieval mechanism in MS, there are others who concluded quite contrasting interpretations as to what might be going on. For example, DeLuca et al. (1994) have concluded that the verbal memory impairment seen in patients with MS is a result of poor initial learning. To support this, the authors have argued that the previous studies that have implicated inadequate retrieval processes, have failed to control for the amount of information initially acquired during learning.

More recently Beatty, Wilbanks, et al. (1996) examined 99 patients with MS using the Buschke Selective Reminding Test (SRT). This test enables one to differentiate between acquisition and retrieval from long-term memory. When compared with healthy controls, the MS patients were found to be impaired on all measures of the SRT, with the exception of recognition memory. On further analysis however, three separate profiles of memory impairment were observed. One cluster of patients performed very similar to the controls, the second cluster showed impairment in acquisition, retrieval and short-term memory. The third and largest cluster demonstrated mild impairment in short-term memory and marked impairment in retrieval from secondary (long-term) memory. Importantly neither a faulty retrieval

mechanism nor slowed acquisition were considered to be sufficient to account for the patterns of memory impairment evident in the patients with MS. This led the authors to conclude that different 'profiles' of memory impairment can be identified in MS.

It is clear from this selective review that there has been a substantial collection of research conducted within the last decade on the nature of memory impairment in MS. Whilst it is difficult to be conclusive, the emerging picture appears to be that the encoding and storage of information in immediate memory seems to be reasonably intact, whilst recent and remote memory are often observed to be impaired. Despite the fact that many studies and indeed earlier reviews have suggested faulty retrieval mechanisms as the primary memory impairment in MS, other studies which have controlled for the rate of acquisition of information in research participants will help account for the impact of this on subsequent recall. Some studies have also reported the presence of quite distinct clusters of participants with MS, whose profiles are uniform, but who become disguised when the sample is considered in its entirety (Beatty et al. 1996).

Metamemory

More than 25 years ago, Flavell (1971) coined the term metamemory to refer to knowledge about memory processes and contents. Although this concept has gained considerable attention in the literature and has proven important for describing and explaining developmental changes in the memory domain, it has been also been criticised because of its "fuzziness". Nevertheless the ability of MS patients to accurately appraise their own memory, particularly with respect to newly acquired information, has been reported to be compromised (Beatty & Monson, 1991). This observation is clinically important, for it implies that patients' self-reports about memory are likely to be inaccurate. Metamemory may be, in part, a function of the prefrontal cortex. Taylor (1990) compared objective evidence of cognitive

ability (neuropsychological test performance) with patients' subjective assessments of their cognitive function and reported discrepancies. The association was closer when informants' ratings of the subjects' impairment were compared with the objective evidence. Consistent with Beatty and Monson's (1991) observation of metamemory as a function of frontal integrity, Taylor noted that the greatest discrepancies in his sample were observed in patients who performed poorly on tests sensitive to prefrontal lobe lesions.

In a related study, Sullivan et al. (1990) canvassed, via mail, 25,000 Canadians of whom approximately 80% had MS. Using the Perceived Deficits Questionnaire, participants were asked to rate their cognitive performance on four indices: attention, retrospective memory, prospective memory and planning/organisational skills. Five per cent (n=1180) of the sample responded, of whom 30% considered themselves cognitively impaired in at least one area. This figure approximates those from two large community-based neuropsychological studies (Rao et al. 1991a; McIntosh-Michaelis et al. 1991). Whether the two assessment procedures are identifying the same group of patients must, however, be open to doubt, given the documented evidence of metamemory problems in MS. Indeed, Sullivan et al.'s study was unable to provide the answer because objective assessment procedures were not undertaken. McIntosh-Michaelis et al. (1990) on the other hand, demonstrated convincingly that MS patients tended to substantially overestimate their perceptions of memory impairment and difficulties with attention.

Using a rather different approach Langdon & Thompson (1994) carried out a study that sort to uncover which cognitive variables influence the reports of memory impairment in MS patients and their carers. The authors reported that whilst carer reports of memory function were in keeping with objective measures of memory, patients' self-reports of memory function

were related to reported levels of anxiety and irritability and not their actual performance on memory tests. By contrast, emotional status was not found to be related to the carer reports.

In contrast to these findings, Kujala et al. (1996) found that MS patients with early cognitive decline were able to accurately appraise their memory deficits, which may indicate that metamemory is, at least in part, related to the overall severity of cognitive deficits in addition to variables other than formal cognitive test competence.

Speed of Information Processing

Charcot observed that slowness of thinking was one of the hallmarks of mentation in patients with a diagnosis of MS. A century later, Cummings (1986) reiterated the significance of the symptom and went on to propose that it was one of the defining features of a broad category of dementing illnesses that were primarily subcortical in origin. Speed of information processing has been assessed in MS patients with a number of different tests of which the symbol-digit modality tests (SDMT) is one of the most widely used. In this test, subjects are required to substitute numbers for symbols and responses are timed. A number of studies have reported deficits in MS patients (e.g. Franklin et al. 1988; Feinstein et al. 1992a).

Another popular measure of cognitive speed is the Paced Auditory Serial Addition Test (PASAT) (Gronwall & Wrightson, 1974). Initially devised as a means of assessing cognitive difficulties following traumatic brain injury, it has since been applied to other neurological disorders. In this test, subjects are presented aurally with a series of digits from 1-9 and instructed to add each new digit to the one that preceded it. Using this test, Litvan et al. (1988) observed that patients with MS were particularly impaired in information processing in the two fastest rates of presentation on this test. DeLuca et al. (1994) observed greater degrees of impaired when they

reported MS patients to be poorer than controls on all speeds of the PASAT. Moreover, DeLuca et al. reported a significant correlation between processing competence and the number of trials it took patients to learn a verbal memory task.

More recently, Diamond et al. (1997) contrasted the performance of MS patients on both auditory and visual information processing tasks, by comparing PASAT performance with a visual analogue of this popular task called the Paced Visual Serial Addition Test (PVSAT). Patients were observed to be impaired on both tasks, with no significant difference between modalities.

Graffman et al. (1991) importantly observed that MS patients do not uniformly perform less well on tests of information processing, but have difficulty on those that necessitate effortful rather than automatic processing.

As with any clinical sample, it is important when possible, to utilise subgroups of patients according to criteria that may have a masking influence on certain findings from a heterogeneous sample. This was borne out in Kujala et al. (1994) study. In this study, the authors compared patients with MS into qualitatively different stages; 22 with mild cognitive deterioration, 23 with preserved cognitive capacity and 35 healthy controls. The three stages of information processing investigated were automatic visual processing, controlled processing and motor programming. The authors found that the cognitively impaired group were slower than the other two groups on each of the stages of information processing identified and that the MS patients that were considered to be cognitively intact, displayed mild signs of slowing in automatic visual processing.

In conclusion, the research evidence strongly suggests that slowed information processing is a key feature of the cognitive profile of MS sufferers. Although it may be accentuated by physical difficulties, it is nevertheless observed on tests of pure cognitive ability and therefore implicates a cognitive basis, which is likely to impact on other key areas of cognition like verbal memory.

Attention

Attention deficits are known to be present early in multiple sclerosis, even in patients with clinically isolated lesions (e.g. optic neuritis) in whom brain lesions are already detectable on MRI and are likely to represent the early neuropsychological manifestation of MS (Feinstein et al. 1992). A number of studies have reported impairment in visual and auditory attention using tasks such as digit-symbol substitution and paced auditory and visual addition tasks (e.g. Litvan et al. 1988; Filley et al. 1989, Rao et al. 1989a). Beatty et al. (1996) have argued that the poor digit span they observed in a number of their MS sample may indicate that the memory difficulties in this group may in fact be secondary to an attentional impairment. In a second study using the sample of their earlier publication discussed above, Kujala et al. (1995) focused on attentional capacity in MS. They reported that the cognitively impaired group were slower on all tests of attention, but were not significantly different from the other two groups in the number of errors made on these tests of attention.

What seems clear from studies of attention in multiple sclerosis is that not unlike investigations into speed of information processing, measures employing vocal rather than motor responses and accuracy rather than simply speed, are more likely to provide a more valid approximation of attention difficulties in patients with MS, since patient's performance will not be compromised by their physical disabilities.

Models of executive function – an overview

The term executive function has been defined by a number of authors. For example, Baddeley & Wilson (1988) defines it as referring to those mechanisms by which performance is optimised in situations requiring the operation of a number of cognitive processes. Similarly, Nathaniel-James et al. (1997), describe executive functions as referring to functions that come into play when one is required to respond appropriately in novel and/or problem solving situations. Specifically, people with executive deficits may have problems such as poor strategy formation, including impaired planning and poor organisation skills. In addition, they may perseverate, have poor set shifting skills and problems suppressing inappropriate responses. Some people who are more profoundly impaired may also have problems related to an inability to self-regulate or monitor their behaviour. These may include self-control problems like increased disinhibition, aggression and impulsivity.

Problems of the type outlined above have long been associated with frontal lobe lesions (Shallice, 1988), particularly when the prefrontal region has been affected. From early twentieth century (e.g. Bianchi 1922) the dominant view of the function of the frontal lobes was that it was the seat of the most critical higher level of control functions and that lesions to these structures would give rise to disorders of these functions. Later in the twentieth century, related views coexisted with a contrasting view that the frontal lobes have little in the way of intellectual functions. Proponents of this view included Feuchtwanger (1923) and were later reinforced by Hebb's (1945) initial investigations.

Luria's (1966) view of the frontal lobe function was quite a marked departure from Hebb's. Luria's position was that the frontal lobes have a system for the programming, regulation and verification of activity. This theory was supported by descriptions of the behaviour of patients with

frontal lesions on a number of tests. Despite the hugely insightful nature of his work, Luria's ideas have been criticised for a number of reasons. Perhaps the most important, or at least the most often voiced criticisms, are that the patients on which his theory was examined often had lesions extending outside the frontal lobes (see Canavan et al. 1985) and patients with lesions including frontal structures often had little or no problem with his tests.

Perhaps the most influential current model of frontal lobe function is that of Norman & Shallice (1980 [1986]), which was later developed by Shallice (1988). This model has been viewed as one possible realisation of Luria's theory in information-processing terms. These authors have argued that the prefrontal cortex is the seat of one overriding system – the Supervisory System. However, more recent discussions (e.g. Shallice & Burgess, 1996), have emphasised that a 'system' in this context, is viewed in this way because of the manner in which it interacts with other outside systems, rather than suggesting that it only carries out a single process. The Norman- and Shallice theory argues that a variety of processors are used in action and thought-processes and that the control of their on-line operation involves two qualitatively different types of mechanism. The lowest control level (schemas) is held to utilize action or thought. These are essentially program-like entities, one for each qualitatively distinct basic well-learned thought operation or type of action. The selection of which schema or schemas is or are to be operative at a given time is carried out by contention-scheduling. This mechanism is argued to resolve conflicts through lateral inhibition between independently activated schemas.

Contention scheduling, however, is held to involve routine selection between potentially demanding competing schemas, which are themselves well-learned. By contrast, coping with novelty is held to involve a separate mechanism – the Supervisory System – which modulates the operation of

contention scheduling by providing additional activation or inhibition of schemas competing in the lower-level mechanism.

In the initial specification of the model (Norman & Shallice, 1980) the Supervisory System was held to be necessary for behaving appropriately in five types of situations:

1. Ones that involve planning or decision-making.
2. Ones that involve error-correction or 'trouble-shooting.'
3. Ones where the responses are not well learned or contain novel sequences of actions.
4. Ones judged to be dangerous or technically difficult.
5. Ones that require the overcoming of a strong habitual response or the resisting of temptation.

However, Shallice & Burgess (1991) have suggested that these five types can be reduced to two. The first type would be where a wrong response has or is likely to be given by unmodulated contention scheduling and the second is where the situation is in some essential respect novel.

It was argued that patients with damage to the Supervisory System should have difficulty in both situations. However, over the last decade, it has become clear that this need not necessary be the case. For instance, Shallice & Burgess (1993) and (Burgess & Shallice, 1994), have suggested that the Supervisory System may be fractionable, at least with respect to the features of the cognitive and behavioural sequelae observed in some patients. Thus, it is argued that there is a possibility that the supervisory or executive system may consist of a number of processes, rather than a single resource, that may be selectively impaired in any individual patient, each having its own psychological manifestations. Indeed, there is recent evidence to support this (Burgess et al. 1998), although it would seem that there are limits to the

fractionation of this system. Given these recent developments, the 'purer' logic of the original theory would seem to be a little undermined. Nevertheless, the approach of making the more complex theory that a executive system exists but that it can fractionate is already bearing fruit.

Methodological difficulties in executive function research

The nature of cognitive testing, particularly in the context of empirical research, presents a host of methodological difficulties. However, there would appear to be particular difficulties associated with the study of executive function. It is however beyond the scope of this thesis to address all the possible issues that may arise, but an attempt will be made to highlight issues that are particularly pertinent to this thesis.

From the outset, a foremost impediment to examining executive functions is the contradictory need to structure a situation were patients can demonstrate if and to what degree they can make structure for themselves (Lezak, 1995). Usually, it is the examiner in neuropsychological assessments who determines what is to be done, what materials are to be used and how. There is thus little scope for discretionary behaviour in many of the tests that are believed to be sensitive to frontal dysexecutive function. The inevitable task for the examiner then becomes how to transfer skills like structuring and planning from the examiner to the participant within the structured assessment.

Rabbitt (1997) has discussed a number of important difficulties in this area of research. One of these issues relates to the terms used to classify the demands of diagnostic tests. For example, he argues that the term "inhibition" has to date, no empirically demonstrable construct validity, despite the fact that it has been assessed with tasks (e.g. Hayling Test, Burgess & Shallice, 1997) that are seen as operational definitions of this term. However, he makes the point that given that executive tasks are

complex, attempts to fit them into categories borrowed from everyday language like "monitoring" or "planning" are inevitably going to be problematic.

The nature of executive tasks are such that many tests are non-specific with respect to localisation and the cognitive processes involved. For example, one of the most widely used tests of executive, the Modified Card Sort Test (Nelson, 1976) requires many processes for adequate performance such as changing set, memory and shape perception. A deficit in any one of these specific processes on this test may result in poor performance. Moreover, whichever process is believed to be at fault will suggest a different circumscribed area of brain damage. Thus, the concept of "task impurity" which in fact relates to all of neuropsychology, is especially problematic in this domain.

Perhaps the most problematic methodological difficulty pertaining to this thesis concerns the validity of 'executive' tests. At the most basic level, Rabbitt (1997) points out that executive tests are unreliable diagnostic indices for dysexecutive behaviour. Thus, they have questionable ecological validity. Although this problem is related to those outlined above, there is a specific difficulty with measurement error. Rabbitt argues that because executive tests often have poor test/retest reliability, as they do not strongly predict performance on themselves, the consequential measurement error will blur relationships between scores on executive tests and other performances against which one tries to validate them. It is this sort of issue that has prompted authors like Wilson et al. (1997) to argue that executive tasks offer little assistance in problems of rehabilitation of patients with frontal injury. Questions in this context might include "how do patients' problems affect their function in everyday life?" or "can the patient return to a previous lifestyle?" (Rabbitt, 1997). Until these issues are satisfactorily addressed, empirical studies of executive function will remain problematic.

Executive function impairments in MS

Within recent years, impairment of executive function has been consistently observed in neuropsychological studies of MS patients (Beatty et al. 1989b; Beatty 1993; Mendozzi et al. 1993, Foong et al. 1997). Impairment in executive function in multiple sclerosis has been observed to be similar to patients with frontal lobe damage and has therefore led to the hypothesis that the presence of focal demyelinating lesions in the frontal structures could account for these deficits (Arnett et al. 1994). To date, the focus of the majority of studies of executive function in MS has been to try to relate observed executive deficits to the severity and site of cerebral lesions using magnetic resonance imaging (MRI) (Huber et al. 1987; Rao et al. 1989a; McGhee 1992, Foong et al. 1997). Whilst it may be erroneous to assume that impairment on executive tests signifies frontal lobe disease, these studies continue to be of theoretical interest.

Cognitive inflexibility, similar to that observed in patients with focal frontal lobe lesions is often observed in patients with MS when assessed using the Wisconsin Card Sorting Test (WCST). However there are differences between groups of MS patients on this test. For example, patients with the chronic-progressive form of MS perform worst on this test of abstract concept formation and set shifting than patients with relapsing-remitting MS (Mahler, 1992). However, because of the complex nature of the WCST and the many possible reasons that a patient way perform poorly on any given occasion, it is sometimes difficult to interpret the reasons for failure (e.g. poor concept formation vs. perseveration). Beatty & Monson (1996) compared the performance of patients with MS on the WCST and the more recently developed California Card Sorting Test (CCST), which enables one to separate impairment in concept formation from perseveration responses, when the same incorrect problem-solving strategy is used. They found a wide range of error scores with the WCST for the MS sample, while significantly fewer errors were found with the CCST along with no

significant difference in the number of perseverative responses. The significance of this finding is that it was considered to reflect the problem-solving difficulties in people with MS can be explained by impaired concept formation rather than from perseveration. However Beatty & Monson argued that the different patterns of performance on the CCST by the MS patients makes it somewhat uncertain whether their problem-solving deficits can be attributed to frontal lobe damage.

Many previous studies of executive function in MS have predominately focused on measuring abstract or verbal working memory in isolation. (e.g. Mendozzi et al. 1993; Arnett et al., 1994). However, more recently, Foong et al (1997) carried out a study that incorporated a battery of executive skills that included computerised tests of planning and spatial working memory. The authors reported that relative to a group of matched controls, patients with MS were found to have impairments in verbal fluency, Stroop, cognitive estimation, spatial span, spatial working memory and use of strategy and planning, although not all of these skills were impaired to the same extent. For instance, the authors reported that planning ability in this group was relatively preserved, since differences in thinking (planning) times between the MS and control groups on the Tower of London Task from the Cambridge Neuropsychological Test Automated Battery were only significant at the most difficult levels of the task.

Poor performance on sequencing tasks has also been observed in MS. For example, Beatty & Monson (1993) reported MS to be impaired on a picture-sequencing task compared to a group of healthy controls. However, this same group performed within the normal range on a purely motor-sequencing test.

What is clear from the above review is that executive skills have up until now, been studied in a very limited way. With the noticeable exception of

Foong et al (1997) discussed earlier, the majority of studies have reported impairments on the WCST or another test with a similar format. This raises the question of whether the literature in this area lacks breath. Given that there are also a lack of models to account for the executive impairments frequently reported in studies, there would seem to be a need to expand on this literature. Not just by reporting impairments on other tests of executive function, but also to try to understand its impact on MS suffers.

CHAPTER 3

Rehabilitation of MS, aims and hypotheses

The Oxford English Dictionary defines 'rehabilitation' as a process that 'helps a person who is physically or mentally disabled re-adapt to society'. This definition is inadequate within a neurological setting because both physical *and* mental difficulties may present jointly. Neurological disease may result in a combination of problems including alterations of behaviour, physical disability and diminished cognitive abilities. Whilst this is not an exhaustive list, the potential interplay between these functions presents particular problems for neurological rehabilitation if the individual is to 'successfully' renter the community.

COGNITIVE REHABILITATION AND MULTIPLE SCLEROSIS

To date very little has been written about therapy for cognitive difficulties in MS. Nevertheless, the approaches that have been used may be divided into two broad categories; restorative or compensatory (Sohlberg & Mateer, 1989). Restorative refers to a process whereby cognitive deficits are identified and specific, remedial therapies introduced with the aim of increasing performance in that area. In contrast, compensatory strategies do not try to bring about a recovery of function, but rather, attempts are made

at maximising those abilities an individual retains. It is the latter approach that has received the most attention in MS.

Compensation strategies

Before describing this particular form of therapy, it is perhaps worth noting that in those MS patients who perceive themselves as cognitively impaired, the strategies that are spontaneously adopted are compensatory in nature. Thus, Sullivan et al. (1990) reported that patients frequently employed the use of an external memory aid such as a notepad.

Compensatory strategies are based on three tenets: structuring, scheduling and recording. The underlying principle is to bring as much structure and stability to the patients environment. This, in turn, ensures a measure of predictability, thereby reducing demands on planning, organisation and memory (Sullivan et al., 1990). A primary step in the process is to assess the individual's current cognitive strengths and weaknesses through neuropsychological assessment. An estimate premorbid IQ is useful as a predictor of what the patient was capable of intellectually prior to the onset of MS. In addition to this information, an assessment of the patient's environment is also mandatory, since this provides information on the daily demands confronting the MS patient. With this information, the therapist can identify those areas of daily functioning that are most affected by cognitive difficulties and these are discussed with the patient before a specific plan is implemented. Depending on the patient's cognitive ability, this structure may be applied to factors ranging from work-related tasks to the more mundane activities of daily living such as cleaning, meal preparation, grocery shopping, and transportation (Bennett et al., 1991).

Remedial Strategies

Unlike another neurological disorder like head injury (Grafman, 1984), relatively little attention has focused on remedial strategies in MS patients. The reasons are likely to be related to the nature of cognitive dysfunction in MS. Whereas in stroke and head injury the insult is sudden and is followed by a period of expected, albeit variable recovery, MS-related cognitive change follows an altogether different course. The onset may be insidious and deterioration, if it occurs over time, is unlikely to be interrupted by periods of cognitive improvement. For this reason, compensation strategies in MS are considered more useful (Minden & Moes, 1990).

Despite a preference for compensatory approaches, remediation has been attempted in MS with limited success. For example, a process of graded practice for improving memory, using computer-run programmes had been implemented in at least one MS rehabilitation setting, but results have yet to be reported (La Rocca, 1990). Jonsson et al. (1993) examined the short and long term effects of cognitive treatment (including compensation, substitution and direct training) and neuropsychotherapy in 20 patients with mild to moderate cognitive and behavioural impairment associated with MS. Despite the fact that the treatment effects were disappointing when evaluated with an extensive cognitive test battery, the results of the Beck Depression Inventory provided some support for the ability of the treatment programme to improve patients' mood. However the minimal success of the cognitive rehabilitation programme provides some support to the view of Bennett et al. (1991) that rehabilitation should focus on compensatory strategies to help people with MS to minimise the impact of cognitive deficits on their lives.

Regardless of which approach is adopted, it would seem obvious that attempts at cognitive rehabilitation should not take place in isolation, but should be one part of a comprehensive treatment strategy that starts the

moment multiple sclerosis is diagnosed. Such an approach which focuses primarily on the patient, but includes family members when appropriate, embraces not only cognitive strategies, but also includes treatment for neurological symptoms (e.g. the interferon compounds), psychological symptoms (psychotherapy, antidepressant and anxiolytic medication) and help for psychosocial difficulties.

IN-PATIENT NEUROLOGICAL REHABILITATION IN MULTIPLE SCLEROSIS

Langdon & Thompson (1999) have argued that in multiple sclerosis, the overall goal of in-patient neurorehabilitation is to improve function in a largely unpredictable chronic progressive disease. The primary objective in this context appears to be to reduce the level of both disability and handicap, which in turn maximises independence and function. Despite the fact that there has been little systematic research in to the outcomes of this type of intervention, there has been a few studies (e.g. Kidd et al. 1995; Freeman et al. 1996; Freeman et al. 1997) that have supported and extended the effectiveness of in-patient rehabilitation programmes aimed at achieving these goals. In some instances (e.g. Freeman et al. 1997) it has also been found that functional independence in undertaking activities of daily living can be increased despite unchanging neurological status.

Although no two centres deliver comprehensive care in the same way, a multidisciplinary team carries out this form of intervention. In addition, the patient usually actively participants in both the design and progress of their rehabilitation programme. This means that a patient's rehabilitation is inevitably based on a complex interaction between the team's beliefs as to what is achievable and the patient's and their family's aspirations. This means that physical, emotional and cognitive factors in some combination

are very likely to have some impact on a how well a patient progresses in a rehabilitation setting.

Although it would perhaps seem obvious that physical impairments would significantly influence the level of independence a patient with MS is likely to achieve, there is very little 'systematic' evidence to support this as being a factor that limits recovery. An exception to this is a study by Feigenson et al. (1981) who observed that MS patients with severe cerebellar symptoms have a propensity to make less progress in several daily activities when undergoing rehabilitation compared with those without severe tremor. This finding has recently been supported by Langdon & Thompson (1999).

While a number of studies have demonstrated a greater prevalence of depression in MS compared with other neurological conditions (Sadovnik et al. 1996) there has been very little evidence to demonstrate whether this influences rehabilitation benefit. However Langdon & Thompson (1999) in a comprehensive study which examined the impact of a number of cognitive and emotional variables influencing rehabilitation outcome, did not observe a relationship between depression and any of the outcome measures used.

THE CLINICAL SIGNIFICANCE OF COGNITIVE IMPAIRMENT FOR NEUROLOGICAL REHABILITATION

For the course of the last decade, there has been an increased interest in the practical relevance of the cognitive deficits observed in MS populations. The overall picture from the results addressing this question suggests that cognitive decline in people with MS can have a detrimental effect on their employment status, social functioning, interpersonal relationships and execution of activity of daily living (Edgley et al., 1991).

Perhaps the strongest evidence that cognitive deficits exerts an adverse effect on MS patients' social functioning comes from Rao et al.'s (1991) community study of 100 patients, who were almost evenly divided on the basis of detailed neuropsychological assessment into cognitively intact and impaired groups. The two groups were closely matched on demographic characteristics and factors such as duration of illness, disease course, physical disability and the percentage taking medication. They groups were then compared across a number of different parameters that included measures of physical disability, an occupational therapy assessment, self-report measures of depression, anxiety and sickness related disability and an informant's (relative or friend) rating of the participant's emotional adjustment. The cognitively impaired patients were found to be at a considerable social disadvantage with difficulties spanning work, vocational activities, relationships, sexual function and activities of daily living. The study was, however, cross-sectional and the authors therefore cautioned against drawing direct etiological inferences. Follow-up data supporting these conclusions comes from Amato et al. (1995) who also noted that cognitive and neurological deficits did not appear to develop in parallel, but cognitive dysfunction was a predicator of handicap in everyday life, even in patients in the incipient phase of MS.

Doble et al. (1994) have demonstrated that MS patients have significantly poorer motor and process abilities when performing activities of daily living and that process skill impairment may be due to underlying cognitive impairments.

What impact does cognitive status have on rehabilitation outcome? Studies that have addressed this question in a direct way are almost non-existent. However, Langdon & Thompson's study mentioned earlier, in addition to measures of anxiety, depression, physical disability and neurological status, also carried out cognitive assessments on patients and performed a multiple

regression analysis to determine which cognitive and neurological factors related to improved disability following in-patient rehabilitation. The cognitive battery was wide-ranging and included measures of general intelligence, verbal and spatial reasoning, memory, language, arithmetic and visual perception. Of these cognitive variables, only the patients' vocabulary skills, derived from their performance on the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) together with cerebellar function, proved to be a significant model for predicting rehabilitation outcome and accounted for 57% of the variance in the patients' improvements.

In conclusion it is clear that many factors may determine how beneficial rehabilitation is for MS suffers. The limited number of findings in this area strongly suggests that emotional, physical and cognitive factors in some combination, rather than any single factor, are likely to determine the usefulness of this form of intervention.

RATIONALE, AIMS AND HYPOTHESES FOR THE THESIS

The clinical significance of general cognitive impairment for neurological rehabilitation has been addressed earlier. However, the potential significance of executive functions and metacognitive abilities in particular, for MS patients undergoing in-patient rehabilitation, has yet to be investigated. Why are these important? Executive functions by their very nature, orchestrate relatively simple independent actions like moving a limb, or routines actions, what Shallice (1988) calls 'contention scheduling' into complex goal directed behaviour (e.g. getting dressed or making an evening meal). When executive deficits occur, behaviours important to independent living like cooking, self care and other aspects of psychosocial functioning may break down. When faced with these disabilities, MS patients with executive difficulties may become more dependent on environmental cues and are increasingly likely to perseverate. When one considers the impact of these difficulties on MS patients undergoing in-patient rehabilitation, these deficits may greatly complicate and compromise efforts at rehabilitation.

The capacity to be aware of oneself and to reflect on thinking or action patterns themselves (i.e. metacognitive functions) may potentially have a profound impact on how well MS suffers take to a period in-patient rehabilitation and ultimately, how much progress is made. The difficulty for patients with impaired metacognitive functioning is that although they may still be able to carry out a wide variety of both simple and complex action routines, they may be unaware of when responses are inappropriate to

circumstances, or may fail to "kick-in" when more automatic executive control mechanisms are failing or unavailable.

Metacognitive abilities have to date only being investigated in a selected number of patients with frontal lesions and schizophrenia, despite the obvious impact that these abilities may have on patients' psychosocial functioning and independence. Given the fact that MS patients often have executive deficits, as part of their widespread cognitive impairments profile, it would seem reasonable to suspect that metacognitive abilities, which are believed to be governed by the same region of the brain (frontal lobes) may also be compromised in this population. The identification of metacognitive impairments in MS would seem particularly pertinent for rehabilitation, since over or indeed under estimating executive abilities would potentially sabotage the success of a patient's treatment programme and likely to significantly influence the level of independence and functionality achieved.

RESEARCH HYPOTHESES OF THE THESIS

1. Participants with MS will perform significantly worst than controls on measures of executive function.

2. There will be significant negative relationships between healthy volunteers ratings of their performance on tests of executive function and their actual performance, but no significant relationships in the MS group.

3. A significant relationship will be observed between healthy controls' ratings on the DEX questionnaire and those of others' ratings. No significant relationship will be observed between MS participants' ratings on the DEX and those of their carers' ratings.

4. There will be significant positive relationships between metacognitive impairments in MS and the duration of MS symptoms.

5. Measures of executive and metacognitive impairments will significantly predict rehabilitation outcome scores.

CHAPTER 4

Participants and methods

PARTICIPANTS

All participants gave written informed consent before taking part in the study. Ethical committee approval was obtained from the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

MS Participants

A consecutive series of twenty two participants with clinically definite MS, who were admitted to a neurorehabilitation unit and who's first language was English, were recruited for this study. 16 were secondary progressive, 5 were primary progressive and one was relapsing-remitting. 14 were female. The mean age was 44.68 years (range 30-62 years). The mean duration of disease was 13.06 years (range 1-34).

An informant (one for each MS participant) was also recruited to comment on the participant's everyday signs of executive difficulties. The criteria for being a participant informant was that they had to be a relative or carer who has close, preferably daily contact with the participant.

Healthy control participants

The MS participants were matched as closely as possible with 30 healthy control participants for age, sex, premorbid and current IQ. The control participants were recruited from hospital staff (nurses, porters and administration staff) and from neighbours of the author. 17 of the controls were female. The mean age of this group was 40.94 (range 33-58). Like with the MS group, an informant (friend or relative) for each of the healthy controls was recruited to comment on the presence of everyday signs of executive difficulties.

Participants were not paid for taking part, but did receive travel expenses in circumstances where they had to travel to the hospital by public transport.

Exclusion criteria

Each of the MS participants' medical notes were reviewed. Individuals whose visual acuity was less than 6/12 or those with significant motor impairment that would confound performance on the neuropsychological assessment were excluded. In addition, participants with severe depression (assessed using the Hospital Anxiety and Depression Scale and clinical interview) or other significant psychiatry history, a head injury that rendered them unconscious, or anyone whose weekly alcohol consumption was greater than 21 units were excluded from further study.

COGNITIVE ASSESSMENT

Each of the participants were assessed using the following tests and questionnaires:

General Intellectual Functioning

(i) Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981). This is the most widely used test of current general ability and has been validated in MS research (e.g. Ron et al. 1991; Langdon & Thompson, 1999). For this study, only the shortened version of the verbal sub-scale was used (Vocabulary, Arithmetic, Digit Span and Similarities). This decision was taken because the physical disabilities associated with MS often makes it inappropriate for them to attempt the performance items. Instead, three spatial tests of reasoning from the VESPAR were administered. These are described below.

(ii) Verbal and Spatial Reasoning Tests (VESPAR) (Langdon & Warrington 1995). This test was specifically designed to reduce the confounding effects of peripheral sensorimotor dysfunction on cognitive tests performance. It is made up of matched sets of 25 verbal and spatial items, which assesses reasoning in three modes: categorisation, analogy and series completion. As mentioned above, only the spatial subtests of this test were used. These subtests have been validated in MS populations (e.g. Camp et al. 1999).

(iii) National Adult Reading Test (NART) (Nelson & Willison 1992). This reading tests comprises 50 single words, arranged in order of difficulty, which are irregular in that they do not follow the common rules of English letter-to-sound rules. Assessment of a participant's reading vocabulary with these words provides an estimate of premorbid

cognitive ability. This test has been validated in MS research (see Ron et al. 1991).

Executive Function

Rationale for selecting the executive tests

During the pilot study, some MS participants, because of the physical disabilities associated with MS, experienced difficulties with the motor aspects of carrying out some traditional tests of executive function (e.g. Trail Making, Modified Card Sort Test). In view of this, it was decided to select tests on the basis that they were standardised, but did not require a motor response and thus eliminating the possible confounding effects of sensorimotor dysfunction on test performance. In addition, the executive tests that make up the battery were also selected on the basis that they assess some of the same problems addressed in the DEX questionnaire and are thus in keeping with the need to sample impairments that are sometimes displayed by people with dysexecutive problems in their everyday life. None of the following tests have been validated in MS research.

1 The Hayling & Brixton tests (Burgess & Shallice 1997).

(i) The Hayling Sentence Completion Test is comprised of two sets of 15 sentences each having the last word missing. In the first section, participants have to complete each sentence with a word that make sense in the context of that sentence as quickly as possible. This test yields a simple measure of response initiation speed. In the second section, the participant is asked to complete sentences with a word that does not fit. This gives a measure of both response suppression ability and thinking time.

(ii) The Brixton Spatial Anticipation Test consists of 56 pages, each showing the same basic collection of ten circles numbered 1-10. On each page, one circle is coloured in blue. The position of the coloured in circle in most presentations, moves around from page to page according to set rules. The participant is shown one page at a time and is asked to work out where the next coloured circle will be by trying to pick up on the pattern or rule, based on what they have seen on the previous pages. This test provides a reliable measure of rule attainment.

2 Temporal Judgement Test and the Dysexecutive Questionnaire (from the Behavioural Assessment of the Dysexecutive Syndrome; BADS) (Wilson et al. 1996).

(i) In this test, participants are asked four short questions which assesses their judgement and estimating abilities. The questions concern commonplace events and participants are requested to estimate how long each will take to accomplish (e.g. How long does it take a window cleaner to clean the windows of an average size house?). Participants are informed that they are not expected to know the exact answer, but they are to make a sensible guess.

(ii) The Dysexecutive Questionnaire (DEX) is a 20-item questionnaire that samples many of the symptoms associated with executive impairment. The questions sample four broad areas of possible changes: motivation, emotional or personality, behavioural and cognitive changes. The questionnaire comes in two forms, one for self-rating by the participant and one for independent rating by someone who knows the participant well and who has preferably, daily contact with them. Each item is

rated on a 5-point Likert scale ranging from 0= never to 4= very often.

For each of the executive tests, all participants were asked to rate their performance on a five - point Likert scale ranging from 1 (very poor) to 5 (very good). The purpose of this was to assess participants' metacognitive knowledge on performance on each of the tests.

MS participants underwent the cognitive assessment during the first week of their admission to the unit, which took in the region of 1 ½ to 2 hours to complete. Relatives/carers completed the independent rater version of the DEX questionnaire during one of their visits to the unit.

The healthy controls completed the cognitive assessment either on the rehabilitation unit, or in their own homes, which generally took between 1 ¼ to 1 ¾ hours to complete. The healthy controls' independent raters completed the appropriate version of the DEX questionnaire either in their own homes, or via telephone with the author.

EMOTIONAL DISTRESS

MS Participants' current level of anxiety and depression was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmund & Snaith, 1983). This is a 21-item self-report questionnaire. Each question is rated on a 5-point Likert scale, which ranges from 0 (not at all) to 4 (very often). Anxiety and depression are scored separately. A total anxiety or depression score between (8-10) on either scale is considered significant.

REHABILITATION OUTCOME ASSESSMENT

The World Health Organization's International Classification of Impairments, Disabilities and Handicaps (1980) was used as the conceptual basis for choosing which outcome measures to assess.

Physical and cognitive disability

Since the primary aim of the rehabilitation programme was to increase functional independence, reductions in physical and cognitive disability were selected as two of the outcome measures of this study.

The Functional Independence Measure (FIM) (Granger et al. 1990). Disability was assessed by using both the motor and cognitive domains of the FIM. This measure is comprised of 18 items, which assess the level of functional everyday independence in nine subscales (transfers, locomotion, self-care and sphincter, comprehension, expression, social interaction, problem solving and memory). Each item is rated on a scale of 1 through 7 (1 = total assistance required; 7 = independent). The score range is 0-91, with an increase indicating improvement. The scores were obtained from MS participant interviews by members of the multidisciplinary therapy team. This method of administration had been shown to be valid (Brosseau & Wolfson 1994). There is some support for both the reliability and validity of this measure (Kidd et al.1995).

Neurological Impairment

The Expanded Disability Status Scale (EDSS) (Kurtzke 1983) is a single index of severity of MS ranging from 0 (normal) to 10 (death). It is the most widely used measure of neurological impairment in MS and attempts to capture the full extent of MS symptoms in a standardised way. Whereas the lower section of this scale addresses impairment, grades 4 through 10 are strongly dependent on one aspect of disability, locomotion. Though some reservations

have been expressed about the psychometric properties of this instrument (e.g. Willoughby & Paty, 1988), it has been used in most clinical trials and has been adopted as part of the "minimum data set for MS" (Slater (1984). Presently, there is no well-evaluated alternative available. This data was collected by the medical senior house officer on the rehabilitation unit. Both the FIM scales and EDSS were measured on admission and discharge.

The author was blind to the results of these assessments until the conclusion of the entire data collection process. The therapeutic and medical staff were blind to the results of the cognitive assessments during their rating of participants on the FIM and EDSS measures.

THE REHABILITATION PROGRAMME

Before being admitted to the unit, each MS participant underwent a assessment by a multidisciplinary team, which was made up of a physiotherapist, an occupational therapist, a neurologist and a nurse. When required, a neuropsychologists and speech and language therapist also participated in the assessment process. In most instances MS participants were admitted for a 3-5 week goal-orientated programme.

The rehabilitation approach adopted in this study is very similar to that adopted by Freeman et al. (1997) and is based on a comprehensive model of care that considers that rehabilitation management extends beyond symptomatic treatment and stresses the achievement of the best possible quality of life for the person within the limits of the disease (Shapiro & Langer (1994). While no two rehabilitation units deliver care in the same way, the literature reveals a 'shared aims' of practice between centres, with the key elements identified as (1) a multidisciplinary team approach (2) interventions

tailored to meet the individual's needs and (3) a patient-centred functional goal-setting approach (e.g. Freeman et al. 1997).

Each patient followed an individually designed goal-orientated programme, which was derived from the problem list constructed on arrival and geared towards achieving long-term goals towards a degree of independent domestic function. Each programme always included occupational therapy, physiotherapy and nursing input. The general goal-orientated approach of this particular unit constituted an informal multiple baseline design. Every week, concrete and specific behavioural goals were set to address certain tasks of personal and home activity. Therapy was focussed towards these goals, which were often achieved by the predicted date.

CHAPTER 5

Results

Statistical analysis

The principle method of analysis for examining the group differences was independent t-tests. Since only 4 MS participants obtained a score above 0 on the scales for anxiety and depression on the HADS, it was not felt necessary to control for these variables in the analysis. The relationship between selected cognitive and self-rating measures were assessed using nonparametric (Kendall's tau) correlation coefficients, as the scores produced from the self-rating measures were not continuous. The degree of inter-group relationship on the DEX questionnaire was assessed using parametric (Spearman's r) coefficients. While full Bonferroni correction was not employed for multiple correlations due to the limited sample sizes, a conservative significance level ($p<0.01$) was used in interpreting the results. Since the outcome measures are considered as ordinal, these were analysed using Wilcoxon Signed Ranks Test. Predicting performance on the outcomes measures in the MS group was analysed using statistical (forward selection) multiple regression.

To establish whether the data was normally distributed, each variable was subjected to formal inference tests of skewness and kurtosis using a conservative level of significance for small samples (.01). Although varying degrees of skewness and kurtosis were observed, no values were found to be significantly different from 0 and therefore the data was considered normal.

Age

The mean ages of the groups were, 44.68; SD 9.39 (MS participants) and 40.00; SD 7.32 (control participants). Although the MS participants were on average four and a half years older than the controls, this difference was not found to be significant [t (50) = 1.81, p >0.5].

General Intelligence

There was no significance difference between the groups in their estimated premorbid optimal level of functioning (NART), or on measures of current verbal (WAIS-R) or spatial (VESPAR) ability (see table 1). However, as can be seen in table 1, there was a trend for the control group to perform more competently on tests in this domain.

Table 1

Mean scores and standard deviations for tests of premorbid and current intelligence

Tests	MS group	Control group	t-value	p-value
Premorbid IQ (NART)	105.60 (12.95)	109.33 (7.72)	.95	.34
WAIS-R Verbal IQ	98.50 (12.45)	105.63 (13.16)	1.33	.20
VESPAR				
Category	15.59 (3.24)	17.22 (2.28)	1.34	.14
Analogy	15.47 (4.90)	17.89 (4.17)	1.23	.22
Series	18.25 (3.81)	20.01 (4.05)	1.44	.18

PERFORMANCE ON MEASURES OF EXECUTIVE FUNCTION

The mean scores, standard deviations and significance tests for the groups are provided in table 2.

No significant difference was observed on the Temporal Judgement Test. On the Hayling Test, no significant difference was found between the groups on the response initiation measure (time A), however, significant differences were observed on time B and on the measure of response suppression (B errors). A significant difference was also observed between the groups on the measure of rule attainment (Brixton Test). This difference was observed to be the highest amongst the executive test measures (see table 2).

Table 2.

Means and standard deviations for tests of executive function

Tests	MS group	Control group	t-value	p-value
Hayling Test				
Time A	8.34 (7.53)	6.75 (5.48)	.62	.49
Time B	35.91 (28.52)	20.97 (10.85)	2.10	.02
B Errors	12.73 (12.54)	5.88 (5.08)	2.12	.02
Brixton Test	21.42 (9.56)	12.63 (6.57)	2.36	.01
Temporal Judgement	2.23 (1.02)	2.50 (1.07)	.62	.53

METACOGNITION AND THE RELATIONSHIP WITH EXECUTIVE TESTS PERFORMANCE

Table 3 gives the mean ratings that each group provided for their performance on the executive tests. It is noticeable that the MS participants rated themselves as performing less well than the controls on all tests. This is in keeping with the mean tests results provided in table 2.

Table 3

Means and standard deviations for self-rating on executive tests performance

Tests	MS group	Control group
Hayling Test (self-rating)		
Time A	3.67 (.86)	4.00 (.76)
Time B	2.67 (1.06)	2.88 (.99)
B Errors	2.71 (1.10)	3.50 (.76)
Brixton Test (self rating)	2.68 (.67)	3.00 (1.41)
Temporal Judgement (self-rating)	2.23 (1.02)	2.50 (1.07)

To establish whether MS participants could accurately monitor and self-reflect on their actual test performance, participants' ratings of performance on each of the executive tests were correlated with the appropriate test score. The correlations were then compared between groups. Table 4 provides the results of the non-parametric correlations (Kendall's tau) what were performed on the data.

The results of these analyses show that the MS participants were in most instances, with the exception of their rating on the Temporal Judgement Test, significantly more accurate at reflecting on their performance on executive tests. No significant correlations were observed in the control group between self-ratings and actual test scores at $p<0.01$. However, it should be noted that a correlation at $p<0.05$ was observed in the control group between the self-rating error score and the actual Hayling Test error score. The difference between the correlations between groups were all significant at least at $p<0.01$.

All participants filled out the self-rating DEX questionnaire and all but 2 carer and 3 others' ratings were completed. Pearson product moment correlations

were computed between the participants self-rating and carer/other's ratings within each group. Figures 1 and 2 show the degree of relationship between these scores within the MS and control groups respectively. They also show that the extent of dysexecutive symptoms in the MS group is considerably more varied. Significant correlations were observed within the MS group ($r = .81$; $p < 0.001$) and control group ($r = .73$; $p < 0.001$). The difference between these correlations was not significant ($p > 0.05$).

Table 4

Intercorrelations between self-rating and executive test scores

	Hayling A time	Hayling B time	Hayling B errors	Brixton errors	Temporal Judgement
MS group ratings	-.47*	-.62**	-.63**	-.52*	.09
Control group ratings	.16	-.38	-.61	.07	-.05

* $p < 0.01$, ** $p < 0.001$

Separate correlations were computed for the MS group between measures of metacognition (self-rating scores of executive test performance and the DEX questionnaire) and the duration of the disease. A significant negative correlation was found between the self-rating Hayling Test error score and the duration of disease ($r = -.52$, $p < 0.01$).

Figure 1.

Relationship between self-ratings and carers' ratings in the MS group

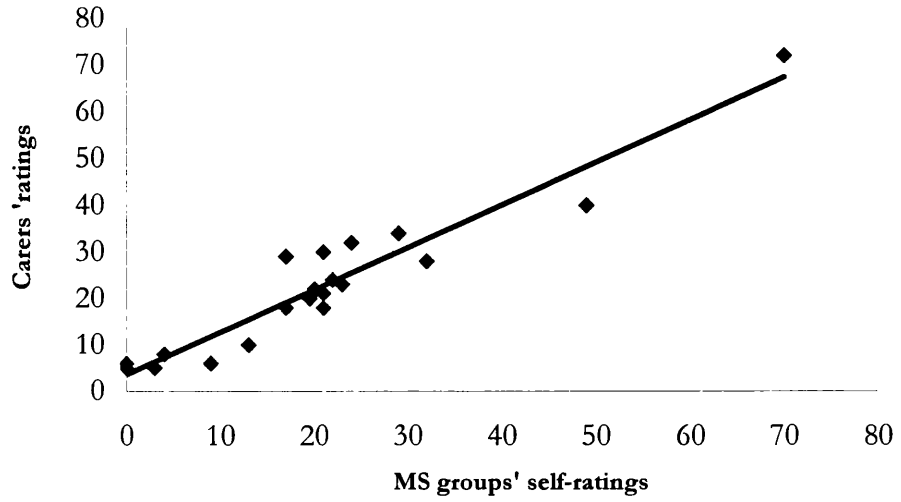
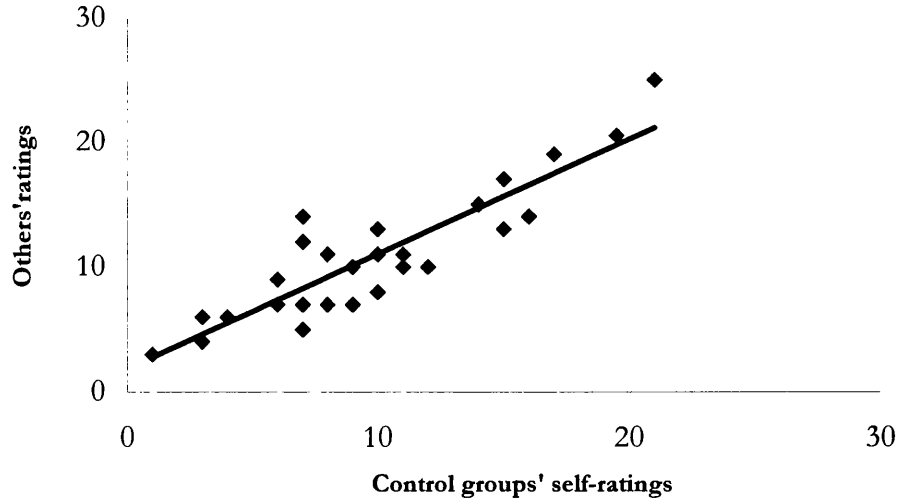


Figure 2.

Relationship between self-ratings and others' ratings in the control group

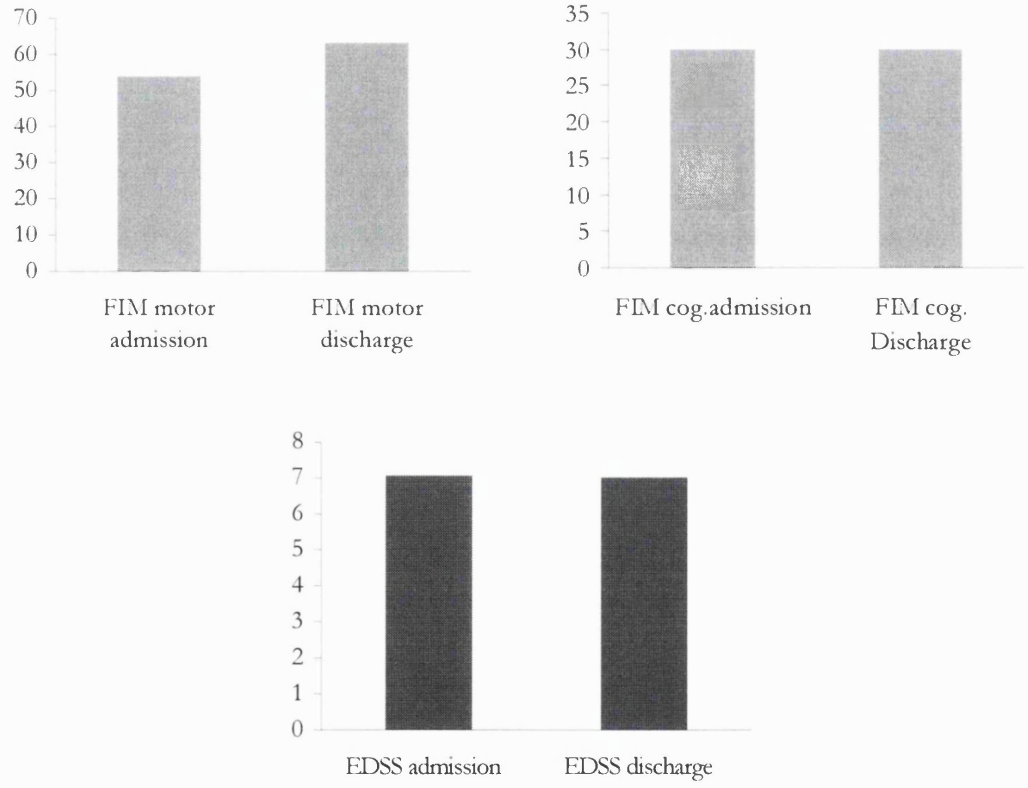


Changes on outcome measures

Figure 3 shows the changes on each of the outcomes. The median FIM motor score on admission was 62.50 and the median FIM motor score on discharge was 66.50. The median motor gain was 4 points. This was found to be significant ($z= 2.31$, $p <0.02$). The median FIM cognitive score on admission was 32.50 and 33.00 on discharge. The median change (.50) was not found to be significant ($z=.49$, $p > 0.05$). The median EDSS score on admission (7.00) and on discharge (6.50) indicates that overall, MS participants slightly declined on this measure. This change was not significant ($z = .31$, $p > .05$).

Figure 3.

Comparisons between changes on outcome measures before and after rehabilitation



In addition to these analyses, the clinical significance of the change on the FIM motor scale was assessed by computing the effect size. The measure of improvement, expressed as an effect size was .51, which is classified as a medium effect (Cohen, 1992). Thus, the MS participants showed on average, a moderate improvement on their FIM motor scores over the course of rehabilitation.

PREDICTING REHABILITATION OUTCOME

Statistical considerations

There were a number of salient issues to consider prior to the regression analyses. Although neuropsychological tests scores are typically treated as parametric, the FIM and EDSS scores are regarded as ordinal data. In addition, as the number of participants was small, the ratio of participants to independent variables was compromised and therefore the statistical power of the regression equation to accurately predict outcome in each case was reduced. Despite the limitations that these practical issues imposed, it was felt that the interactive effects of a number of the variables that might influence rehabilitation gain, are perhaps only likely to be revealed using parametric statistics. It should be noted that the regression analyses reported here are only able to identify linear relationships between the variables, even though some of these variables may not be linearly related.

Statistical (forward) regression was chosen because the primary goal of these analyses was to build models to predict rehabilitation outcome, rather than to test particular models. In addition, this technique was also felt to be useful in reducing the potential problem of multicollinearity by not including highly correlated predictors.

FIM cognitive outcome

The FIM cognitive score on discharge was selected as the dependent variable. The independent (predictor) variables chosen to predict change on the FIM cognitive scale were all of the executive tests (Brixton errors, Hayling time A and B, Hayling error score and the Temporal Judgement Test total score) and the measures of metacognition (self-rating scores of executive tests performance and the DEX questionnaire). In addition, a discrepancy score between participants NART IQ and WAIS-R scores was computed and included as an independent variable to control for any general cognitive decline. Age, gender, duration of illness and FIM cognitive scores on admission were also included to take account of each patient's starting point. Only the Hayling time A was found to significantly predict change on the FIM cognitive scale and accounted for 51% of the variance in improvement ($r = .75$, r^2 adj. $= .51$, $F_{(1,19)} = 17.79$, $p < 0.007$). The standardised regression coefficient (beta) was -.75.

FIM motor outcome

The independent variables selected to predict change on the FIM motor scale were similar to those listed above, with the exception of the FIM cognitive scale, which was substituted for the FIM motor scale on admission. This was the only variable selected by the regression procedure and was found to significantly predict change on the FIM motor scale, accounting for 58% of the variance ($r = .79$, r^2 adj. $= .58$, $F_{(1,19)} = 20.55$, $p < 0.002$). The beta coefficient was .79.

EDSS score

Again, the same independent variables were included as predictors, but the FIM motor score on admission was substituted for participants' EDSS admission score. This variable alone[1] significantly predicted the EDSS score

[1] The t-statistic that relates to the beta value in these analyses produces the same p-value that the F-statistic for the overall regression did.

on discharge and accounted for 69% of the variance ($r=.84$, r^2 adj. $=.69$, $F_{(1,19)}=23.72$, $p<0.001$). The beta coefficient was .84.

CHAPTER 6

Discussion & Conclusion

This thesis set out to examine five hypotheses within two distinct but related areas: executive function and metacognition in people with multiple sclerosis. The main goal was to further characterise dysexecutive syndrome in MS and determine whether dysexecutive and metacognitive difficulties are predictive of rehabilitation outcome.

The first hypothesis asked whether MS participants would perform significantly worst than healthy controls on tests of executive function. This hypothesis was for the most part supported. MS participants were observed to perform significantly worse on measures of rule attainment (Brixton Test), response suppression (Hayling Test - errors) and efficiency in suppressing inappropriate responses (Hayling Test – time B). However, no significant differences were observed between the groups on measures of response initiation (Hayling Test - time A) and estimation and judgement (Temporal Judgement Test).

The second hypothesis stated that significant correlations between controls' ratings of their performance on executive measures and their actual performance would be observed, but that no such pattern of results would be found in the MS group. This hypothesis was not supported. On the contrary, the reverse pattern was observed, namely that with the exception of the correlation between self-rating and actual performance on the Temporal Judgement Test, significant negative correlations between self-rating and

actual test performance were observed in the MS group on all measures. No significant correlations at $p < 0.01$ were observed in the control group.

The third hypothesis stated that whereas a significant correlation between controls' self rating of everyday executive problems on the DEX and those of others' would be observed, no significant relationship would be found in the MS group. This hypothesis was only partially supported. Like the controls, a highly significant positive relationship was also observed in the MS group between their self-ratings and those of others who knew them well.

Hypothesis 4 addressed the question of whether there is a significant relationship between metacognitive impairments in MS and the duration of symptoms. Although the results relating to the above hypothesis suggests that the MS participants as a group did not have any metacognitive impairments, correlations were nevertheless performed between measures of metacognition and duration of disease. A significant negative correlation was found between the self-rating Hayling Test error score and the duration of disease. No other significant correlations were observed.

The last hypothesis stated that measures of executive function and metacognition would significantly predict rehabilitation outcome scores. This hypothesis was only supported with respect to predicting change scores on the FIM cognitive scale, where it was observed that Hayling time A and no other variable, significantly predicted FIM cognitive scores following rehabilitation. Changes in FIM motor and EDSS scores were significantly predicted only their respective scores on admission.

Dysexecutive test performance

The finding of dysexecutive difficulties in multiple sclerosis relative to a matched control group, is in keeping with the many findings now being reported in the literature (e.g. Beatty, 1993; Mendozzi et al. 1993, Foong et al. 1997) and in this context, the present work serves to support such findings. Perhaps of more interest is the kind of dysexecutive difficulties observed in this study. The poorer performance of the MS participants on the Brixton Test is a new finding. However, the skill that is being assessed, namely rule or concept attainment, has been investigated previously using other tests which fall into the same class of test as the Brixton.

The most well known of these is the WCST which as discussed previously, has been found to be performed poorly by MS patients (Mahler, 1992). However one of the difficulties of interpreting WCST performance is that a patient can fail for a number of reasons, some of which may not be related to primary executive difficulties at all. For instance, Nelson (1976) argued amongst other things that each response card of this test may share two or more attributes with the stimulus cards and that it then becomes difficult for the patient to comprehend the clinician's or experimenter's feedback and for the experimenter to understand why a patient is failing the task.

The Brixton Test stimuli avoid many of the problems of interpretation associated with the WCST and as such, it is considerably easier to understand a patient's performance. In the context of the present study, MS participants' performance on this test clearly demonstrates that they have problems in realising rules. However, in keeping with the authors' original study using this tests (Burgess & Shallice, 1996) it is also possible to go beyond the limitations of other rule attainment tasks such as the WCST (i.e. concept attainment perseveration problems) and examine other types of qualitative errors that a patient may make. For instance, Burgess & Shallice identified 3 types of errors participants with frontal lesions make. The first were classified as

perseverations at the stimulus-response level, the second were applications of other rules that were previously relevant and the third were bizarre responses and guesses. Although a formal examination of these issues was not specified as a hypothesis for this thesis, it is perhaps interesting to note that a larger majority of the MS groups' error responses were guesses rather than perseverations or the application of previously correct rules. Indeed, on a number of occasions, some MS participants spontaneously mentioned that they were 'guessing' on some of the trials. This observation may suggest that the MS groups' performance on this task may in fact be qualitatively different from that classically observed with the WCST (Milner, 1963), where patients with frontal lesions often make preservative errors and from other studies of WCST performance in MS patients. This possibility would seem to be an interesting area for further research.

Like the Brixton Test, this is the first investigation to report impaired performance on the Hayling Test in MS. However, MS patients have been reported to perform poorly on other tests that probably tap the same skills as the Hayling Test such as verbal fluency and the Stroop Test (Foong et al. 1997). In the present study however, although patients performed more poorly on all three measures of the Hayling Test, their performance on Hayling time A was not significantly different from the controls. This suggests that at least in MS, response initiation and suppression can be dissociable. By contrast, performance on both measures of Hayling B were significantly worse, suggesting that response suppression and the efficiency of suppression, as measured by the time it takes to produce a verbal response, are more of a problem for people with MS.

One possible conjecture from this result would be to suggest that these two measures are correlated and therefore one might predict that people with MS would perform poorly on both. Indeed, Burgess & Shallice have reported significant relationships between these measures in other populations.

However, the author has observed (Nathaniel-James et al. 1996) that in other clinical populations, namely schizophrenia, patients can perform poorly on the responses they provide to part B, but adequately on the time it takes them to provide a response. Taken collectively, this finding suggests that these two skills may be functionally dissociable in MS, despite their reliance on similar cognitive processes, the most likely of which is strategy use (Burgess, 1997).

The lack of a significant difference between the MS and control participants on the Temporal Judgement (TEMPJ) test requires some consideration. Firstly, with respect to face validity, the items on this test would seem to be appropriate to assess estimation and judgement. However, on other issues, namely concurrent validity, this test has been called into question. For instance Norris & Tate (2000) reported that the TEMPJ had a very low correlation with the Cognitive Estimates Test (.11), the executive test that samples a similar cognitive domain. However, perhaps most relevant here may be an interaction between the number of test items, test sensitivity and the considerable variability in estimation skills in the general public.

The TEMPJ only has four items and is less reliable than the other BADS tests (Wilson et al. 1996). The Cognitive Estimates has been shown to be highly insensitive to general neurological pathology (Burgess et al. 1998), although Burgess and colleagues acknowledge that this might not be the case for all forms of neurological disorder. Nevertheless, it seems reasonable to suggest that the TEMPJ with only four items is even more likely to be insensitive to problems of judgement and estimation. This is on top of an already varied ability range within the general population. For instance, on the Cognitive Estimates, the norm-based range of acceptable answers to the question, "What is the population of Britain Today," ranges from 10 million 499 million (see Shallice & Evans, 1978). This degree of variability makes it particularly difficult to identify these executive problems. In clinical practice, it is common to note particularly bizarre responses to estimations rather than

totalling the 'minor' errors. However, with only a limited number of items, the TEMPJ is perhaps not the most robust measure to use in this context with MS participants.

Before discussing the relationship between executive function, metacognitive abilities and rehabilitation outcome, it would seem appropriate to briefly discuss other factors that could have contributed to the executive dysfunction observed in the MS group. The disease process of MS confounds the measurement of cognitive function in many ways. The methodological problems inherent in assessing cognitive function in this context are complex (e.g. Fennell & Smith, 1990). Most noticeably, since the pathology is diffuse in the cerebral hemispheres, assessment will be made in the context of physical impairments, which may compromise motor functions. In the context of this study, patients with even mild dysarthria may have performed less well on the Hayling Test in particular, given its reliance on a verbal response.

In addition, it is conceivable that there were coincident cognitive impairments which may have affected patients' executive test performance. For instance, attention is often compromised by MS (e.g. Kujala et al. 1994), and the executive tests used in this study, indeed, as in many studies in this field, rely on a restricted aural presentation of the task description and stimuli. Any general dementia is also likely to lead to poor executive performance, but in this context, it would be difficult to interpret this as implying that the patients have focal executive difficulties (Langdon, 1997). Although there have been few detailed studies of language function in MS, naming and reading have been reported to be mildly affected, whilst spelling and comprehension are intact (Jambor, 1969). Although not examined explicitly, it is possible that mild expressive language difficulties in this MS sample may have confounded performance on the Hayling Test. As discussed in Chapter 2, Short-term/working memory impairment is a reliable finding in group studies of MS patients. Thus, it is likely that at least some of the present sample would

have performed poorly on cognitive tests in this domain. Perhaps the most likely impact that this may have had on the executive test findings was on the Brixton Test, since it is essential for participants to keep in mind both their previous response and the actual position of the coloured circle on the preceding stimulus page. Patients who had trouble doing this may have found it particularly difficult to anticipate the position of the coloured circle on subsequent pages, not necessarily due of executive difficulties, but rather because of poor short-term/working memory.

There are methods to explore the possible contribution of these confounding factors to the results found. For instance, a single-case study approach is a powerful way to explore such issues, since patients can be assessed on a wide battery of tests and patterns of impairment and indeed dissociations can help identify non-executive impairments more closely and the existence of resource artefacts (Shallice, 1988). However, since the primary aim of this study was to predict rehabilitation outcome, a more appropriate method would have been to administer a battery of tests which was inclusive of the most likely contributors and then to covary their effect using appropriate statistical analysis. This method would have served to both establish co-existing non-executive impairments and their impact (if any) on the executive impairments observed. This approach should be considered in future studies in this area.

Relationship between Metacognitive abilities and executive function

Perhaps one of the most surprising findings of this study was to find that MS participants with selective dysexecutive difficulties, not only were able to reflect well on the accuracy of their performance on executive tests, but also were able to do so more accurately than healthy controls. With the exception on their ratings on the TEMPJ, MS participants' self-ratings of the other executive tests were strongly related to test performance. By contrast, controls

as a group, seem to have found this task more difficult to do. This is a difficult result to explain. The performance of the MS group whilst initially surprising, may be explained by the format of the tasks themselves. For instance, on the Brixton Test, participants receive consistent feedback as to the accuracy of each response because as the pages are turned over, they get to see what the correct position of the blue circle should be. Similarly, the Hayling Test gives some feedback at least with respect to participants' responses to section B. An explicit instruction on the part of the examiner when faced with a participant who produced a category a response (i.e. a straight forward sentence completion) is to inform the participant that s/he has produced a word that completes the sentence and to ensure that they understand that this is not what is required.

With these forms of feedback, participants can potentially consistently update their knowledge of how well they are doing and thus more accurately reflect on their performance. Cornoldi (1998) refers to this process as 'metacognitive conceptualisation', which describes people's beliefs and interpretations about their cognitive activity. He argues that this aspect of metacognitive reflection is subjected to modifications and articulations due to the particular context of the moment. This concept would seem to have validity here. Whilst this explanation may account the MS participants' good performance on the self-rating tasks which were found to significant correlate with actual task performance, it may explain the lack of relationship on the TEMPJ Test. Unlike the tests described, the TEMPJ does not provide any feedback as to the accuracy of participants' responses. Moreover, it is less clear what a 'good' or 'correct' answer is, since subjects are asked to provide estimates, which in actual fact, fall within acceptable ranges. In these respects, the response and scoring formats of this test are quite different from those just described.

Metacognitive conceptualisation is theoretically and practically a separate process from the type of reflection an individual may have in advance, which

Cornoldi & Vianello (1992) call 'metacognitive knowledge'. This can be general or specific knowledge, concerning particular aspects of cognitive functioning. The research on metacognitive functioning in MS to date appears to have exclusively examined the latter process (e.g. Kujala et al. 1996; see Chapter 2). The implications of the current work are that there may be a dissociation in MS between these two aspects of metacognition, with impaired metacognitive knowledge but intact metacognitive conceptualisation.

A second explanation for the performance of the MS group on the self-rating task may have something to do with the extent of their dysexecutive difficulties. Burgess et al. (1998) in a recent study looking at the ecological validity of tests of executive function, used factor analysis to determine which individual dysexecutive symptoms form coherent subsets that are relatively independent of one another. Of relevance here was the observation that lack of insight loaded under a factor called 'intentionality', which by implication, suggests that individuals may need to demonstrate difficulties in this domain to have metacognitive problems. Unfortunately, the cognitive battery used in the present study did not include any tests that could be considered to be grouped under this factor, so it is not known whether this sample had these difficulties. However, one conjecture could be that they did not and therefore would have no difficulties on the self-rating tasks of their executive tests performance.

At a psychological level, it is highly conceivable that the MS participants are more emotionally concerned about their cognitive function, particularly whilst on a neurorehabilitation unit, where considerations about their current abilities and disabilities are constantly monitored and discussed. In addition, over the course of the disease, they are likely to have developed a concept of their own level of executive performance, as they probably have done for physical problems associated with their disabilities. Indeed, for the vast majority of this group, this is not the first time they have undergone a

neuropsychological assessment and therefore are likely to have previously reflected on their performance. By contrast, the controls are very unlikely to have given previous consideration to their cognitive abilities and therefore the task of rating their performance has much less saliency for them.

One possible statistical explanation that may account for the performance of both groups is that of a statistical artefact. With the exception of TEMPJ, the MS participants have a considerably wider spread of scores. For instance, on Time B, the range is 127 points compared with the control group's range of 39. With such a wide range, it is easier for the MS participants to discriminative accurately, whereas for controls, it becomes harder for them to differentiate across a more restricted range. It is important to note that when the range is restricted in both groups (as it is on the TEMPJ), their ratings are highly comparable and not significantly related to their actual performance.

It is not possible to be conclusive as to which of these explanations is the more likely for the results observed. Indeed, it may well be a combination of some of these ideas that ultimately serves to provide the best account for these findings. There is clearly a need for further research in this area.

Metacognition and its relationship with behavioural indicators of the dysexecutive syndrome

The DEX questionnaire was included to assess whether patients were self-aware of their everyday executive problems. In the light of previous studies of insight in MS (e.g. Beatty & Morrison) the highly significant correlations between patients and their carers' ratings on the DEX are at first surprising. In studies of other non-MS patients with executive difficulties (e.g. Burgess et al. 1998) a marked discrepancy in ratings was observed between a group of mixed etiology neurological patients and their carers. However the majority of these patients (59%) had suffered a head injury rather than a progressive disease. The significance of this for a progressive disease such as MS on insight is that MS patients in most cases will have undergone a steady

cognitive decline, which over time will have affected their day to day functioning on a regular basis. It is conceivable that this steady progress is likely to enhance their abilities to recognise changes in behaviour, compared to patients with a head injury, where changes in behaviour are often rapid.

The findings of this study on the metacognitive abilities of MS sufferers suggests that unlike some other patient populations with dysexecutive difficulties, MS patients do not appear to have significant problems in evaluating either their current executive abilities on formal tests, or their everyday behaviour. However, in view of the statistical considerations discussed earlier, more research in this area may be warranted to substantiate the current findings.

Rehabilitation outcome

The observations on the FIM motor scale are in keeping with previous research findings (e.g. Freeman et al. 1997; Langdon & Thompson, 1999) in that although in both of these studies the patients had different starting points, the magnitude of change was similar. However, the current findings on the FIM cognitive scale appear to differ from those of Langdon & Thompson. These authors reported that their MS participants' median score on admission was 35 points, which is the top of the scale. Not surprisingly, the group achieved the same median score on discharge, with the vast majority (82%) achieving this score. By contrast, only 4 participants (18%) in the current study achieved this score. Moreover, the range of scores was considerably more varied on both admission and discharge than those reported in the study of Langdon & Thompson. This suggests that at the most basic level, the participants in this study are less functionally independent in areas such as comprehension, expression, social interaction and problem solving.

The unchanging scores on the EDSS are very much in keeping with previous studies (e.g. Freeman et al. 1997) that have reported improvements in functional independence in the context of static neurological impairment. Freeman and colleagues have argued that these findings are not surprising. One of their arguments is that improvements in underlying disease pathology are not expected to change as a result of rehabilitation, particularly in patients in the progressive stage of the disease. As a contrast, the authors argue that in clinical trials of therapeutic agents (e.g. Johnson et al. 1995) the primary goal of the intervention is to influence features like relapse rate and therefore one is more likely to see changes in disease burden.

It is also important to look at the scale itself to understand why changes in function might not be mirrored by changes in neurological disability. As mentioned previously, an EDSS of 10 signifies death and a score of 0 denotes a normal neurological examination. Between these two extremes, the scale rates the level of disability with a major emphasis on the patient's ability to walk. The EDSS is thus heavily weighted in favour of pyramidal tract and brain stem involvement, with relatively little emphasis on any functional considerations. With this in mind, it is easy to see how changes in functional independence, for instance grooming, can occur independently of improvements on the EDSS.

The fact that changes in the EDSS were not significant however does not mean that individual patient scores did not change on this measure. Other studies, particularly those that have included patients with relapsing-remitting MS (e.g. Aisen et al. 1996), where there is a likelihood of spontaneous neurological recovery and consequent improvement in impairment, have shown changes on the EDSS.

Predicating rehabilitation outcome

To consider first the FIM motor scale. The only significant predictor of improvement on this scale was the patients' FIM motor scores on admission. In a study, which included 196 MS patients as part of a larger group, a relationship was reported between functional status on admission and rehabilitation gain (Carey et al. 1988). The current finding also partly supports those of Langdon & Thompson (1999), although the authors also found verbal skills and cerebellar function to be significant contributors to their regression model. The current finding however serves to support studies that suggest a strong influence for the starting level of disability on rehabilitation outcome. This is perhaps not surprising because rehabilitation of a chronic neurological condition can only generally occur within the physical restriction that the disease dictates (Langdon & Thompson 1999). This has also been demonstrated in non-progressive conditions (e.g. Pfeffer et al. 1996) reported that stroke patients' admission scores on the FIM related to both the probability of achieving and the time taken to reach self-care and mobility outcomes goals).

No measures of executive or metacognitive function were found to predict change on the FIM motor scale. Initially, this might appear to be a little surprising, given the growing literature on executive impairments in MS discussed in chapter 2. However on reflection, it is perhaps reasonable to suggests that intact executive and metacognitive skills might not be an essential prerequisite to changes in repetitive and in most cases, re-learning of old motor skills of everyday activity, which are typically targeted by rehabilitation programmes and measured on the FIM motor scale. Indeed, it is possible to teach self-care skills to people with learning disabilities with significant cognitive deficits. (e.g. Bouffard, 1990). How can one account for this? Learning theory research might provide some answers. For example, procedural (implicit) memory is seldom affected following brain damage,

whilst explicit memory is very sensitive to brain damage (Ewert et al. 1989; Timmerman & Brouwer, 1999). Since amnesic patients can learn via procedural memory, it is perhaps possible that self-care skills can be learned via an implicit route. The relevance of this to the present study is that since the MS patients in rehabilitation are re-learning essentially old skills rather than new ones, it is likely that they maybe acquiring or re-acquiring their functional motor skills through procedural rather than any explicit mechanisms and thus less dependent on the supervisory attentional system. The implication here is that the impact of control processes on improvement in functional motor skills as measured by the FIM motor scale, has yet to be established.

The value of the Hayling A score above all the other measures of executive function and metacognition requires some thought. Hayling A is one of a group of tests that measure word generation and there is functional imaging evidence attributing this skill to activation in the frontal lobes (Nathaniel-James et al. 1997). Other tests included in this category include the Verbal Fluency Test (e.g. Benton, 1983) and the word generation tasks of Warburton et al. (1996), in which participants had to produce appropriate verbs to given concrete nouns. It is this latter task that is most similar to Hayling A both cognitively and in terms of its functional anatomy. However, although the cerebral structures that subserve these different tasks (including Verbal Fluency) are similar, it is not clear that the skills required are to do them are the same. For instance, the author has previously reported (Nathaniel-James et al. 1997) that the functional anatomy of Hayling A and the error measure of Hayling B are very similar. However Burgess & Shallice (1996) have reported that in contrast to controls and patients with lesions elsewhere, patients with unilateral anterior lesions performance on Hayling A was not related to the error score on Hayling B. Taken collectively, these studies suggests that tests which activate similar functional regions may nevertheless be independent.

What these studies clearly do demonstrate is that the Hayling A is sensitive to prefrontal lobe lesions and measures an independent executive function. However, since this is true for the other executive tests used in this study, it is important to try and explain why this measure in particular predicts FIM cognitive change. Of particular importance in this context is the fact that Hayling A rather than Hayling B predicted FIM cognitive change, even though the MS and control groups were not found to perform significantly different on the former measure. This is a difficult finding to explain. However, one possible explanation maybe that although the MS participants were not as a group impaired on Hayling A, there may nevertheless be individuals within the group who were inefficient in language. Even a mild inefficiency in language might interact with the FIM cognitive scale. Indeed, previous findings that language predicts rehabilitation outcome in MS have been reported (e.g. Langdon & Thompson, 1999).

A related explanation that might account for the ability of the Hayling A to predict FIM cognitive outcome might be to do with a possible relationship between the language components assessed on both the Hayling A and the FIM cognitive scale. To consider first the FIM cognitive. Two of the five areas of this scale are concerned with the use of language skills: comprehension and expression. The other areas of functioning (social interaction, problem solving and memory), have less items devoted to them. This scale thus devotes more items to language than any other cognitive domain. Poorer performance on the comprehension items (i.e. when a helper is considered necessary to prompt the individual) is characterised by slowed speech rate in response to directions and conversation. For the expression items, it is necessary for individuals to be able to express themselves using 'intelligible speech or clear expression of language' to score within the range for independence. It is possible that the sheer number of language items on this scale makes it more likely that scores will be related to other cognitive measures that assess language skills in a more or less direct way.

In this context, of all the executive tests included in this study, the Hayling A is the one that most sincerely assesses the efficiency of language skills by asking participants to generate words to complete sentences as quickly as they can, a task that clearly requires verbal planning skills. Intuitively, the interpretation of the Hayling A in this way would seem to make sense since communication is obviously essential to the rehabilitation processes and verbal inefficiency could disadvantage a patient. Moreover in rehabilitation, collaborative, educational process which could be affected by language inefficiency, relies on consistently accurate communication and thus it is easy to see how difficulties in this area may impact on rehabilitation outcome.

It is also important to consider those executive tests that did not reach statistical significance in the analysis. From a statistical perspective, with the exception of the TEMPJ, wide variances in performance were observed in the MS group on all of the executive tests. It is thus possible that this alone may have accounted for the observed findings. However it is also important to consider the sensitivity of the cognitive measures. Indeed, the Hayling and Brixton Test are highly sensitive measures of dysexecutive difficulties and are thus capable of detecting the subtle cognitive changes that characterise MS. By contrast, the FIM cognitive scale has not been designed with this level of sensitivity in mind and thus reduced rule learning and response suppression problems are unlikely to register on the seemingly comparative undemanding criteria of the FIM cognitive subsections.

One possible theoretical explanation for why no other executive test was able to predict FIM cognitive change may be provided by Naugle & Chelune (1990). These authors argue that performance on everyday activities is multi-determined by characteristics of the person and by factors inherent in the task environment. Thus, although an individual may display fairly stable cognitive impairments on standardised neuropsychological tests, in the everyday world, the person may be able to use compensatory strategies to modify task

demands and successfully complete ADL activities. Thus, in the current sample of patients, it is possible that compensatory strategies (which are frequently taught by the rehabilitation therapists) may in fact have lead, or significantly contributed to, the improvements observed on the FIM cognitive scale, independent of participants' level of dysexecutive problems on the tests. The possibility of compensatory mechanisms to modify the contribution of executive skills to rehabilitation outcome in MS would seem to warrant further consideration and study .

Like all cognitive tests which are used in the context of rehabilitation, it is important to consider their ecological validity with respect to independent functioning and self-care. Acker's (1990) overview of research relating neuropsychological measures to aspects of self-care and independent living has reported that there is good evidence demonstrating positive relationships between standardised measures of cognitive ability and broad outcome measures everyday functioning. For instance, Acker & Davis (1989) studied individuals with acquired brain injury and found that visual perception, motor skills and memory functioning were positively related to global ratings of competence to live independently. Whilst this is of course encouraging, there is little research which has attempted to address the ecological validity of current tests of executive function. Two of the exceptions to this are Burgess et al. (1998) and Norris & Tate (2000). The main findings of Burgess et al. study were that each of the measures of executive function assessed predicted some aspect of the dysexecutive syndrome at the behavioural level, but perhaps more importantly, the tests loaded differently when subjected to factor analysis. The 3 factors were Inhibition, Intentionality and Executive Memory. Unfortunately, with the exception of the TEMPJ, none of the tests used in the present study have been specifically examined for their ecological validity. Ideally, it would have been helpful to have chosen a selection of tests explored in Burgess's et al. study, to control for the possibility that some of the executive tests used in the current study do not in fact reflect difficulties

in real life. However, as previously discussed in chapter 4, many of these traditional tests would not have been suitable for this MS population. It therefore begs the question of whether the executive tests used here have the necessary levels of ecological validity to predict rehabilitation outcome in MS.

CONCLUSION

The primary aim of this thesis has been to try and further characterise dysexecutive and metacognitive impairments in MS, by attempting to understand what impact they may have on in-patient rehabilitation outcome. Despite the significant advances in neuropsychological assessment tools and our theoretical understanding of cognitive control processes, the impact of dysexecutive difficulties in MS in the context of neurological rehabilitation remains largely enigmatic. Nevertheless the findings of this thesis have provided some of the clues on which subsequent research questions can be built to unravel this conundrum.

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Appendix I

Information Sheet (control participants)

Multiple sclerosis (MS) is a chronic disease of the central nervous system, affecting the brain and spinal cord. A number of patients with MS at some time in their lives, undergo in-patient rehabilitation. However at present, there is limited information as to which patients are most likely to benefit from this form of treatment. The aim of the study is to try and identify some of the characteristics of people with MS that are likely to predict how well they will respond to in-patient neuro-rehabilitation. To do this, we are asking a large number of people with MS to participate in this study, by undergoing a cognitive assessment. This particular type of assessment will look at the way people go about working with novel and in some cases problem-solving tasks. All of the tasks which make up this assessment are carried out on a table top and many only require people to respond verbally to questions asked by the examiner. Others only ask that people point to shapes and patterns when prompted. Some of the tasks are simple to perform, others may be more difficult. This will be the same for everybody.

In order to identify areas of difficulty in these tasks in people with MS, it is necessary to compare their scores with the normal range, that is, the scores obtained from healthy people. To establish the normal range requires healthy people completing the same tests. This is why you have been approached. The assessment will take approximately 1-11/2 hours to complete. All details are strictly confidential and will only be used in the relevant statistical analyses. Your participation is completely voluntary. You are free to withdraw from the study at anytime.

Appendix II

THE NATIONAL HOSPITAL FOR NEUROLOGY & NEUROSURGERY

RESEARCH ON HUMAN VOLUNTEERS

Subject / Patient Consent Form.

Brief description of project: ___

This study is concerned with the impact of cognitive functions in multiple sclerosis on neurorehabiltiation .
_____
_____

Consultant(s) in charge / Director of project: Professor A. Thompson

The subject/patient (Name): _____ Hospital no: _____
has given his/her consent to participate in the above named study.

The nature, purpose and possible consequences of the procedures involved have been explained to me by:
Name: Dr David A. Nathaniel-James

Position: Clinical Psychologist in Training

Signature:_____Date: _____
and witnessed by:
Name _____

Position: _____
Address: _____
_____

Signature: _____ Date: _____

Signature subject/patient/guardian: _____

Date: _____

Address: _____
_____

Please return this form to :

Research & Development Administrator,
The National Hospital for Neurology & Neurosurgery,
Room RG04, 68 Guildford Street, London WC1
Telephone: 0171 837 3611 ext. 3096.

IT IS A REQUIREMENT OF THE JOINT RESEARCH ETHICS COMMITTEE THAT ANY ADVERSE EFFECTS WHICH MAY OCCUR DURING A CLINICAL TRIAL ARE REPORTED TO THE ETHICS COMMITTEE CHAIRMAN IMMEDIATELY - VIA THE RESEARCH & DEVELOPMENT OFFICE.