NEUROPSYCHOLOGICAL IMPAIRMENT IN MULTIPLE SCLEROSIS: MRI, MRS AND CLINICAL CORRELATES

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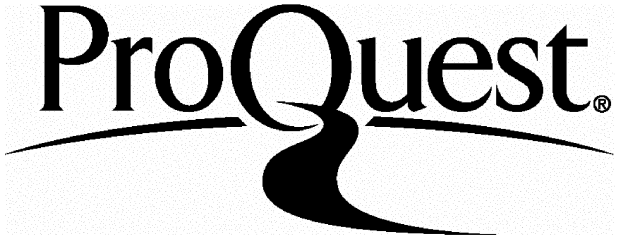

ABSTRACT

The aim of this thesis was to extend previous studies that have attempted to relate neuropsychological deficits and pathological abnormalities in multiple sclerosis (MS) by using standardised and sensitive neuropsychological tests and improved quantification techniques on MRI.

Study 1

Deficits in executive function and the relationship to frontal lesion load as detected on MRI were investigated in 42 MS patients. A battery of neuropsychological tests examining executive skills including computerised tests of planning and spatial working memory was administered to all subjects. Performance on these tests was impaired in the patient group when compared to a group of matched controls but not all executive skills were affected to the same extent. Although a number of executive test scores correlated with the severity of frontal lesion load, it was difficult to disentangle the specific contribution of frontal lobe pathology to the impairment on executive tasks. This study highlights the difficulties in attempting to attribute specific cognitive abnormalities to focal brain pathology in the presence of widespread disease such as in MS.

Study 2

Proton MRS was performed in the same group of MS patients and matched controls from Study 1 to examine the biochemical correlates of

neuropsychological performance. There was a significant reduction of the NAA/Cr ratio in lesions and/or normal appearing white matter (NAWM) in the patient group compared to the control group. However, there was no association between the MRS abnormalities and neuropsychological deficits in the MS patients.

Study 3

13 MS patients were examined with a battery of neuropsychological tests during acute relapse and six weeks later. Their performance was compared to the performance of 10 matched controls. Gd-enhanced MRI was also performed in patients on both occasions. There was evidence that the performance on tests of attention improved in patients whose Gd-enhanced lesion load decreased during the period of the study. This suggests that certain neuropsychological deficits detected during an acute relapse may be reversible. In addition, the improvement in some of the attentional test scores correlated significantly with the improvement in acute lesion load.

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INTRODUCTION

Neuroimaging techniques, in particular MRI, have been valuable in establishing the diagnosis in multiple sclerosis (MS) and have paved the way for research into the neuropathological abnormalities and progression of the disease. Cognitive impairment is well recognised in MS and there has been much progress in characterising the neuropsychological deficits in these patients. However, much less is known about the natural history of these neuropsychological deficits and their changes during relapses and remissions. Attempts to correlate neuropsychological deficits and brain pathology have been made but have proved difficult especially when trying to determine the relationship between discrete neuropsychological deficits and focal pathology. The technical advances in recent years (use of gadolinium, the advent of magnetic resonance spectroscopy and improved techniques in quantification of lesion load on MRI) together with a better understanding of neuropsychological skills have made it possible to explore more fully these brain-behaviour relationships and this thesis represents such an attempt.

This thesis is divided into two main sections:

Section 1 contains a review of the literature.

Section 2 is comprised of three interlinked studies with the central purpose of further delineating the neuropsychological deficits in MS and their relationship to brain pathology. The first two studies specifically examined

deficits of executive function in MS patients and the relationship to structural and biochemical correlates using neuroimaging techniques. The third study was an investigation into the short term natural history of neuropsychological deficits.

CHAPTER 1

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is one of the commonest neurological diseases with a reported prevalence of 50-60 per 100,000 population (Baum & Rothschild, 1981). It is well recognised that there is a geographical variation in the prevalence rates with reports of greater prevalence in the Northern hemisphere, Europe and Australia compared to Asian countries. There appears to be a correlation between the prevalence rates and distance from the equator (Silberberg, 1977). There is also a greater incidence in females with the common age of onset between the ages of 20-40.

The precise aetiology of MS is still unknown although there have been suggested mechanisms. These involve external factors such as viral infection which is thought to result in an abnormal immunological reaction demonstrated by the abnormal immunological findings in these patients and genetic susceptibility as evidenced by the different prevalence rates in different countries. However, the observation that those who emigrate during childhood take on the risk of the adopted country indicates that environmental factors are also important.

The diagnosis of MS is mainly based on clinical findings and the most widely used diagnostic criteria are those of Poser *et al.* (1983). A diagnosis of clinically

definite MS requires a history of two or more discrete attacks of at least a month apart and involving at least two separate sites in the central nervous system. In addition, abnormalities on investigations such as MRI, evoked potentials and cerebrospinal fluid (CSF) examination for oligoclonal bands or increased immunoglobulin G are used to support the diagnosis.

One of the most striking clinical features of MS is its variable course and progression. For many patients, early in the course of the disease, it is characteristic for relapses to remit almost completely (relapsing/remitting MS) but later there is an insidious progression (secondary progressive MS) with less marked exacerbations and remissions. In some patients, the disease runs a benign course with minimal physical disability whilst in others it can be a primary progressive form which progresses steadily from the outset (primary progressive MS). Clinically isolated syndromes such as optic neuritis in which there are only single episodes of clinical disease activity can be the earliest manifestation of MS. Follow-up studies of patients with optic neuritis have shown that more than three quarters will go on to develop MS (Francis *et al.*, 1987) and a similar proportion of patients with brain stem or spinal cord lesions (Miller *et al.*, 1989) will also do so.

The disease is characterised by multiple demyelinating lesions involving the central nervous system with a predilection for certain areas such as the periventricular white matter, optic nerves, cerebellum, brain stem and spinal cord. The pathological process involves the destruction of the myelin sheath around axons leading to defective nerve conduction. The evolution of lesions or

plaques in MS has been studied extensively over the years. In the initial stages, active inflammatory processes precede the demyelination. This results in the acute lesions being oedematous, poorly demarcated and infiltrated by lymphocytes, plasma cells and macrophages which lead to the destruction of myelin. The blood brain barrier (BBB) is also disrupted in the acute stages. The small plaques can coalesce with the progression leading to larger lesions. Chronic lesions are well demarcated and there is evidence of gliosis with the proliferation of astrocytes and microglial cells. Some peripheral remyelination can also be observed, however, with the progression of the disease, this new myelin also becomes susceptible to demyelination.

CHAPTER 2

COGNITIVE IMPAIRMENT

It has been recognised since the writings of Charcot (1877) that cognitive impairment occurs in multiple sclerosis (MS) but it is only in recent years with the use of extensive and standardised neuropsychological test batteries that there have been more accurate prevalence estimates. Approximately 40% of patients with clinically definite MS in community samples (Rao *et al.*, 1991) and 50-60% of hospital samples (Ron *et al.*, 1991) have some degree of cognitive impairment. Although severe cognitive impairment is usually a feature of advanced disease, cognitive impairment amounting to dementia can occur early even in the absence of severe physical disability.

Neuropsychological deficits

Clinically, the neuropsychological deficits observed in MS resemble fairly closely the prototype of subcortical dementia (Rao, 1986). The concept of subcortical dementia was applied and defined by Albert *et al.* (1974), initially in patients with progressive supranuclear palsy, but later extended to other conditions sharing common clinical features and where subcortical pathology predominates. The typical neuropsychological deficits observed in patients with subcortical dementia are retrieval failure, slowed information processing, impairment of abstraction and visuospatial processing with a relative

preservation of intelligence and language functions (Cummings, 1986) which is not dissimilar to that observed in MS patients.

Attention deficits are known to be present early in the disease, even in patients with clinically isolated lesions (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 (Litvan *et al.*, 1988, Filley *et al.*, 1989, Rao *et al.*, 1989a). More specifically, deficits in information processing speed has been evaluated in recent studies with attempts to determine the extent to which these are cognitive rather than motor in origin. An early study (Jennekens-Schinkel *et al.*, 1988b) found that MS patients had slower reaction times compared to controls but that the cognitive component of these tasks was slowed down in a similar way in patients and controls when the task complexity increased and that the slowness was more likely to be motor rather than cognitive in origin. This was not confirmed in a subsequent study by Rao *et al.* (1989a) in which mental speed was assessed independently of motor reaction time using a visual scanning test. In this study, MS patients exhibited a slowing of mental processing independent of motor involvement. In a more recent study, Kujala *et al.* (1994) examined different stages of information processing (automatic, controlled processing and motor programming) in MS patients with and without cognitive impairment as determined by performance on a battery of neuropsychological tests. They reported that there was greater slowing in all stages of information

processing in patients with cognitive impairment compared to those who were cognitively intact. Their findings lend support to the idea that the slowing of information processing is related to cognitive impairment and not to motor slowing. A correlation between atrophy of the corpus callosum and slowing of mental processing speed has also been reported (Rao *et al.*, 1989).

Disturbances in ***memory*** are the most frequently reported deficits and a characteristic pattern of impairment is now emerging. Many studies have reported clear deficits in the performance of tasks involving free recall, and to a lesser extent recognition, when MS patients are compared to healthy controls (Caine *et al.*, 1986, Beatty *et al.*, 1989, Rao *et al.*, 1991). The poor performance in recall tasks can most likely be attributed to a disturbance in the retrieval of information rather than encoding (Caine *et al.*, 1986). Another explanation that has been offered is that attention deficits and the slowing of information processing account for the disruption of encoding and retrieval mechanisms (Beatty *et al.*, 1989) but this has not been supported by others (Litvan *et al.*, 1988, Van den Burg *et al.*, 1987) who have observed the dissociation between memory and attention deficits. This dissociation between recall and recognition has also been reported in Huntington's disease and other conditions which predominantly affect the subcortical structures.

Impairment of retrograde memory, as tested by the ability to remember past personal and public events, warrants further research. Rao *et al.* (1991) using a test that required patients to identify past US presidents, reported no significant

deficits but this is in contrast with the early study of Beatty *et al.* (1988) that reported such deficits in chronic progressive patients.

It is only recently that the presence of ***executive deficits*** has been addressed in neuropsychological studies. Some have reported poor performance on measures of abstract reasoning such as the Category test and Wisconsin Card Sort Test (WCST) (Heaton *et al.*, 1985; Rao *et al.*, 1987, Mendozzi *et al.*, 1993) whilst others have reported deficits in verbal working memory (Litvan *et al.*, 1988). The impairment of executive function has been observed to be similar to that observed in patients with frontal lobe damage and this has led to the suggestion that the presence of focal demyelinating lesions in the frontal lobe structures could account for these deficits. This suggestion has received support from the findings of Arnett *et al.* (1994) who reported that patients with high frontal lesion loads performed worse on the Wisconsin Card Sort Test (WCST) and made more perseverative errors than patients with a low frontal lesion load. To date, other executive skills such as spatial working memory, planning and use of strategy have not been investigated.

A consistent finding of the neuropsychological studies in MS is the relative preservation of language functions. Aphasia is rarely seen in MS, occurring only when the demyelinating lesions extend into the gray matter structures of the dominant hemisphere (Friedman *et al.*, 1983, Olmos-Lau *et al.*, 1977).

Clinical correlates and natural history of the cognitive decline

It has been recognised that cognitive impairment can be an early feature of the demyelinating process and may predate other disabling manifestations of the illness. In rare cases, dementia can be the predominant clinical feature in the absence of significant neurological disturbance as illustrated in two recently reported cases (Hotopf *et al.*, 1994). The patients presented with progressive dementia which was initially attributed to psychiatric illness but were later diagnosed as having MS on the basis of MRI, CSF and electrophysiological findings. Cognitive impairment occurs more frequent and is more severe in patients with a chronic progressive course (Beatty *et al.*, 1988, Rao *et al.*, 1987). Rao *et al.* (1987) examined abstract or conceptual thinking by using the Wisconsin Card Sort Test in comparing chronic progressive and relapsing remitting patients and found the chronic progressive group to be more impaired. This applies to a range of cognitive abilities as demonstrated in a large study comparing cognitive functioning in patients with chronic progressive MS to those with relapsing/ remitting disease using the Halsted-Reitan battery of neuropsychological tests (Heaton *et al.*, 1985).

Disease duration and **level of physical disability** do not correlate highly with the extent of cognitive impairment (Ivnik, 1978b, Peyser *et al.*, 1980). This is partly due to the fact that the commonly used scales to measure disability, in particular Kurtzke's Extended Disability Status Scale (EDSS), are mainly weighted by deficits resulting from spinal cord pathology and therefore a high score would not necessarily reflect cerebral lesion load. A closer correlation has been reported with the extent of cerebral pathology as measured by MRI.

The evidence to date suggests that cognitive impairment can occur early in the course of the disease and can be just as disabling as physical impairment for MS patients. In a study by Rao *et al.* (1991b) which examined MS patients with minimal physical disability (EDSS scores of less than 4), it was shown that patients with significant cognitive impairment experienced problems at work, at home, in relationships and with sexual function compared to patients who were cognitively intact.

Although the neuropsychological deficits in MS have been well described, less is known about their **natural history** and it has been observed that there is considerable individual variation in the progression of cognitive impairment. Patients with clinically isolated syndromes such as optic neuritis which is a common harbinger of MS, have been reported to have cognitive impairment in a series of studies performed at the Institute of Neurology, London (Feinstein *et al.*, 1992). The most significant deficits were in the areas of auditory and visual attention with little evidence of memory disturbance which suggested that tests of attention may be one of the most sensitive measures of cognitive impairment in early MS. Deficits in these patients were usually mild compared to those with definite MS.

Progressive deterioration in cognitive impairment does not appear to be universal. A two year follow-up study reported that cognitive decline was mild or absent in 90% of patients (Filley *et al.*, 1990) and similar results were reported by Jennekens-Schinkel *et al.* (1990) in a four year follow-up study. A five year follow-up study by Feinstein *et al.* (1992) emphasised the different rate of

progression of cognitive deficits depending on the clinical course of the disease. Patients with clinically isolated lesions who later developed clinically definite MS were reported to have little cognitive deterioration except for those who had entered a chronic progressive course. In the chronic progressive group, those who initially had attention deficits were subsequently found to have memory deficits at follow-up whilst no deterioration had occurred in those who had not developed further clinical symptoms or had a relapsing remitting course.

Psychiatric disorder in MS and relationship to cognitive impairment

Patients with MS are known to have an increased vulnerability to psychiatric disturbance. In cross-sectional studies, almost two thirds of patients have psychiatric symptoms although not all require psychiatric treatment (Rabins *et al.*, 1986, Ron and Logsdail., 1989). Depression is the commonest psychiatric disturbance in MS with symptoms of anxiety, irritability, anger and somatic complaints occurring more frequently than apathy or withdrawal. It has been reported that depression correlates more closely with perceived psychosocial stressors rather than lesion load detectable on MRI (Ron and Logsdail, 1989) indicating the complex interactions between brain pathology and environmental factors that determine psychiatric symptomatology.

Bipolar affective disorder has also been reported to occur more often in MS than in the general population (Schiffer *et al.*, 1986, Joffe *et al.*, 1987) but this remains to be confirmed by appropriate epidemiological studies. On the other hand, the incidence of schizophrenia and affective psychosis does not appear

to be increased in MS although short lived psychotic episodes, indistinguishable from primary psychoses, have been reported. A recent study (Feinstein *et al.*, 1992) comparing a group of psychotic to non-psychotic MS patients matched for duration, type of MS and total MRI brain lesion load, reported that the distribution of MRI lesions was different in both groups with lesions around the temporal horns being significantly commoner in those with psychotic symptoms.

A psychiatric symptom more closely associated with the presence of brain disease is euphoria. Euphoria is best defined as a state of persistent cheerfulness without the motor overactivity of mania whilst eutonia is a milder form characterised by an apparent lack of concern about the illness or related disability. These elevated mood states are static and are more akin to a personality change, as that observed with frontal lobe pathology, than to an affective disorder and have been reported to occur in patients with more severe and generalised MRI abnormalities (Ron & Logsdail., 1989). Pathological laughing and crying, an abnormal display of emotion not always related to the underlying mood state is rarer but has been reported in association with pontine, brain stem and periventricular lesions (Rabins *et al.*, 1986, Reisches *et al.*, 1988).

An important consideration when assessing cognition in MS patients is whether the presence of psychiatric symptoms may be responsible, at least in part, for the observed deficits. Some researchers have reported that that low mood could significantly affect performance on tests of immediate and delayed recall

(Feinstein *et al.*, 1992), however, one other study which re-examined depressed MS patients after recovery from depression, failed to demonstrate any improvement in cognitive performance (Schiffer & Caine, 1991). These findings are also supported by those of Ron and Logsdail (1989) who found that the overall cognitive performance in a group of MS patients with clinically significant psychiatric morbidity did not differ from that of other MS patients.

CHAPTER 3

NEUROIMAGING CORRELATES OF COGNITIVE IMPAIRMENT

Magnetic resonance imaging (MRI)

a) Detection of MS lesions

MRI provides high resolution spatial images which are derived from the NMR signal of mobile protons (hydrogen nuclei) from water and fat. Spatial resolution of images is produced by applying a magnetic field gradient across the sample so that protons in different regions of the field will resonate at different frequencies and thereby their location is established. As different tissues including pathological ones have different proton densities, MS lesions can be readily detected on MRI. Studies comparing histological abnormalities and post mortem brain scans have demonstrated that there is a good correlation between MS lesions detected on MRI and histological sections (Stewart *et al.*, 1986; Ormerod *et al.*, 1987).

It has been reported that T2-weighted spin echo sequences are more sensitive than T1-weighted one in the detection of MS lesions (Ormerod *et al.*, 1987). More specifically, moderately weighted T2-weighted sequences, where the CSF appears less intense than normal white matter, are ideal for visualising periventricular lesions whereas heavily weighted T2-weighted sequences, where lesion intensity is greater than gray matter but CSF intensity is not

excessive, is best for identifying subcortical lesions (Miller and McDonald, 1994).

The range of T1 (longitudinal) and T2 (transverse) relaxation times have been found to overlap for acute and chronic MS lesions and therefore do not differentiate the age or activity of lesions (Ormerod et al., 1987; Miller et al., 1988). However, significant elevation in T1 and T2 have been reported in the normal appearing white matter (NAWM) in some MS patients (Ormerod *et al.*, 1987; Miller *et al.*, 1989). It has been suggested that the increase in T1 relaxation times may reflect microscopic abnormalities such as perivascular inflammation, demyelination and astrocytic hyperplasia (Allen, 1991).

New lesions are presumably different pathologically from the chronic established areas of demyelination and cannot be reliably distinguished from old lesions on the basis of morphology or intensity on MRI scans. However, with the use of contrast enhancing media, namely Gadolinium-DPTA, it has been possible to distinguish acute from chronic lesions thereby shedding light on the pathogenesis of lesion formation (Miller *et al.*, 1988). Serial MRI studies using Gd-DPTA provide a valuable index of disease activity despite the limited period of enhancement. It has been shown that only 22% of Gd-enhanced lesion still enhance after four weeks (Miller *et al.*, 1988). An important finding accruing from these studies is the fact that asymptomatic lesions in the brain can be seen on serial MRI indicating that MS may be a more active process than what clinically appears to be the case (Willoughby *et al.*, 1989).

The prognostic value of MRI is also good and a MRI follow-up study by Morrisey *et al.* (1993) has reported that the presence of four or more MRI lesions at presentation with a clinically isolated syndrome are strongly predictive of the risk for progression to MS over the next 5 years. However, in patients with definite MS, it is yet to be determined whether MRI will be predictive of subsequent clinical disability.

b) Correlation between cognitive deficits and MRI

i) Global indices

With the advent of MRI, much research into correlating cognitive dysfunction with brain pathology has been undertaken. In essence, it is important to consider that the quantification of lesion load is not without problems as lesions seen on MRI are usually at different stages of evolution and may have a different impact on function (Kermode *et al.*, 1990).

It is now well recognised that the severity of cognitive impairment correlates significantly with MRI lesion load (Rao *et al.*, 1989; Franklin *et al.*, 1988; Huber *et al.*, 1987; Ron et al., 1991) and it has been speculated that there may be a critical threshold that must be crossed before cognitive deficits appear (Rao *et al.*, 1989). This has been a consistent finding with the different methods used in assessing MRI scans but more reliably as automated methods for quantification of lesion volume have become available. Using a semi-automated quantification method, Rao *et al.* (1989) measured total lesion area, ventricular-brain ratio and size of corpus callosum and found significant correlations with performance on a comprehensive neuropsychological battery of tests

administered to 53 MS patients. It was reported that total lesion area was a robust predictor of cognitive performance especially for measures of learning, abstraction, language and visuospatial skills whilst callosal size best predicted information processing speed .

Correlations between cognitive decline and more subtle parameters of brain abnormality, such as the elevation of T1 relaxation times in NAWM have also been reported in patients with chronic progressive MS (Feinstein *et al.*, 1992)

ii) Focal deficits and focal lesions

Attempts at correlating specific cognitive deficits with pathological lesions in related brain areas have been more difficult and require further investigation. This has proved problematic for a number of reasons, the main ones being the difficulty in assessing the contribution of focal pathology in the presence of widespread brain abnormalities and the quantification of lesion load.

In recent years, investigators have attempted to correlate executive deficits with focal frontal lobe pathology. Swirsky-Sacchetti *et al.* (1992) and Arnett *et al.* (1994) have reported that poor performance on the WCST is closely related to the severity of frontal lesion load. The results of these studies cannot be seen as conclusive because they were performed in small samples and the sensitivity of the WCST to focal frontal pathology in the presence of widespread pathology may be questioned (Anderson *et al.*, 1991). It is evident that further research using this type of methodology may

assist in clarifying the patterns of cognitive loss observed in MS and their neural substrates.

iii) Short term fluctuations and natural history

The waxing and waning of neurological symptoms and signs is well documented but this has not been the case for cognitive deficits, even if fluctuations are also likely to occur. There have been recent serial studies which have attempted to examine the correlation between acute brain lesions and neuropsychological performance although the methodological problems of such studies attempting to select patients with high lesion activity are not inconsiderable. In one serial study, Feinstein *et al.* (1993) studied a small number of patients with frequent relapses and remissions and a 'benign' group with little clinical activity using psychometric tests and Gadolinium- enhanced MRI over a six month period. As a whole, MS patients showed slower learning with repeated testing compared to healthy controls and in some patients, a decline on specific cognitive skills could be charted when new brain lesions became detectable. Another serial study of a small group of relapsing remitting patients did not find any correlation between new lesion load with decline of test performance in the few cases that deteriorated cognitively (Mattioli *et al.*, 1993). However, in this study, the patients were only mildly disabled and were examined over a shorter follow-up period. To date, neuropsychological deficits have not specifically been studied during acute relapse but there has been some evidence as reported in a single case study (Rozewicz *et al.*, 1996) that cognitive deficits can improve in parallel with neurological symptoms following an acute relapse.

Proton magnetic resonance spectroscopy (MRS)

a) MRS abnormalities in MS lesions and NAWM

MRS is a non-invasive technique that is capable of detecting the distribution of metabolites other than water in tissue. Nuclei are surrounded by small local variations in the magnetic field caused by different chemical and molecular environments leading to variations in the resonant frequency (known as chemical shift) which give rise to a spectrum of signals. The spectrum provides information as to what chemicals are present by the position of the peak in the horizontal frequency axis and the position is represented as parts per million (ppm) in relation to a central radio frequency. The different peaks that can be seen in a proton spectrum are shown in Figure 5. The area under each peak can represent the quantity of the different metabolites as it is directly proportional to the number of nuclei contributing to the peak.

The three strongest signals in proton MRS are from N-acetyl aspartate (NAA), creatine (Cr) and choline (Cho). The precise function of these metabolites in the central nervous system is not absolutely known. NAA is the second most abundant amino acid in the human brain, second only to glutamate. The neuronal localisation of NAA has been shown with immunocytochemical techniques to be present not only within the cell body but also distributed throughout the axon and proximal dendrites (Simmons *et al.*, 1991). It is thus considered to be a marker of neuronal integrity. Creatine and phosphocreatine both contribute to a single peak in the spectrum and a reduction in this metabolite is thought to be associated with cellular loss as

seen in Creutzfeldt-Jakob disease (Bruhn *et al.*, 1991). Choline is thought to be a putative neuronal and extraneuronal marker and a decrease may reflect reduction in brain cellularity (Breiter *et al.*, 1994).

MRS data can be analysed in different ways. The most common method is to express the relative concentration of metabolites as ratios such as NAA/Cr but this assumes that creatine is constant and does not alter in disease states. Absolute quantitation of the concentration of metabolites may be more accurate although this procedure is more complicated as it requires instrumentation parameters to be specified for each spectrum and corrections have to be made when calculating the peak areas.

More recently, MRS has been used to examine some of the chemical components of the MS lesions and their evolution over time and this technique may have an important role in distinguishing acute from chronic lesions and in characterising their evolution. One study reported that spectra localised to chronic plaques showed a decrease in the NAA/Cr ratios whilst spectra from acute lesions showed either an increased ratio of Cho/Cr or an increase in tissue lactate (Matthews *et al.*, 1991). Other studies have reported a reduction in NAA/Cr ratios in both acute and chronic lesions (Miller *et al* ., 1991; Arnold *et al.,* 1992; Matthews *et al.*, 1991; Van Henke *et al.*, 1991). More recently, a serial study which used short echo proton MRS to examine acute lesions in a group of MS patients detected a marked increase in lipid resonances in association with the initial inflammatory phase of the acute lesions indicative of myelin breakdown (Davie *et al.*, 1994).

MRS abnormalities have also been demonstrated in NAWM of MS patients with a reduction of NAA/Cr ratios (Davie *et al.*, 1994). It has been suggested that this may be due to microscopic demyelination (Allen, 1991) and can therefore be a sensitive marker of white matter abnormalities which may not be detected by other techniques.

b) Correlation between cognitive deficits and MRS

To date, there have only been a few studies examining the biochemical correlates of neuropsychological performance in patients with brain disease using proton MRS. The results of these studeis are conflicting. One study (Rocchetta *et al.*, 1995) reported that right temporal lobectomy patients who had impaired verbal memory post-operatively were found to have reduced NAA/(Cho+Cr) ratios on proton MRS in the contralateral temporal lobe whilst another study suggested that temporal creatine levels correlated with memory deficits in schizophrenia (Buckley *et al.*, 1994). However, in contrast, no correlation was found between neuropsychological performance and NAA/Cr ratios in a group of patients with SLE (Davie *et al.*, 1995) or in a group of cognitively impaired HIV seropositive patients (Meyerhoff *et al.*, 1994).

Functional neuroimaging

Functional imaging techniques, including positron emission tomography (PET) and single photon emission computed tomography (SPECT) scanning provide assessment of regional metabolism and cerebral blood flow in cortical and

subcortical structures. There have been very few studies using these techniques to evaluate cognitive disturbance in MS although potentially they may enable the detection of the 'functional' effects of localised lesions and therefore provide more accurate information about the effects of these lesions. An early PET study of 15 MS patients found significant global reduction in cerebral oxygen utilisation and blood flow in both white and gray matter compared to controls but without any localising regional abnormalities (Brooks *et al.*, 1984). Surprisingly, in these patients, cortical atrophy was better than PET in predicting the presence of cognitive impairment. A more recent SPECT study found a relative reduction in frontal and temporal perfusion rates in MS patients with cognitive problems compared to controls (Pozzilli *et al.*, 1991). This study also reported that left temporal hypoactivity correlated with poor performance in tests of verbal fluency and verbal memory. Although it has been suggested that functional imaging could be more sensitive measure of cognitive impairment than neuropsychological testing, this remains to be determined.

The three studies presented in this thesis are linked by the common aim of investigating the nature, natural history and neuroimaging correlates of neuropsychological deficits in MS. The following hypotheses were tested:

Study 1

1. Executive deficits independent of general intellectual decline can be detected in MS patients.
2. The extent and severity of executive deficits would be correlated with frontal lesion load as measured on MRI.
3. This correlation would remain significant after controlling for total lesion load.

Study 2

1. The severity of executive deficits would be correlated with the reduction in NAA/Cr ratio detected with MRS in lesions and NAWM of the frontal lobes in MS patients.
2. The reduction in NAA/Cr ratio will correlate with the frontal lesion load.

Study 3

1. Fluctuation in neuropsychological deficits can be detected during acute relapse in MS.
2. Improvement in neuropsychological performance will be greater in patients in whom a reduction of Gd-enhanced lesion load is observed following acute relapse.

CHAPTER 4

STUDY 1. EXECUTIVE DEFICITS IN MS AND RELATIONSHIP TO MRI LESION LOAD

Executive or supervisory processes as defined by Shallice and Burgess (1991) are required in situations which involve decision making or planning, error correction, novel sequences of action and overcoming strong habitual responses. Therefore, the different components of executive function can include working memory, initiation and inhibition of responses, problem solving, strategic planning and conceptual ability. Previous studies of executive deficits in MS have mainly focused on abstract reasoning using the WCST (Rao *et al.*, 1987; Mendozzi *et al.*, 1993), verbal working memory (Litvan *et al.*, 1988) and attempts to correlate performance on the WCST with focal brain pathology (Arnett *et al.*, 1994; Swirsky-Sacchetti et al., 1992). Thus, the aims of this study were twofold. Firstly, to examine executive skills in MS patients in a more systematic way than has been attempted hitherto and secondly to try to establish the contribution of frontal lobe lesion load to these deficits using sensitive techniques in MRI lesion quantification.

METHOD

Subjects

42 patients (16 male, 26 female) with clinically definite MS according to the criteria of Poser *et al.* (1983) were selected for the study. They were recruited from the outpatient clinics and neurorehabilitation unit at the National Hospital for Neurology and Neurosurgery. Their ages ranged between 24-50 years. Patients were excluded if their visual acuity was less than 6/12 or if there was motor impairment that would interfere with using a computer touch screen accurately. Patients were also excluded if they were experiencing a clinical relapse at the time of evaluation which was defined as the development of new signs or worsening of existing signs within the past month. Patients who appeared to be severely depressed on clinical interview were not selected for the study. With respect to disease category, 28 patients had secondary progressive, 10 had relapsing/remitting, 3 had primary progressive and one had benign MS, using a classification reported elsewhere (Miller *et al.*, 1991).

40 healthy controls (20 male, 20 female) were chosen to match the patient group as closely as possible with respect to age and estimated premorbid IQ. Any subject whose alcohol intake exceeded the recommended levels (21 units for males and 14 units for females per week) was excluded from the study. Informed consent was obtained from all subjects.

Physical disability

All the MS patients had a neurological examination at the time of the study and physical disability was assessed on the Kurtzke Expanded Disability Status Scale (EDSS).(Kurtzke, 1983)

Psychiatric symptoms

The Hospital Anxiety and Depression Questionnaire (Zigmond and Snaith, 1983) was administered to all subjects. This self rating scale has subscales for anxiety and depression (range of scores 0-21 for each). Scores greater than 10 on each subscale are indicative of 'caseness'.

Neuropsychological tests

A battery of neuropsychological tests to assess level of general intellectual ability and executive skills was administered to each subject. It included the following:

1. *National Adult Reading Test (NART)* (Nelson and Willison, 1991).

This test provided an estimate of premorbid IQ and was used to match the patients and controls.

2. *Advanced Progressive Matrices, Set 1* (Ravens, 1958)

A set of 12 non-verbal abstract reasoning tests was presented. The number of problems correctly completed was converted to an age adjusted scaled score which was used as a measure of current intellectual functioning.

3. *Verbal Fluency Test*

The subject was required to generate as many words as possible (excluding proper nouns) beginning with the letter S in 90 seconds and as many animals as possible in 90 seconds. The two scores obtained were the total number of acceptable words generated for each condition.

4. *Cognitive Estimates* (Shallice and Evans, 1978)

Each subject was required to make estimates in response to 10 questions such as 'What is the length of the average man's spine?' or 'What is the largest object normally found in a house?'. Estimates were scored according to normative data (range 0-3) and higher scores reflected worse performance.

5. *Stroop* (Stroop, 1935)

A computerised version of this test was administered to each subject. Two control conditions were presented prior to the test. In the first condition, each subject was required to read printed words of colours on the screen and in the second one, to name the colours of squares shown on the screen. In the test condition, names of colours printed in a different colour ink were presented. The subject was required to name the colour in which each word was printed and not read the words denoting names of the colours. The time taken to complete this task and the number of errors made were recorded.

The next three tests were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992). The CANTAB tests were selected as they have been found to be sensitive in assessing frontal lobe dysfunction in patients with focal frontal pathology (Owen *et al.*, 1990; Owen *et al.*, 1991) and in patients with more widespread brain disease involving the frontal lobes such as in Korsakoff's syndrome, Parkinson's disease and HIV (Joyce and Robbins, 1991; Robbins *et al.*, 1994; Sahakian *et al.*, 1995). The tests were run on a personal computer with an Intasolve touch-sensitive screen and subjects were instructed to respond to stimuli by touching the screen.

6. *Spatial Span Test*

This is a computerised version of the Corsi Block Tapping task (Milner, 1971) and assesses the ability to remember a sequence of squares lighting up on the screen. For each trial, nine white squares randomly arranged, are shown on the screen. Some of the squares light up in colour, one by one, in a variable sequence and subjects were instructed to remember the sequence. At the end of the presentation, the subject is required to touch each of the boxes that had lit up in the same order as they were originally presented. The task begins with the simplest level of a two box sequence. After each successful trial, the number of boxes in the sequence was increased by one to a maximum of nine. If the subject's response was incorrect at any particular level, an alternate sequence of the same length was presented. This continued until the subject failed three consecutive trials at any one level whereupon the test was terminated. The spatial span

was calculated as the longest sequence that the subject could recall accurately on at least one trial.

7. Spatial Working Memory

In this test, the subject was required to search for a blue token hidden within a number of boxes shown on the screen. The test started with two practice trials each with two boxes. Levels of three, four, six and eight boxes were presented and there were four trials at each of the levels. The subjects were instructed that at any one time, there would be a single blue token hidden in one of the boxes. The subject was required to 'open' each box by touching the boxes in turn until the blue token was located and to place it in an empty column on the right hand side of the screen. When this has been completed, the next token would then be hidden. The subjects were instructed that once a blue token had been found within a particular box, then that box would not be used again to hide a token for that particular trial. Since every box was used once, on each trial the total number of blue tokens hidden corresponded to the number of boxes on the screen.

Two types of possible search errors were recorded at each level of difficulty. The '**between errors**' score referred to the number of returns to a box in which the blue token had previously been located in earlier searches whereas the '**within errors**' referred to the number of returns to a box previously opened and shown to be empty during the same search sequence. Both scores are a measure of spatial working memory but the 'between errors' is a more stringent one. An index for an efficient strategy

termed as '**strategic count**' was also recorded and reflected the use of a pre-determined search sequence beginning with a particular box and then returning to start each new sequence with the same box as soon as a token has been found. This was estimated from the number of search sequences starting with the same box, within each of the trials at the more difficult six and eight box levels. The total of these scores provided a single measure of strategy with a high score (many sequences beginning with a different box) representing low use of strategy and a low score (many sequences starting with the same box) representing more extensive usage of strategy.

8. *Planning task*

This spatial planning task is based on the Tower of London task developed by Shallice (1982). Two displays, each of three coloured balls held in suspended socks, are presented, one in the top half of the screen and the other in the bottom half. The subject was instructed to rearrange the balls in the lower display to copy the pattern shown in the upper one. The balls had to be moved one at a time by touching the required ball and then the intended position.

A minimum of two, three, four or five moves was required to solve each problem. Subjects were instructed to attempt to solve the problem in the minimum number of moves and to think about the solution prior to executing the sequence. There were two blocks of test trials with six problems each. The first block contained two problems at each of two, three and four minimum move solutions and the second block contained two problems at

four moves and four at five minimum move solutions. The computer recorded the number of moves made and the time taken to initiate the first move, select the subsequent ball and to complete the problem for each test trial. This was used to estimate initial and subsequent thinking/planning times.

After each block of test trials, a block of "yoked control" trials was presented. On each trial, the computer moved one ball at a time in the upper display which was a replication of the moves made by the subject in the corresponding previous block of test trials. The subject was instructed to follow the moves made in the upper display by moving the balls in the lower display. The selection and execution latencies recorded from the 'yoked control' trials provided baseline estimates of motor initiation and execution times. The maximum number of moves allowed corresponded to twice the number of minimum number possible plus one, or plus two in the "five move" problems. If the maximum number of moves was exceeded, the trial was terminated and the next one would be presented. The three measures that were evaluated in this task were movement times, thinking times and accuracy.

MRI

Imaging was performed on a NMR 1.5 Tesla GE Signa System. Axial slices were obtained using a pulse sequence VEMP 35/90/2400. A series of 36 contiguous, axial slices (3mm thickness) with a TR of 2400 msec and TE of 35 msec was selected for measurement of lesion volume.

The lesion areas on hard copies were delineated by a neuroradiologist. Measurements of lesion load were obtained using a semi-automated contouring technique to mark the images displayed on a SUNSPARC station. This technique has been shown to be highly reproducible and objective in segmenting lesions on MRI (Grimaud *et al.*, 1996). A software lesion volume measurement programme was utilised to compute the total cerebral lesion load by summing the lesion volumes measured for each slice. A protocol based on neuroanatomical landmarks was used to delineate the frontal regions on each slice. Firstly, the central sulcus, in the most superior slice it appears in, and the Foramen of Munro in the inferior slices were identified. A line drawn through the central sulcus was used to delineate the frontal regions. This line was adjusted for each slice by measuring the distance between these two landmarks and dividing it equally by the number of slices. Lesions anterior to this line were considered to be in the frontal region excluding those in the insula and temporal lobes. Total frontal lesion volume was then calculated in the same manner as the total brain lesion load for each patient. The contouring technique in lesion volume measurement is shown in Figure 1.

Statistical Analysis

The data were analysed using the Statistical Package For the Social Sciences (SPSS). Independent t-tests and ANOVA for repeated measures were applied to examine group differences. Where appropriate, non-parametric tests (Mann-Whitney) were used. Logarithm (base 10) transformation was applied to latency data to reduce skewness prior to

statistical analysis. Spearman's correlation analysis was used to examine the relationship between MRI frontal lesion volumes, neuropsychological scores and physical disability.

RESULTS

The demographic and clinical data for patients and controls are shown in Table 1. There was no significant difference between the MS and control groups with respect to age or gender.

Neuropsychological tests

NART

There was no significant group difference in premorbid IQ as estimated by the NART.

APM

Performance on this test was significantly worse in the MS group compared to controls ($z=-6.36$, $p<0.001$) as seen in Table 2 suggesting that current intellectual functioning was impaired in patients. The performance on APM was used as a covariate in the analysis of the data to determine the extent to which the patients' impaired intellectual functioning had affected their performance on tests of executive function (see below).

Verbal Fluency Test

The MS group generated significantly fewer words than the control group for both conditions (i.e. words beginning with 'S' and the category for animals).

Cognitive Estimates

Scores on this test were significantly higher in the MS patient group than controls, indicating worse performance.

Stroop

In the test condition for the Stroop, MS patients took significantly longer time to complete the task and made more errors than the controls although the mean number of errors was very small.

The results of the above tests are summarised in Table 2.

Spatial span

There was a significant difference in spatial span between patients and controls (Table 3).

Spatial working memory

The group mean scores for **between search** and **within search errors** at each level of difficulty are shown in Table 3 and Figure 2. Patients made more between and within errors than controls at every level of difficulty and the number of errors also increased as the level of difficulty increased for

both groups. There were very few within errors in comparison to the number of between errors for both groups. ANOVA for repeated measures was used to analyse the data (Table 3). For both the between and within errors, there were significant effects of Group and level of Difficulty at four, six and eight boxes. Group x Difficulty interactions were also significant, particularly for the between errors, indicating that the differences between MS patients and controls became greater as the level of difficulty increased.

Strategy scores were significantly different between patients and controls and the latter obtained a lower mean score indicating greater usage of strategy. The strategy score was highly correlated with the between errors score (summed at six and eight boxes) for the control group ($r=0.711$, $p<0.001$) as well as the patient group ($r=0.714$, $p<0.001$) suggesting greater usage of strategy at the more difficult levels for both groups. Using the strategy score as a covariate in the ANOVA analysis of between errors at the six and eight levels, significant group differences persisted indicating that the patients' poor performance on this test could not be solely accounted for by poor use of strategy ($F=34.45$, $df=1,78$; $p<0.001$). Similarly, using the spatial span as a covariate in the analysis of the between errors, significant group differences also persisted indicating that the impaired immediate recall in the MS patient group was not a major contributing factor in their poor performance on the working memory task ($F=27.08$, $df=1,78$; $p<0.001$).

Planning task

a) Movement times

In analysing the data, **motor initiation** and **motor execution** times were extracted from the yoked trials of the Tower of London test. The motor initiation time refers to the time taken to select the first ball for each level of difficulty. The motor execution time represents the time taken between making the first move to completing the problem. As this varied with the number of moves taken, the total execution time was divided by the number of moves to give an estimate of motor execution time per move.

The **motor initiation** and **execution** times were significantly longer for patients compared to controls as shown in Table 4. None of the Group x Difficulty interactions were significant (Table 5). This suggests that overall, the MS patients were slower at initiation and execution times but the group differences did not change significantly with the increasing level of difficulty.

b) Thinking times

The **initial thinking time** was calculated by subtracting the motor initiation time as calculated on the 'yoked control' task from the copying initiation time. **Subsequent thinking time** was the time taken between selection of the first ball and the completion of the problem minus the motor execution time from the corresponding control task. As this measure varied with the problem length, the subsequent thinking times were divided by the number of moves to give an estimate of thinking time per move. Any negative value

produced from the subtractions was reduced to 0 indicating minimal thinking time. The group mean latencies are summarised in Table 4.

There was no significant group difference in initial thinking times or group x difficulty interaction when all problems were considered (Table 5). This indicates that patients did not differ from controls in the time taken to initiate the first move in attempting to solve the problem. There was however, a significant effect of task difficulty with longer initial thinking times as the level of difficulty increased.

Subsequent thinking times per move were analysed for a) all problems and b) problems solved in the minimum number of moves. For both conditions, there were no significant group differences but there was a significant effect of difficulty. The Group x Difficulty interactions were significant for both conditions (Table 5). Further analysis comparing the groups at each individual level showed that group effects were significant only for the more difficult 4 and 5 move solutions when all problems were considered and for level 5 when only minimum move solutions were considered. Overall, the MS patient group did not take significantly longer time than controls to solve the problems except at the most difficult levels.

c) Accuracy

The different aspects of accuracy were assessed by the two measures: I) proportion of problems solved in the minimum number of moves which reflect efficient planning ability and ii) number of excess moves (mean

number of moves above the minimum possible) which is a more general measure of problem solving ability. The group mean scores are shown in Table 4. The control group solved a significantly greater number of problems with the minimum number of moves allowed than the patient group ($z=-4.46$, $p<0.001$). At each level of difficulty, patients tended to take more moves in solving the problems ('excess moves') than controls. There was a significant effect of Group and level of Difficulty. The Group x Difficulty interaction was also significant (Table 5). The results indicate that the MS patients were less efficient in their performance than the controls on this task.

Covariance of current intellectual functioning with executive tests

In order to examine the contribution of current intellectual functioning, as determined by the APM, to the patients impaired performance on tests of executive function, analysis of covariance was done using APM as a covariate. Results indicated that although APM made a significant contribution in most of the tests, the main group effects were not affected as shown in Table 6. This suggests that the executive deficits in the MS patients cannot be solely attributed to general cognitive decline.

Physical disability

There was no correlation between physical disability as measured by the EDSS and any of the neuropsychological variables.

Psychiatric symptoms

The difference between the two groups was significant on the depression scale ($F=12.59$, $df =1,65$; $p=0.001$) but not on the anxiety scale. However, group mean scores on the depression scale did not reach 'caseness' (score >10) with mean scores of 4.88 for MS patients and 2.61 for controls. Only one MS patient reached caseness on the depression scale with a score of 13. This patient had a 2 year history of depression and was on antidepressant treatment. A further 3 MS patients and 3 controls reached 'caseness' on the anxiety scale (scores of 11-15). The neuropsychological test scores for each of these subjects did not differ significantly from their group mean scores.

Correlation with MRI frontal lesion load

Most patients were found to have widespread lesions especially in the periventricular white matter which is the usual pattern seen in multiple sclerosis. Total lesion load ranged from 1089 to 135951 mm^3 and the frontal lesion load ranged from 177 to 65019 mm^3 which represented a mean of 42.4% of the total lesion load. The frontal lesion load correlated highly with the total lesion load ($r=0.96$, $p<0.001$).

Neither frontal nor total lesion load correlated with physical disability as measured on the EDSS or with ratings of anxiety and depression.

The correlations between MRI frontal lesion load and neuropsychological scores are shown in Table 7. The neuropsychological variables in which

significant group differences were found were selected. Scores on tests of Verbal Fluency, Cognitive Estimates and Stroop were significantly correlated with frontal lesion load. On the Spatial Working Memory test, the between error scores, particularly at the more difficult levels, and the strategy score correlated significantly with frontal lesion load. On the planning task, subsequent thinking times at the most difficult level (when all solutions were considered) correlated significantly with frontal lesion load and there was a trend towards a significant correlation between the subsequent thinking times at the most difficult level and frontal lesion load when only minimum move solutions were considered. Scores for the number of solutions solved in the minimum number of moves also correlated significantly with frontal lesion load. In order to dissect the specific contribution of frontal lesion load in these correlations, the analysis was repeated controlling for total lesion load. This resulted in all the previous significant correlations becoming non significant.

Using forward multiple regression analysis, the significant ($p<0.05$) neuropsychological variables predicting frontal lesion load were the Spatial Working Memory between errors scores (summed at level 6 and 8) and the Stroop test times. The same variables also significantly predicted total lesion load.

Grading system

In order to explore further the contribution of frontal lesion load to the impairment of executive skills, a grading system was devised to examine the

patients' level of performance in the Spatial Working Memory between errors scores (summed at level 6 and 8) and the Stroop test based on the performance of the control group. The scores on each of these tests were available in 40 patients and assigned grades as shown below:

Grade 0 = within 1 standard deviation from the group mean score of controls

Grade 1 = within 2 standard deviations

Grade 2 = greater than 2 standard deviations

The grades for the two tests were summed to give an overall measure of performance (impairment index). The patients (n=40) were divided into four groups based on their impairment index:

Group A = impairment index of 0-1 (8 patients)

Group B = impairment index of 2 (9 patients)

Group C = impairment index of 3 (7 patients)

Group D = impairment index of 4 (16 patients)

Group A was considered to be the unimpaired group. ANOVA revealed a significant difference in frontal lesion load between the groups with a much lower frontal lesion load for the unimpaired group (Group A) compared with the other groups ($F=4.39, df=3$; $p<0.01$) and there were no significant differences between the other groups. Total lesion load of Group A was also significantly smaller than that of the other three groups ($F=4.27, df=3$;

$p<0.01$), which did not significantly differ between themselves although total lesion load tended to increase with severity of cognitive impairment. The results are shown in Table 8 and Figure 3. Frontal lesion load accounted for 37% of total lesion load in Group A and 43.3% in the three other groups combined.

DISCUSSION

The results of this study suggest that patients with multiple sclerosis present with deficits in executive function which cannot be fully explained as a result of general intellectual decline. On the other hand, the contribution of frontal lobe pathology to this aspect of cognitive impairment is difficult to delineate and according to the present findings is less significant than previously reported.

Previous studies of executive function in MS patients have mainly focused on measuring abstract ability or verbal working memory in isolation (Arnett *et al.*, 1994; Mendozzi *et al.*, 1993; Swirsky-Sacchetti *et al.*, 1992; Litvan *et al.*, 1988). This study has documented impairment on a wider range of executive skills. Abnormalities in verbal fluency, Stroop, cognitive estimation, spatial span, spatial working memory, use of strategy and planning were detected although not all of these skills were impaired to the same extent. This applies in particular to planning ability which appears to be relatively preserved in the MS patients as exemplified by the fact that differences in the subsequent thinking (planning) times between MS

patients and controls were only significant at the most difficult levels of the task.

Neuropsychological tests

The tests adopted in this study allowed the dissection of various executive deficits. Thus, it was possible to demonstrate that impaired performance on the Spatial Working Memory task could not be explained by less efficient use of strategy or poor immediate recall but indicated a specific impairment of working memory. These results are analogous with earlier studies which have found impairment of verbal working memory in patients with MS (Litvan *et al.*, 1988; Grafman *et al.*, 1991). There are overall similarities in the pattern of performance on the CANTAB tests between the MS patients in this study and those with frontal lobe excisions, Huntington's disease, Multiple system atrophy and HIV (Owen *et al.*, 1990; Lange *et al.*, 1995; Robbins *et al.*, 1992; Sahakian *et al.*, 1995) even if the underlying mechanisms leading to these deficits may have been different. Indeed, the similarities in their performance contrast with the different clinical presentation of these patients. The performance of MS patients on these tests most closely resembles that of HIV infected patients (Sahakian *et al.*, 1995), whilst patients with more extensive frontal lobe pathology (i.e. frontal lobe excisions) (Owen *et al.*, 1990) had greater impairment on planning tasks.

Although the focus was on tests of executive function in this study, it would be misleading to assume that other neuropsychological deficits were absent

in these patients especially in a widespread disease such as MS. It has been well documented in previous studies (Ron *et al.*,1991, Rao *et al.*,1991) that a range of neuropsychological deficits can be detected in MS patients, including attentional and memory deficits, and it would therefore be unusual to observe executive deficits in isolation. It is now recognised that some aspects of executive function may fractionate and can be more severely affected than others in the same individual which has led to arguments about the association or dissociation of these executive skills. The results of this study would support this hypothesis that different aspects of executive function may be subserved by different distributed systems (Burgess & Shallice, 1992).

The executive deficits in the MS patients cannot be attributed to coexisting psychiatric symptoms or primary visual impairment as strict exclusion criteria was used in the selection of patients for the study. It is also unlikely that the patients poor performance on the tests reflected a general decline in intellectual ability as the significant differences in the group mean scores on tests of executive function persisted when APM was used as a covariate. Although APM has been used in the past as a specific measure of abstracting ability, performance on this task was not found to be impaired in a study of patients with widespread frontal lobe dysfunction (Kartsounis *et al.*,1991) suggesting that its use as a measure of current intellectual functioning is more appropriate.

Measurement of lesion load

In this study, an automated programme which calculated lesion volume in thinner slices (3mm) was used which represents an advance over previous studies that calculated lesion load by measuring the area of the lesions (Arnett *et al.*, 1994; Rao *et al.*,1989; Huber *et al.*, 1992). The contouring technique used in this study has also been shown to have greater intra and inter-rater precision when compared to manual outlining and global threshold techniques in measuring MS lesion load on MRI (Grimaud et al., 1996). A number of the executive test scores were found to correlate significantly with frontal lesion load although it was only at the more difficult levels on the spatial working memory and planning task. Similar findings have been reported by others (Arnett *et al.*,1994; Swirsky-Sacchetti *et al.*, 1992) who have postulated a close relationship between frontal lobe pathology and executive deficits. In this study, however, it proved impossible to disentangle the specific contribution of frontal lobe pathology to cognitive impairment in the presence of widespread lesions and although frontal pathology may be crucial in causing the executive deficits, it seems unlikely to be the sole cause. This was illustrated by the finding that the significant correlation of impaired executive skills with frontal lesion load disappeared when total lesion load was controlled for. This was further supported by the finding that frontal lesion load did not differ significantly between the subgroups of MS patients with increasing impairment of executive function (Groups B, C and D). It is possible that the impairment on executive tasks may be secondary to a more diffuse process affecting the general functioning of the brain or causing a disconnection between

prefrontal, limbic and association cortices which has been suggested in traumatic brain injury patients (Stuss *et al.*, 1992; Levin *et al.*,1987). Some support for this possibility accrues from an earlier PET study (Brooks *et al.*, 1984) which found generalised rather than focal reduction of cerebral oxygen utilisation, blood flow (rCBF) and oxygen extraction in MS patients.

Arnett *et al.* (1994) reached different conclusions in their study which compared a selected small group of patients with disproportionately high frontal lesion load to an older, more chronic population with similar lesion load more evenly distributed. Whilst their findings may apply to patients with predominantly frontal lesions, it was not possible to identify such a subgroup in this study which contained patients who had a more widespread distribution of lesions. The findings of this study also differ from those of Swirsky-Sacchetti *et al.* (1992) who entered a variety of test scores and regional lesion loads in a step-wise regression analysis. No attempt was made to control for total lesion load in that study but the fact that the frontal lesion load predicted performance in a variety of tests of language and memory suggests that the overall lesion load may have explained some of these results.

Recent functional imaging studies have highlighted the contribution of several brain regions to the performance of a given task. In this context, functional imaging studies using the Stroop test have reported that not only the right orbitofrontal and anterior cingulate but parietal structures are involved (Bench *et al.*, 1993). As the lesions in multiple sclerosis are

widespread, it is possible that patients' impairment on the Stroop task in this study is partially accounted for by lesions elsewhere and not solely due to frontal lesions. A similar observation has been made by Mellers *et al.* (1995) who found activation of anterior and posterior parasagittal cortex, left parietal cortex and left dorsolateral prefrontal cortex in normal subjects during a working memory task using fMRI.

CHAPTER 5

STUDY 2. USE OF MRS AS AN INDEX OF FOCAL PATHOLOGY

Proton MRS has been shown to be of value in detecting biochemical abnormalities both in lesions and NAWM and may therefore be a sensitive index of disease process. There have been attempts to study neuropsychological deficits in relation to MRS abnormalities in patients with different types of brain pathology such as SLE, temporal lobectomy and HIV (Davie et al., 1995; Rocchetta et al., 1995; Meyerhoff et al., 1994) but the results of these studies have been contradictory. To date, the relationship between neuropsychological deficits and MRS abnormalities has not been explored in MS. The aim of this study was to determine whether there is any correlation between neuropsychological deficits and MRS abnormalities. In this study, MRS was performed in the frontal regions of the brain in both MS patients and controls who had been investigated with a battery of executive function tests.

METHOD

Subjects

There were 42 MS patients and 40 healthy controls. A full description is given in Study 1.

Physical disability and ***Psychiatric symptoms***

Described in Study 1.

MRI

The scanning protocol and measurement of lesion volume have been described in Study 1.

MRS

After imaging, a volume of interest ranging between 3.5 ml and 6 ml was prescribed from the left frontal white matter in all subjects. In the patient group, this incorporated a chronic high signal lesion and/or an area of normal appearing white matter (NAWM). Large lesions were chosen in order to minimise partial volume effects. If a sufficiently large enough lesion could not be identified on imaging then spectra were collected from NAWM alone. Water suppressed spectra were obtained using a stimulated echo acquisition mode (STEAM) sequence (Frahm *et al.*, 1989a). Acquisition parameters were TR 2000 ms, TE 135 ms and TM 12 ms. 256 averages were collected using an 8 step phase cycle in ~ 9 minutes. A total of 1024 points were collected with a spectral width of 750 Hz. Shimming to a line

width of ~1.5 Hz and water suppression were re-optimised for each new location. In the control group, spectra were obtained from an area of left frontal white matter. Data processing included 1.5 Hz line broadening for filtering and base line correction (cubic spline). Peak areas were determined using a line-fitting programme ("SA/GE", G.E. Milwaukee W.I.). Peak were fitted to Gaussian functions using a Marquardt fitting procedure. The peak area ratios of N-acetyl aspartate relative to creatine were calculated.

Neuropsychological assessment

A full description of the battery of neuropsychological tests used has been detailed in Study 1.

Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS). Group means were examined using independent t-tests and ANOVA. Where appropriate, non-parametric tests (Mann-Whitney) tests were used. The relationship between the NAA/creatine ratio obtained from MRS and neuropsychological variables was examined using Spearman's correlation analysis.

RESULTS

The demographic and clinical data for patients and controls have already been reported in Study 1 and shown in Table 1.

MRS

The three resonances visible at an echo-time of 135ms have been assigned as follows (Behar and Ogino, 1991; Frahm *et al.*,1989b): N-acetyl groups at 2.02 parts per million (ppm) and 2.6 ppm, creatine/phosphocreatine at 3.04 ppm and choline containing compounds at 3.2 ppm.

Spectroscopic data were obtained from 40 MS patients and 38 controls. Spectra were unobtainable in two patients and two controls due to movement in the scanner. The NAA/creatine ratio in the volume of interest (VOI) for the MS group was significantly lower than controls ($t=-5.37$, $p<0.001$). The mean ratio for patients was 1.133 (SD=0.231) and 1.393 (SD=0.194) for controls. Results are illustrated in Figure 4.

Due to technical reasons, information was available for only 25 patients to determine whether the VOI contained lesions or NAWM. In 16 patients, the VOI contained lesions although not sufficiently large enough to completely fill the VOI and therefore invariably some NAWM was present. In nine patients, the VOI only contained NAWM. ANOVA indicated that there were no significant differences in the NAA/Cr ratios between these groups of patients: 16 patients with lesions in their VOI, 9 patients with only NAWM in their VOI and the other 15 patients in whom the contents of their VOI were not known. The group mean NAA/Cr ratios were 1.16 (0.29), 1.18 (0.13) and 1.07 (0.20) respectively (standard deviations in parenthesis). For this reason, it was appropriate to include all 40 patients in the statistical analysis.

Representative spectra from a healthy control and a MS patient are shown in Figure 5.

Patient subgroups of MRS abnormalities

Patients were divided into three groups based on their NAA/Cr ratios as shown below:

Group A = within one standard deviation from the group mean NAA/Cr ratio of controls (14 patients)

Group B = within 2 standard deviations (15 patients)

Group C = greater than 2 standard deviations (11 patients)

Group A was considered to have NAA/Cr ratios in the normal range.

Correlation analysis

a) Correlation of MRS abnormalities and lesion load

There was no significant correlation between the NAA/Cr ratio and frontal or total lesion load.

b) Correlation of MRS abnormalities and executive tests

The findings in Study 1 indicated that MS patients performed significantly worse than controls on the Verbal Fluency, Cognitive Estimates, Stroop, Spatial Span and Spatial Working Memory Tests as shown in Table 2 and 3. Patients had been divided into four groups according to their impairment

index which was based on their neuropsychological performance as described in Study 1.

In order to study the possible contribution of MRS abnormalities to neuropsychological performance, Spearman's correlation analysis was used and no significant correlation between the MRS subgroups and the impairment index groups was found.

c) Correlation of MRS abnormalities and clinical signs

No significant correlations between physical disability or psychiatric symptoms as estimated by the HAD scores and NAA/creatine ratios were detected.

DISCUSSION

In this study, the biochemical correlates of neuropsychological deficits in patients with multiple sclerosis were examined using proton MRS. There was a significant reduction in the NAA/Cr ratio in the area of frontal white matter in MS patients compared to controls which is in keeping with other MRS studies in MS (Davie *et al.,* 1994; Miller *et al.,* 1991). However, there was no correlation between the NAA/Cr ratios and frontal or total lesion load.

Apart from lesions, NAWM was examined in the MS patients to ascertain the use of MRS as an indicator of more subtle abnormalities which may not

be detectable on MRI. Previous studies (Davie *et al.*, 1994) using serial proton MRS in MS have observed abnormalities in NAWM suggesting that this may be due to the presence of microscopic demyelination. In the sample of patients where it was possible to determine whether the VOI contained lesion and/or NAWM, the NAA/Cr ratios were not significantly different as might be expected. One possible explanation for this is that the lesions found were insufficiently large enough to occupy the entire VOI and invariably there was NAWM present which may have resulted in the NAA/Cr ratio being higher than if the VOI solely contained lesions. Another possible explanation is that the NAWM may have been abnormal in patients who only had NAWM in their VOI thereby resulting in decreased NAA/Cr ratios.

Although the patients' performance was significantly impaired on most of the tests of executive function compared to controls, there was no correlation between the neuropsychological performance as reflected in the impairment index groups and the MRS subgroups. This suggests that the biochemical abnormalities detected on MRS do not specifically contribute to neuropsychological deficits. Likewise, there was no correlation between the NAA/Cr ratio and physical disability.

There are a number of possible methodological reasons for the poor correlation between the biochemical abnormalities and neuropsychological performance. Firstly, MS is a widespread disease and the lesions in the frontal lobes are not homogenous. In the application of spectroscopy, the VOI may not accurately reflect the general biochemical profile or function in

the entire frontal region. Another possibility is that the method of analysing the spectral data in this study may have contributed to the lack of relationship between neuronal metabolism and neuropsychological deficits. NAA/Cr ratios were reported in this study as they have been used to examine the natural history of MS lesions and it is the most commonly reported technique used in the analysis of MRS data. Recent studies have indicated that absolute quantification of the metabolites may be a more appropriate measure of chemical abnormalities (Maier *et al.*, 1995). If creatine level is not constant, when used as a denominator in the ratio, it may mask or minimise the reduction in NAA. However, it is unlikely that the reduction in the NAA/Cr ratio observed could be due to the concentration of creatine being increased within the MS lesion or NAWM. A post-mortem MRS study by Davies *et al.* (1995) has shown that the absolute concentration of creatine decreases within MS lesions and does not change significantly within NAWM of the brains of MS patients. Therefore it is most likely that the reduction in the NAA/Cr ratio observed in this study reflects an absolute reduction in the concentration of NAA. Clinical MRS studies of disease processes in which neuronal loss is a prominent pathological feature such as in stroke (Gideon *et al.*, 1992), HIV (Chong *et al.*, 1993) and degenerative disorders (Van der knaap *et al.*, 1992) have demonstrated a reduction of NAA. In addition, MRS studies from non-neuronal tumours of human brain such as meningiomas and astrocytomas (Demaerel *et al*, 1991, Frahm *et al.*, 1992) show marked reduction or complete loss of NAA. The finding of a reduction of NAA/Cr is highly suggestive of axonal loss within MS lesions and NAWM.

CHAPTER 6

STUDY 3. NEUROPSYCHOLOGICAL DEFICITS IN ACUTE RELAPSE

Much progress has been made in describing cognitive deficits in MS patients but less is known about their natural history and short term fluctuations during acute relapse or when there is evidence of disease activity on MRI. The aims of this study were to investigate neuropsychological performance in MS patients during an acute relapse and to determine its relationship to brain pathology. MRI using Gd-DTPA was performed to provide a measure of disease activity and to determine its relationship to neuropsychological deficits.

METHOD

Subjects

13 MS patients (4 male, 9 female) with a mean age of 37.15 years were recruited into the study during an acute relapse which was defined as development of new signs or worsening of existing signs within the past month. All patients fulfilled the criteria of Poser *et al.* (1983) for the diagnosis of clinically definite MS and had been admitted to the National Hospital for Neurology and Neurosurgery. Patients were excluded if their visual acuity was less than 6/12 or if there was motor impairment that would interfere with using a computer touch screen accurately. They were examined on two occasions, firstly at the time of recruitment and approximately six weeks later following treatment with intravenous steroids. Four patients had relapsing/remitting and nine had secondary progressive disease.

10 healthy controls (3 male, 7 female) were selected to match the patients as closely as possible with respect to age and estimated premorbid IQ. They were similarly examined on two occasions. Informed consent was obtained from all subjects.

Physical disability

On both occasions, physical disability was assessed in the MS patients as described in Study 1.

Psychiatric symptoms

All subjects were assessed on both occasions using the HAD scale which has been described in Study 1.

MRI

Imaging was performed in the MS patients using an NMR 1.5 Tesla GE Signa System on both occasions. Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) 0.1 mmole/kg was administered intravenously and T1-weighted images with a TR of 540 and TE of 11 were obtained. A series of 36 slices (3mm thickness) was selected for measurement of lesion volume. Controls did not undergo MRI examination.

Gd-enhanced lesion areas on hard copies were delineated by a neuroradiologist. With reference to this, measurements of total Gd-enhanced lesion load excluding lesions in the cerebellum were obtained using the same semi-automated contouring technique from Study 1 to mark the images displayed on a SUNSPARC station.

Neuropsychological tests

National Adult Reading Test (NART) (Nelson and Willison, 1991) was used to provide an estimate of premorbid IQ to match the controls to the patients. An extensive battery of neuropsychological tests to assess attention and memory was administered to each subject on both occasions. The tests selected for the study were considered least likely to be influenced by practice effects and some had parallel forms. These included

the *Spatial Span, Spatial Working Memory, Spatial Recognition and Pattern Recognition Tests* from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian & Owen, 1992) which were administered on a computer with a touch sensitive screen.

Only the tests in which a significant difference was found between the MS and control groups on the initial testing were used in the analysis of the data and are detailed below:

Attention

Paced Auditory Serial Additions Test (PASAT) (Gronwall, 1977)

Subjects were instructed to perform serial additions which required shifting their attention from old to new items. They were instructed to add 31 pairs of randomised digits presented in an auditory fashion so that each digit was added to the one preceding it. Two levels of difficulty were used with items being presented at 4 seconds (PASAT4) and 2 seconds (PASAT2) intervals. The number of correct responses was recorded.

Stroop Test (Stroop, 1935)

(as described in Study 1).

Symbol Digit Substitution Test (Smith, 1968)

A computerised version of this test was used whereby nine different symbols

each representing a number were presented visually to the subject. Nine symbols were shown at a time in various orders and the subject was required to respond by naming the number represented by each symbol according to the original code shown. Eight consecutive trials were administered. A total time for all eight trials and a mean time per trial were recorded. The total number of errors was also recorded.

Memory

a. Immediate recall

Digit Span forwards (WAIS-R)

This subtest from the Wechsler Adult Intelligence scale-revised (WAIS-R) tests immediate recall. The subject is required to repeat each sequence of digits exactly as that read aloud by the examiner. The examiner continues to read the next longer digit sequence until the subject fails both trials. The maximum sequence in this test is nine digits.

Story Recall Test (Coughlan and Hollows, 1985)

Each subject was asked to recall a story immediately after it was read to him/her. The number of items accurately reproduced were recorded. Correct responses were scored as 2 and approximate responses as 1. Each subject's score was converted into a percentage of the maximum score to allow comparison. A different story was presented on the second occasion and the scores were calculated similarly. The story contained 28 items

(maximum score of 56) on the first occasion and 30 items (maximum score 60) on the second occasion.

Spatial Span Test (CANTAB)

(as described in Study 1).

b. Delayed recall

Story Recall Test (as above)

Subjects were asked to recall the short story after an interval of 20 minutes. The number of items accurately recalled was recorded. Scores were converted to percentages to allow comparison between the two occasions. A different story was used on the second occasion as described above.

Statistical analysis

Due to the small sample sizes, the data was analysed in several ways. Overall differences between the MS patients and controls in the performance on the neuropsychological tests were examined using Mann-Whitney tests. Performances on the two occasions of testing were compared for both groups using Wilcoxon Matched-Pairs Signed-Ranks Tests.

Spearman's correlation coefficient was used to examine the relationship between improvement in Gd-enhanced lesion load and changes in neuropsychological performance.

RESULTS

There were no significant differences between patient and control groups with respect to age and premorbid IQ. The results are shown in Table 9. The patients were recruited within six weeks (mean of 3.42) of developing their relapse symptoms. All subjects were tested on two occasions. The mean interval between the two occasions of testing was not significantly different at 47.54 days for MS patients and 51.50 days for controls.

Physical disability

There was a significant improvement in physical disability in the MS group on the second occasion as assessed on the EDSS scale ($z=-2.67$, $p=0.008$). The mean score was 6.31 on the initial occasion and 5.12 on the second occasion. The relapsing/remitting patients had greater improvement in their physical disability than the secondary progressive patients as demonstrated by the significantly lower EDSS scores on the second occasion with means of 3.88 and 5.67 respectively ($z=-2.31$, $p=0.02$).

Psychiatric symptoms

The MS group scored significantly higher than controls on the depression subscale ($p<0.021$) but not on the anxiety subscale on the first occasion although scores on both subscales did not reach caseness. There was significant improvement in both the HAD depression scores ($z= -2.27$, $p=0.023$) and anxiety scores ($z=-2.34$, $p=0.019$) for the MS group but no significant change was observed in either subscale for the controls.

MRI

Patients were divided into 3 groups according to the pattern of Gd enhancement:

Group A: no Gd-enhancing lesions detected on either occasion (n=4)

Although no Gd-enhancing cerebral lesions were detected in Group A patients, it is likely that there were acute lesions in the spinal cord or cerebellum which we did not examine on MRI in this study. These patients experienced symptoms of deteriorating coordination and gait during their relapse. Three patients had secondary progressive disease and one had relapsing/remitting disease.

Group B: an increase in Gd-enhancing lesion load on second occasion (n=3)

These three patients had secondary progressive MS and were recruited within 3 weeks of their relapse. Despite the increase in cerebral lesion load, EDSS scores had improved for two patients and remained unchanged for the third patient on the follow-up testing.

Group C: a decrease in Gd-enhancing lesion load on the second occasion (n=6)

These patients had a significant decrease in Gd-enhanced lesion load ($z=-2.20$, $p= 0.028$).Three patients had relapsing remitting disease and the other three had secondary progressive disease. The relapsing remitting patients were observed to have greater improvement in the Gd-enhanced lesion load as shown in Table 12.

Neuropsychological tests

Tests of Attention

a) MS patients vs controls

Patients performed significantly worse than controls on PASAT 2, Stroop and Symbol digit substitution tests on the initial occasion as shown in Table 10. On the second occasion, there was a significant improvement on the PASAT2 Test ($z=-2.23$, $p=0.026$) and a trend of improvement on the Symbol Digit Substitution Test ($z=-1.84$, $p=0.065$) in the MS group. The control group performance on these tests did not differ significantly between the two occasions.

b) Comparison between patient subgroups

There were no significant differences in performance on these tasks between the patient subgroups (A,B,C). However, there was a general trend of greater improvement in the performance on tests of Symbol Digit Substitution, STROOP and PASAT2 for patients who had a decrease in acute lesion load (Group C). However, this did not reach statistical significance when the Wilcoxon-matched paired tests were applied as shown in Table 12 which is probably attributable to the small number of patients. It was also noted that this improvement was greater in the relapsing/remitting patients compared to the secondary progressive patients in Group C, especially on the PASAT2. In contrast, there appeared to be little change in performance on these tasks in the patients who had no

detectable Gd-enhancing lesions. In the three patients who had an increase in Gd-enhanced lesion load, there was a slight deterioration in performance on these tasks although they were generally less impaired than patients in the other groups. These results are illustrated in Figures 6, 7 and 8.

It was also observed in Group C, that the relapsing remitting patients were less impaired on the attentional tasks on both occasions than the secondary progressive patients. The individual scores of all patients on these tasks are shown in Table 12.

Memory tests

Immediate recall

a) MS patients vs controls

There were significant group differences between the MS and control groups for the immediate recall tasks on the initial occasion. Group differences persisted on the second occasion only for the immediate Story Recall Test. These results are shown in Table 10. There were no significant differences in performance on the two occasions for both the MS and control groups.

b) Comparison between patient subgroups

There were no significant differences between the subgroups in their performance on the immediate recall tasks for either occasion.

Delayed recall

a) MS patients vs controls

Performance on the delayed Story Recall Test was significantly worse in the MS patients compared to controls for both occasions (Table 10).

b) Comparison between patients subgroups

There were no significant differences in delayed recall on either occasion between the subgroups.

Correlation with Gd-enhanced lesion load

Only Group C patients (n=6) were included in this correlation analysis. We used the tests in which there were significant group differences in performance when compared to controls, namely, the Stroop, Symbol Digit Substitution and PASAT tests. The changes in Stroop and Symbol Digit Substitution Test scores were found to correlate significantly with improvement in Gd-enhanced lesion load ($r=-0.99$, $p<0.01$ and $r=-0.82$, $p<0.05$ respectively).

Bonferroni test correction was not applied in the statistical analysis due to the small number of patients in the sample.

Individual patient's performance

A brief description of two patients which illustrates the main findings of this study is given below:

Patient 12 (Group C)

The patient was a 26 year old female who had only been diagnosed with MS three months previously following a relapse although she had experienced neurological symptoms attributable to MS for at least two years. She was recruited into this study after a week of developing sensory symptoms and weakness in her left hand. During the follow-up period, her MRI lesion score improved by 85% and her EDSS score improved from 6.5 to 5. She had the greatest neuropsychological improvement with performance on all attentional tasks, namely PASAT2, Stroop and Symbol Digit Substitution improving on the second occasion as shown in Table 12.

Patient 5 (Group B)

The patient was a 53 year old man who had a 24 year history of secondary progressive MS. He was recruited into the study two weeks after developing increasing weakness and sensory disturbance in his legs. He had to use a wheelchair as he was unsteady walking. Although there was a significant improvement in his physical disability with his EDSS score improving from 9 to 5, his MRI lesion load had actually deteriorated on the second occasion (see Table 4). His neuropsychological performance also deteriorated on the second occasion with performance worsening on the PASAT2 and Symbol Digit Substitution Tests. This case clearly illustrates the discrepancy between physical disability and MRI cerebral lesion load.

DISCUSSION

The results of this study suggest that some neuropsychological deficits detected during an acute relapse of MS may be reversible. In this small sample of MS patients, there was a definite or trend in improvement in tasks of attention especially in the Group C patients who had an improvement in acute lesion load. In addition, changes in the Symbol Digit Substitution Test and Stroop Test were also found to correlate significantly with improvement in Gadolinium-enhanced lesion load. This improvement in neuropsychological performance was in parallel with the improvement in physical disability and psychological symptoms in these patients.

In examining the individual patient's performance in Group C, it was apparent that the relapsing/remitting patients had a greater improvement in Gd-enhanced lesion load which was in parallel with their improvement on the attentional tasks. It was noted that they were also less cognitively impaired than the secondary progressive patients at the outset which suggests that patients who are least cognitively impaired may be most likely to improve following a relapse. This would also be in keeping with previous reports that cognitive deterioration is dependent on the clinical course of the illness and that patients who are in a chronic progressive course were most likely to deteriorate (Feinstein *et al.*, 1992).

Memory deficits, namely, immediate and delayed recall, were detected in the MS patients but did not change following remission from the acute

relapse. It is possible that these deficits may have been dependent on the location of chronic lesions but as this study particularly focused on acute cognitive changes, the total unenhanced lesion load was not measured. Another possibility is that the memory tests used may not be sufficiently specific or sensitive.

This study was restricted by the small sample size as the demands placed on these patients limited recruitment. It is possible that the small sample size may have led to some results not reaching statistical significance. In addition, there was a strict selection of patients who were within six weeks of an acute relapse for the study as studies have shown that only 22% of Gd-enhanced lesions still enhance after 4 weeks (Miller *et al.*, 1988).

Recent serial studies have attempted to examine the correlation between acute brain lesions and neuropsychological performance although the methodological problems of such studies attempting to select patients with high lesion activity are not inconsiderable. The serial study by Feinstein *et al.* (1993) attempted to examine fluctuations in neuropsychological performance in MS patients with clinically active disease over six months and found that patients showed slower learning with repeated testing compared to healthy controls and a decline on specific cognitive skills could be charted in some patients when new brain lesions became detectable. However, there are some methodological differences in this study with the inclusion of both relapsing/ remitting and secondary progressive patients who were in clinical relapse and the use of more advanced quantification techniques to accurately measure lesion

volume. Furthermore, the patients in this study were examined during acute relapse and not just serially. Another serial study of a small group of relapsing remitting patients did not find any correlation between new lesion load with decline of test performance in the few cases that deteriorated cognitively (Mattioli *et al.*, 1993). However, in this study, the patients had only mild physical and cognitive impairment and were examined over a shorter follow-up period. In addition, both previous studies calculated lesion load by the number and size of lesions on Gd-enhanced MRI. The findings in these studies are in contrast to the preliminary evidence in this study of a correlation between improvement in acute lesion load and improvement in neuropsychological performance. This suggests that reversible cognitive changes in the short term may be related to acute inflammatory changes.

The discrepancy between cerebral lesion load detected on MRI and clinical relapse is illustrated by the finding in this study that several of the MS patients had no cerebral enhancing lesions. In addition, the Group B patients were found to have an increase in lesion load upon follow-up in the absence of any clinical or physical deterioration and in one particular case (Patient 1), physical disability actually improved significantly. This is likely to be attributed to the fact that physical disability as measured by the EDSS is probably more related to the presence of spinal cord and not cerebral lesions.

It is unlikely that psychiatric symptoms contributed to the patients' neuropsychological performance in view of the HAD scores failing to reach 'caseness' and the lack of correlation with the neuropsychological test

scores. It is also unlikely that the change in some of the patients neuropsychological performance in this study could be attributed to practice effects. By using parallel forms on some of the tests and in conjunction with the 6-8 weeks interval between testing, practice effects were minimised as demonstrated in the controls' performance not significantly changing on the second occasion. This is in contrast to the previous serial study by Feinstein *et al.* (1993) who reported significant practice effects in both patients and controls who were tested 2nd weekly over a six month period.

CONCLUSIONS

With the advances in neuroimaging there has been increasing interest in studying specific neuropsychological deficits and their relationship to brain pathology. The findings in Study 1 confirm that significant impairment can be detected in a range of executive skills in MS patients. There was evidence that some executive test scores correlated with MRI lesion load although not specifically with frontal lesions as might be expected. This highlights the difficulties in attributing specific neuropsychological deficits to focal pathology in a widespread brain disease such as MS. It is likely that many of the neuropsychological tests available may not solely reflect the contribution of one single region of the brain. Therefore, it is evident that the specific patterns of brain activity during the performance of these tasks in patients with similar executive function deficits but different localisations of brain pathology warrants further investigation.

The findings in Study 2 suggest that there is little correlation between the structural and biochemical indices examined. In addition, there was no association between the MRS abnormalities in the frontal lobe and executive deficits. This would suggest that MRI lesion load and not MRS abnormalities is more closely related to neuropsychological deficits. As MRS may be more useful in detecting change in lesions over time, it is possible that serial NAA/Cr or other MRS indices may be useful in a longitudinal study of neuropsychological impairment.

The third study, although limited by the small sample size, has raised the possibility that certain neuropsychological deficits, namely attentional deficits, detected during acute relapse may be reversible. There was also some evidence that the fluctuation of these deficits may be closely related to acute lesions as detected on MRI. Further serial studies with larger samples would be indicated to confirm these preliminary findings.

In summary, these studies have attempted to clarify the relationship between neuropsychological impairment in MS including short term changes during acute relapse and the neuroimaging correlates. With the continuing developments in neuroimaging techniques, including functional MRI and functional spectroscopy, it remains to be determined whether more accurate or sensitive pathological indices of neuropsychological deficits can be found. This would help to elucidate further the pattern and progression of cognitive dysfunction in MS and possibly in the evaluation of new treatments such as beta interferon.

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TABLE 1. **DEMOGRAPHIC AND CLINICAL DATA FOR PATIENTS AND CONTROLS**

Group means (standard deviations)

	MS patients (n=42)	**Controls (n=40)**
Age	38.64 (7.99)	35.75 (6.49)
Sex (M/F)	16/26	20/20
EDSS	6.26 (1.45)	
Disease category		
primary progressive	3 (7.1%)	
secondary progressive	28 (66.7%)	
relapsing/remitting	10 (23.8%)	
benign	1 (2.4%)	

EDSS Expanded Disability Status Scale

TABLE 2. **TESTS OF GENERAL ABILITY AND EXECUTIVE FUNCTION**

Group means (standard deviations)

	MS patients (n=42)	**Controls (n=40)**	**t-test/Mann-Whitney**
Tests			
NART	109.40 (9.27)	113.15 (8.14)	ns
APM	7.24 (2.68)	9.73 (2.04)	z=-6.36 **
Verbal Fluency			
'S' words	16.31 (7.37)	25.08 (7.52)	t=-5.33 **
category (animals)	20.05 (8.51)	33.35 (7.13)	t=-7.65 **
Cognitive Estimates	6.64 (3.49)	3.58 (2.59)	z=4.47 **
Stroop time (sec)	39.16 (12.92)	23.14 (6.31)	z=-6.36 **
Stroop errors	1.59 (3.44)	0.23 (1.13)	z=-3.25 *

NART National Adult Reading Test

APM Advanced Progressive Matrices

** $p<0.001$

* $p<0.01$

ns not significant

TABLE 3. **SPATIAL SPAN AND SPATIAL WORKING MEMORY TESTS**

Group means (standard deviations) and statistical analysis

	MS patients (n=42)	**Controls (n=40)**	**Mann-Whitney/ANOVA**		
Spatial span	4.83 (1.15)	6.48 (1.24)	z=-5.39, **p<0.001**		
SWM:			Effect of group	level of difficulty	Group x difficulty interaction
between errors					
4 boxes	2.90 (3.48)	0.4 (0.84)	F=44.82 df=1,78	F=242.77 df=2,158	F=38.94, df=2,158
6 boxes	15.34 (7.45)	4.33 (4.87)	**p<0.001**	**p<0.001**	**p<0.001**
8 boxes	29.56 (11.76)	11.80(8.93)			
within errors					
4 boxes	0.29 (0.90)	0.15 (0.43)	F=4.62, df=1,79	F=10.61, df=2,158	F=3.16, df=2,158
6 boxes	0.27 (0.63)	0.18 (0.50)	**p<0.05**	**p<0.001**	**p<0.05**
8 boxes	1.00 (1.47)	0.38 (0.74)			
strategic score	36.66 (4.25)	30.80 (6.05)	z=-4.56, **p<0.001**		

SWM Spatial Working Memory

TABLE 4. **PLANNING TASK**

Group means (standard deviations)

	MS patients (n=42)	**Controls (n=40)**
Motor initiation times (sec)		
3 moves	3.05 (1.91)	1.47 (2.98)
4 moves	3.04 (2.34)	1.53 (0.44)
5 moves	2.78 (1.99)	1.44 (3.25)
Motor execution times (sec)		
3 moves	3.12 (2.60)	1.42 (0.25)
4 moves	2.96 (1.89)	1.57 (0.37)
5 moves	2.98 (2.96)	1.50 (0.24)
Initial thinking times (sec)		
3 moves	5.74 (4.37)	4.85 (3.28)
4 moves	8.86 (9.78)	8.67 (5.91)
5 moves	8.31 (25.48)	10.39 (6.84)
Subsequent thinking times per move (all solutions)		
3 moves	1.78 (4.50)	0.34 (0.53)
4 moves	3.76 (5.93)	1.08 (1.02)
5 moves	2.35 (1.99)	1.10 (1.19)
Subsequent thinking times per move (min. move solutions)		
3 moves	0.25 (0.73)	0.30 (0.51)
4 moves	1.53 (3.02)	0.33 (0.56)
5 moves	0.96 (1.78)	0.35 (0.70)
Excess moves		
3 moves	0.47 (0.63)	0.1 (0.26)
4 moves	1.52 (0.97)	0.98 (0.88)
5 moves	2.66 (2.00)	1.33 (1.26)
Problems solved in minimum number of moves	6.8 (2.17)	8.98 (1.76)

TABLE 5. **ANOVA FOR PLANNING TASK**

	Effect of Group	**Level of Difficulty**	**Group x Difficulty interaction**
Motor initiation times	F=43.71,df=1,75 ***	ns	ns
Motor execution times	F=48,df=1,72 ***	F=23.07,df=3,216 ***	ns
Initial thinking times	ns	F=25.68,df=2,146 ***	ns
Subsequent thinking times (all solutions)	ns	F=33.96,df=3,219 ***	F=3.95, df=3,219 **
Subsequent thinking times (minimum move solutions)	ns	F=5.52,df=3,192 ***	F=3.92, df=3,192 **
Excess moves	F=12.53,df=1,75 ***	F=49.52,df=2,152 ***	F=4.44, df=2,152 **

*** $p < 0.001$

** $p < 0.01$

ns not significant

TABLE 6. **COVARIANCE OF CURRENT INTELLECTUAL FUNCTIONING (APM) WITH TESTS OF EXECUTIVE FUNCTION**

Tests	**contribution of APM**	**main group effect**
Verbal fluency		
'S' words	p<0.01	**p<0.001**
category (animals)	p<0.001	**p<0.001**
Cognitive estimates	ns	**p<0.001**
Stroop	p<0.05	**p<0.001**
Spatial Span	p<0.05	**p<0.001**
Spatial Working Memory (between errors)	p<0.001	**p<0.001**

APM Advanced Progressive Matrices

ns not significant

TABLE 7. **CORRELATION BETWEEN MRI FRONTAL LESION LOAD AND NEUROPSYCHOLOGICAL TEST SCORES**

Neuropsychological tests	**Frontal lesion load (r)**
Verbal fluency	
'S' words	-0.32 *
category (animals)	-0.42 **
Cognitive estimates	0.33 *
Stroop	0.48 ***
Spatial working memory	
between errors 4	0.29
between errors 6	0.65 ***
between errors 8	0.42 **
within errors 4	0.12
within errors 6	0.15
within errors 8	0.16
strategic score	0.32 *
Spatial span	-0.15
Tower of London	
subsequent thinking times	
5 moves (all solutions)	0.35 *
5 moves (minimum move solutions)	0.34

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$

r correlation coefficient

TABLE 8. **FRONTAL AND TOTAL LESION LOAD FOR MS PATIENT GROUPS**

Group means (standard deviations)

Groups	**Impairment index**	**Frontal lesion load (mm^3)**	**Total lesion load (mm^3)**
A (n=8)	0-1	4058.63 (4412.42)	11109.75 (11687.73)
B (n=9)	2	12421.67 (7013.08)	32918.56 (19125.18)
C (n=7)	3	17250.86 (21700.64)	39677.14 (43775.90)
D (n=16)	4	23062.31 (12321.35)	51604.69 (25636.86)

TABLE 9. **DEMOGRAPHIC DATA AND PREMORBID IQ OF PATIENTS AND CONTROLS**

Group means (standard deviations)

	MS patients (n=13)	Controls (n=10)
Age	37.15 (8.91)	38.50 (10.62)
Sex (male/female)	4/9	3/7
Disease category		
relapsing/remitting	4	
secondary	9	
progressive		
NART	109.31 (7.81)	115.00 (4.56)

NART National Adult Reading Test

TABLE 10. **TESTS OF ATTENTION AND MEMORY**

Group mean scores (standard deviations)

Test	1st occasion			2nd occasion		
	MS	Controls	Group difference	MS	Controls	Group difference
Attention						
PASAT4	24.31 (8.16)	27.80 (2.49)	ns	23.92 (7.81)	28.80 (1.40)	ns
PASAT2	14.38 (7.21)	21.20 (5.79)	z=-2.17, p=0.029	16.31 (8.08)	20.90 (3.54)	ns
Stroop	35.01 (10.27)	23.59 (5.39)	z=-2.40, p=0.016	32.00 (10.84)	21.24 (3.89)	z=-2.52, p=0.012
Symbol digit	17.44 (5.96)	11.98 (0.94)	z=-2.97, p=0.003	16.45 (4.69)	11.86 (1.33)	z=-2.94, p=0.003
Memory						
spatial span	4.92 (1.62)	6.30 (0.95)	z=-2.03, p=0.04	5.08 (1.00)	6.00 (1.25)	ns
% story recall (immediate)	43.41 (18.66)	64.73 (11.12)	z=-2.65, p=0.008	37.27 (17.77)	56.67 (5.91)	z=-2.32, p=0.02
digit span forward	6.62 (1.04)	7.90 (0.99)	z=-2.56, p=0.01	6.62 (1.04)	7.50 (1.08)	ns
% story recall (delayed)	43.13 (21.89)	68.08 (12.96)	z=-2.54, p=0.01	43.64 (22.32)	72.71 (12.78)	z=-2.81, p=0.005

ns not significant

TABLE 11. **PERFORMANCE ON TESTS OF ATTENTION IN GROUP C PATIENTS**

(n=6)

Test	1st occasion mean (SD)	2nd occasion mean (SD)	Wilcoxon Matched-pairs tests
PASAT4	22.00(10.64)	21.67(9.31)	ns
PASAT2	13.17(8.75)	16.33(11.00)	z=-1.83 *
Stroop	35.25 (12.02)	25.75 (6.07)	z=-1.83 *
Symbol Digit Substitution	20.67(7.48)	18.48(5.74)	z=-1.89 *

SD standard deviation

* $p<0.07$

TABLE 12. **GD-LESION LOAD AND SCORES ON TESTS OF ATTENTION IN THE INDIVIDUAL PATIENTS ON THE FIRST AND SECOND OCCASIONS**

Gp	DC	Gd-volume (mm^3)		Gd%	PASAT2		Stroop		Symbol Digit	
		1st	2nd		1st	2nd	1st	2nd	1st	2nd
A										
1	rr	0	0		12	13	-	-	17.8	16.0
2	sp	0	0		18	19	44.3	55.0	18.0	17.7
3	sp	0	0		12	13	-	-	-	-
4	sp	0	0		6	7	38.7	36.2	22.1	22.5
B										
5	sp	885	1400		24	19	-	-	12.6	14.3
6	sp	1005	2718		21	22	24.5	29.1	12.4	11.6
7	sp	0	132		15	21	31.1	32.7	11.8	11.9
C										
8	sp	768	294	62	7	7	40.5	-	23.5	21.3
9	sp	1119	951	15	1	1	30.2	-	30.7	25.3
10	sp	4401	2268	48	13	15	53.2	29.7	26.9	24.0
11	rr	2382	360	85	12	19	41.0	31.8	12.6	11.9
12	rr	144	0	100	24	27	19.5	18.7	16.9	14.3
13	rr	1965	54	97	22	29	27.1	22.8	13.4	14.1

Gp patient group (A,B,C)

DC disease category

sp secondary progressive

rr relapsing remitting

Gd% percentage of improvement in Gd-enhanced lesion load

FIGURE 1. **LESION VOLUME MEASUREMENT** (contouring technique)
Total lesion volume (a) and frontal lesion volume (b)

a b

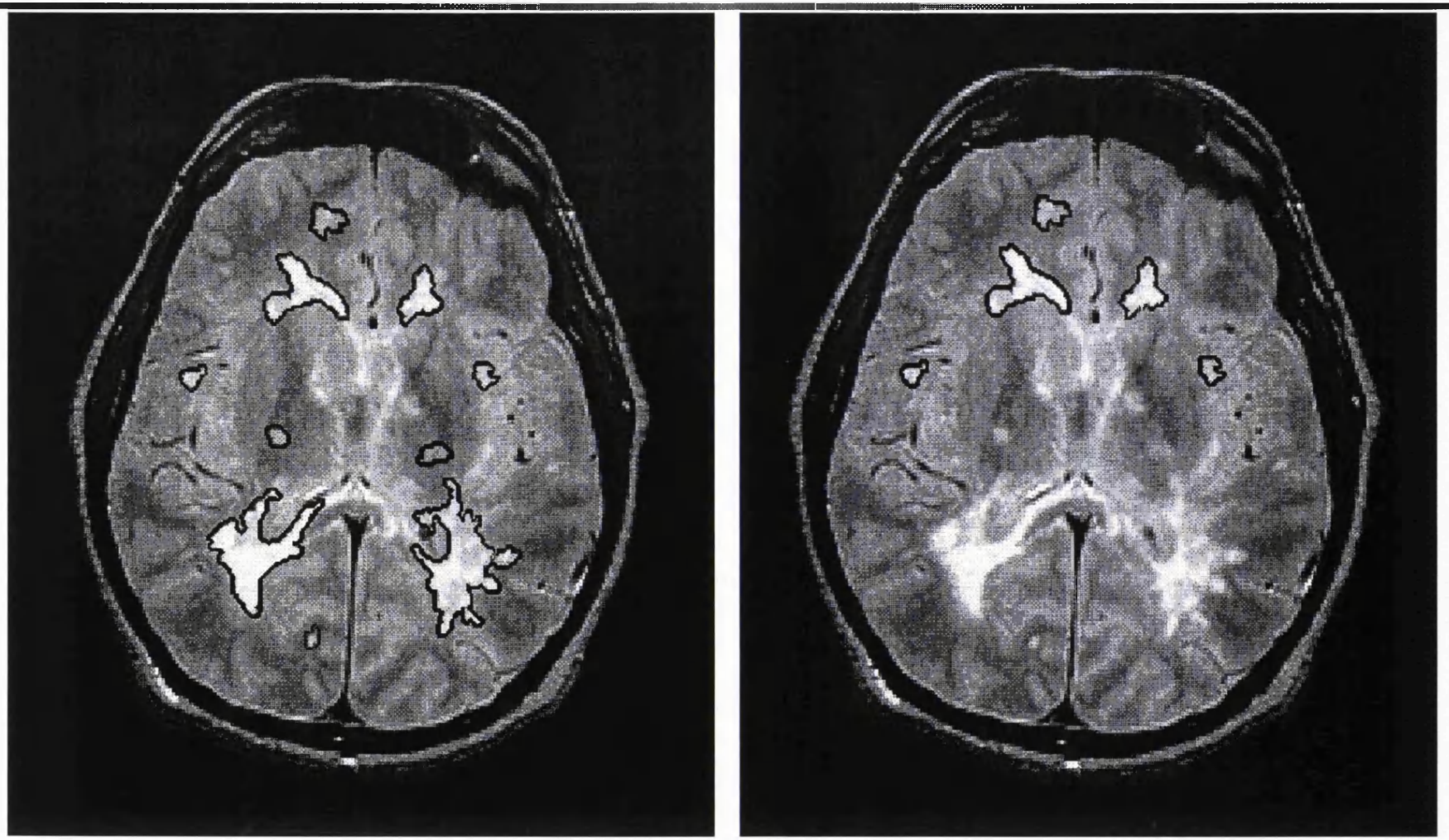
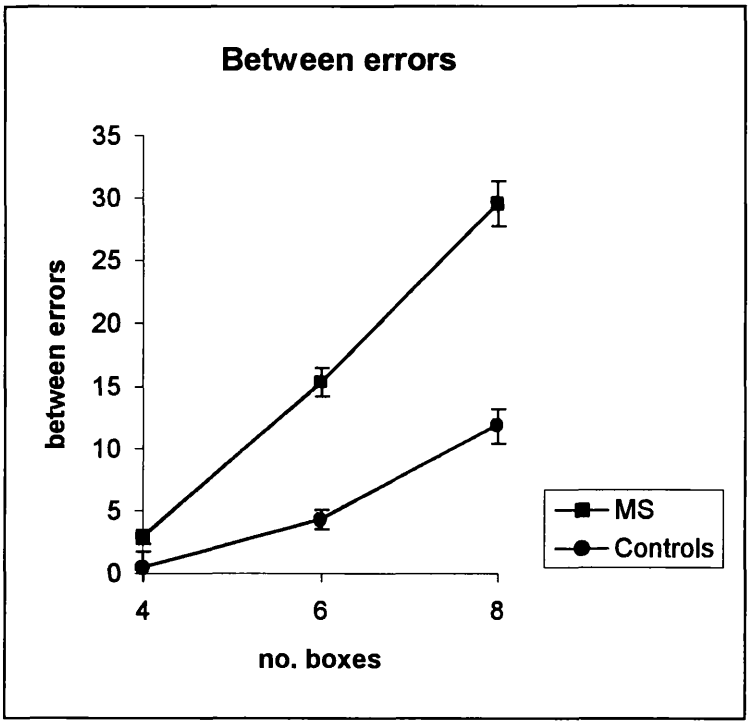


FIGURE 2. **GROUP MEAN NUMBER OF BETWEEN AND WITHIN ERRORS ON THE SPATIAL WORKING MEMORY TASK**

Error bars represent standard error of the mean



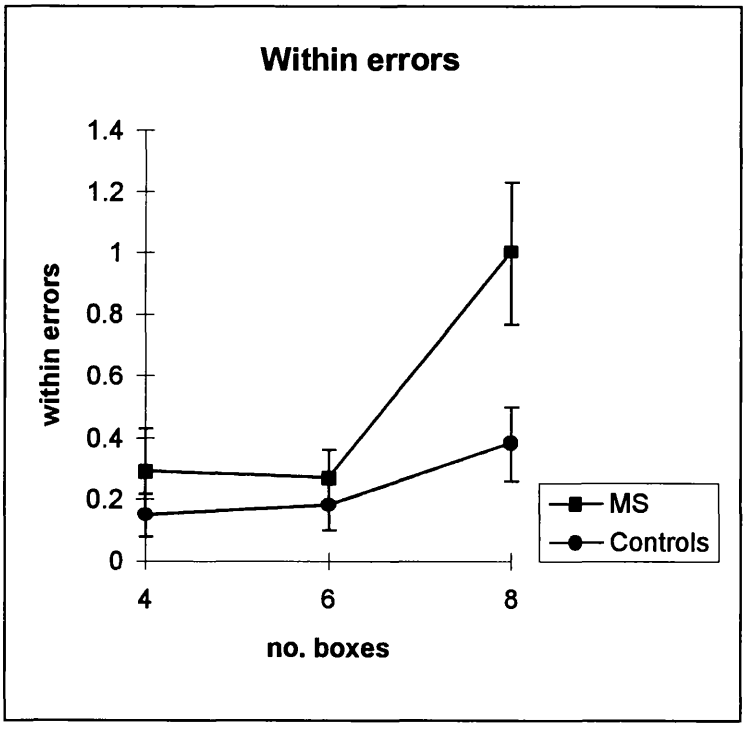


FIGURE 3. **LESION LOAD IN MS PATIENT GROUPS**

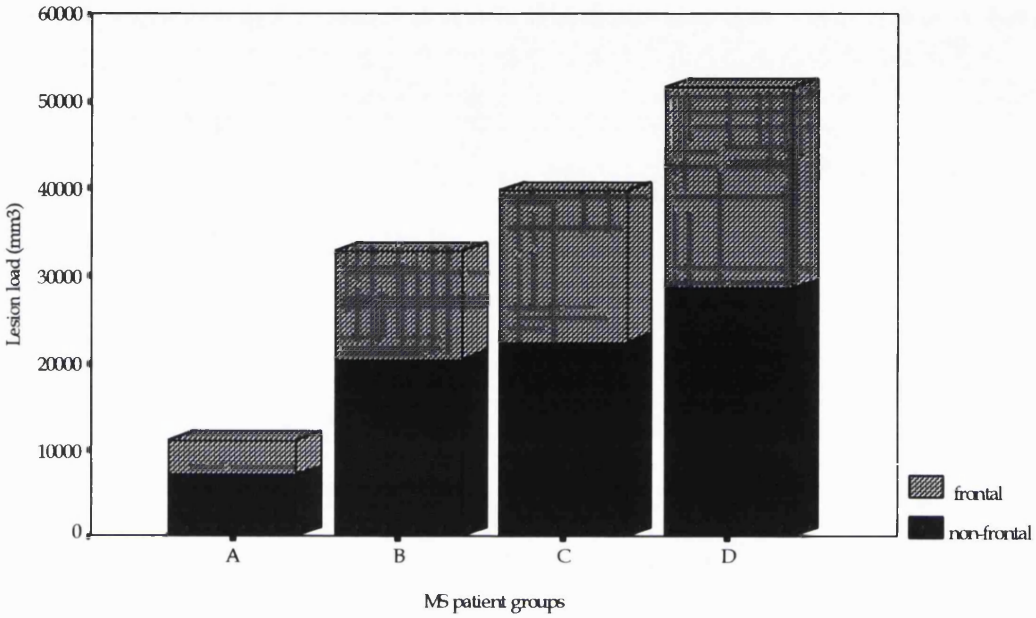


FIGURE 4. **NAA/CR RATIO IN MS PATIENTS AND CONTROLS**

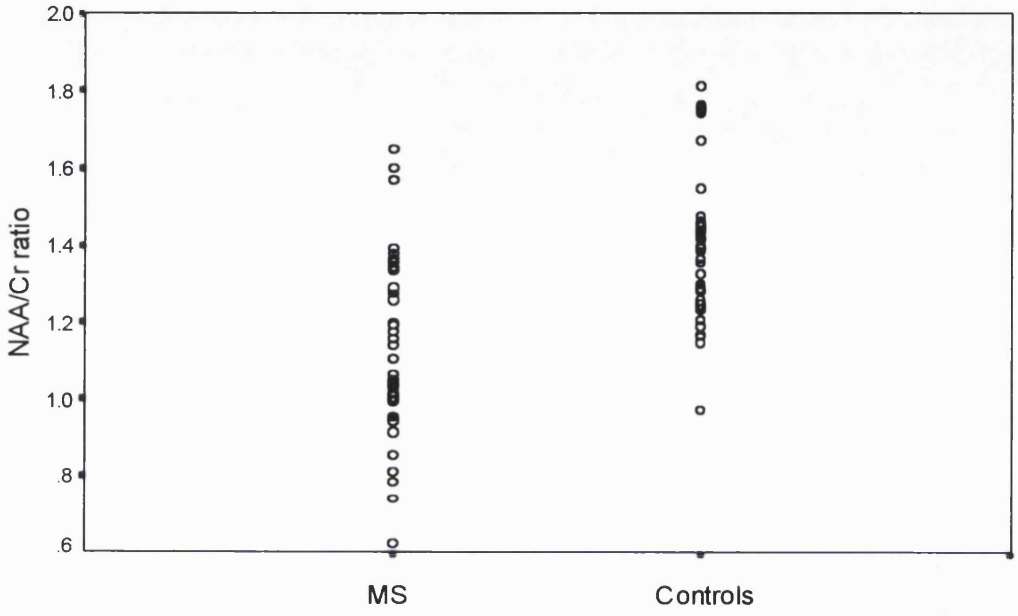


FIGURE 5. **SPECTRA FROM A CONTROL SUBJECT AND MS PATIENT**

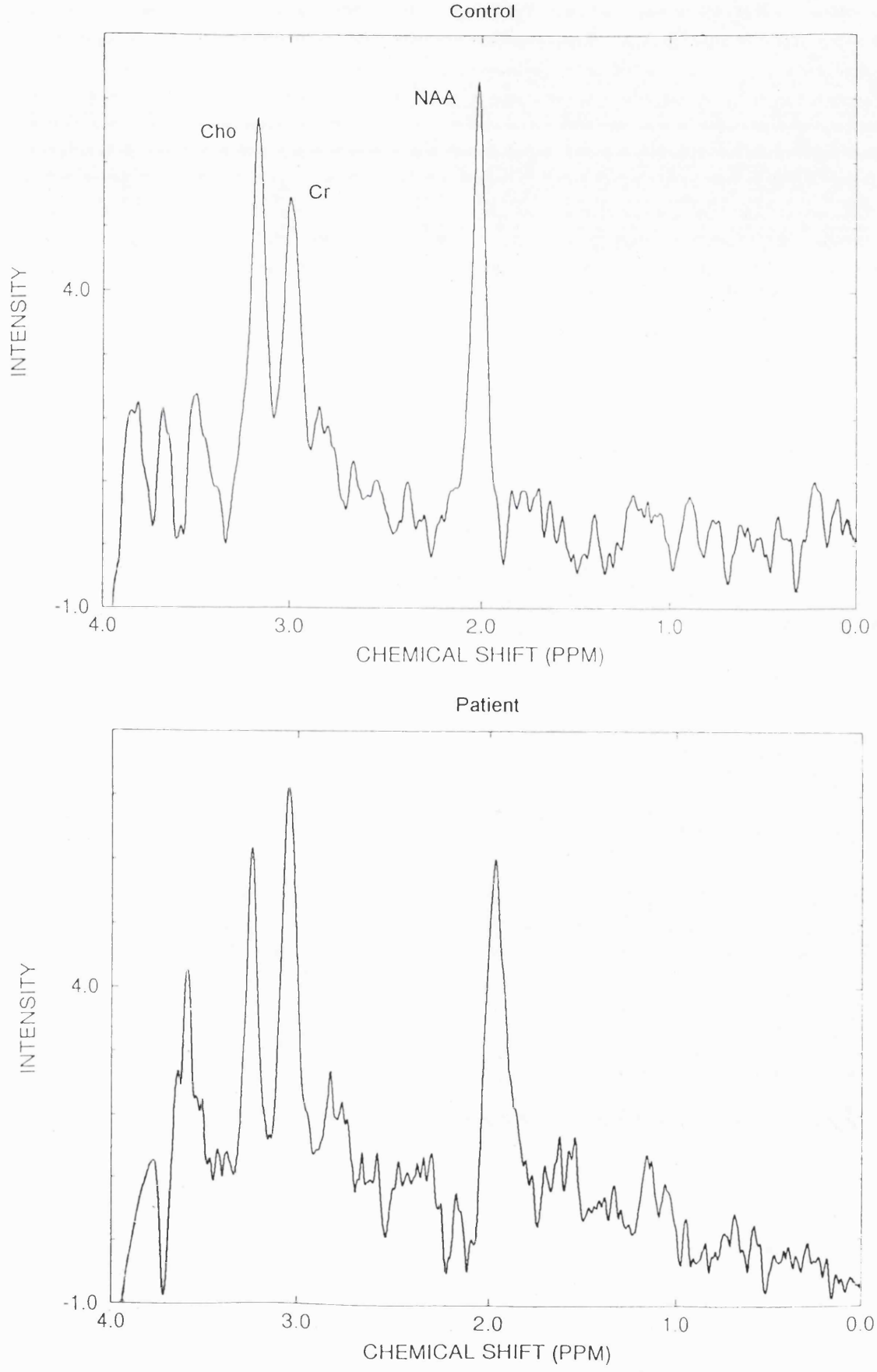


FIGURE 6. **INDIVIDUAL PATIENT'S PERFORMANCE ON THE SYMBOL DIGIT SUBSTITUTION TEST**

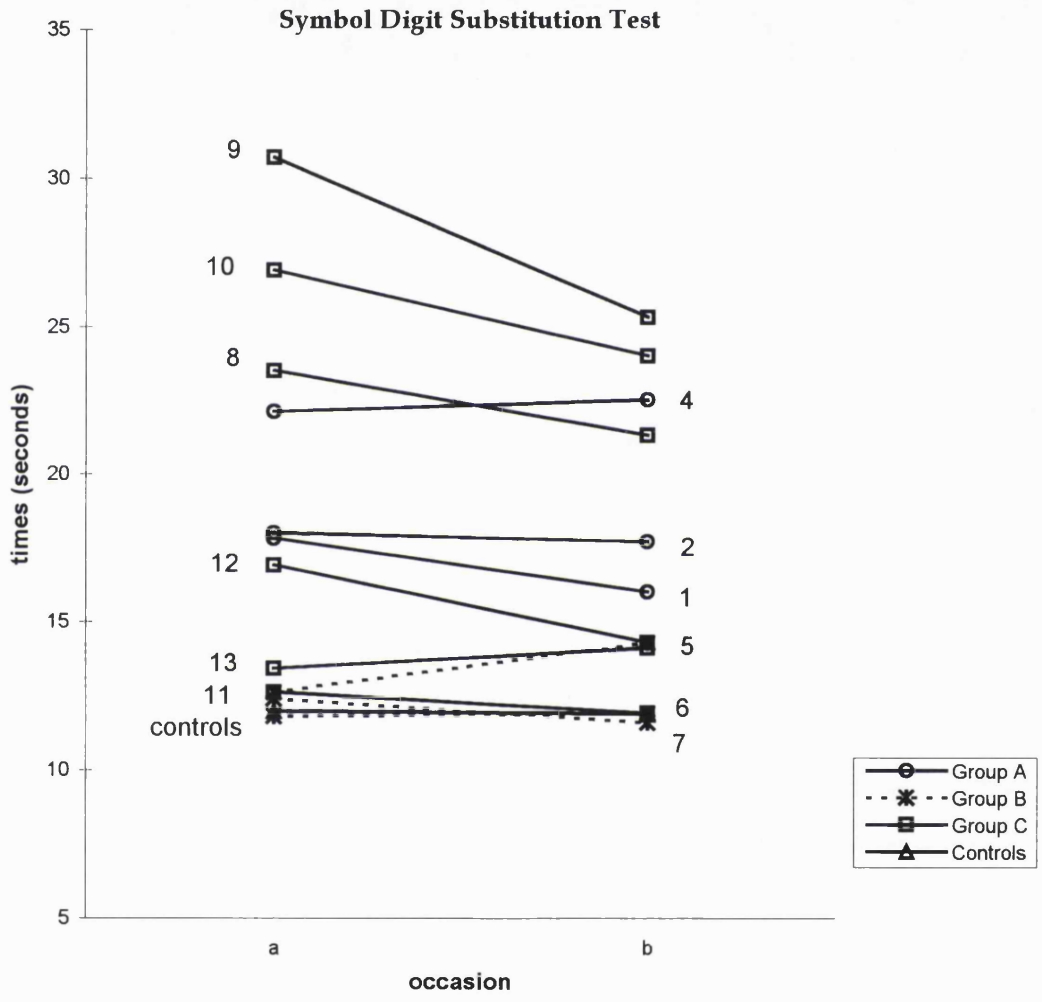


FIGURE 7. **INDIVIDUAL PATIENT'S PERFORMANCE ON THE PASAT2 TEST**

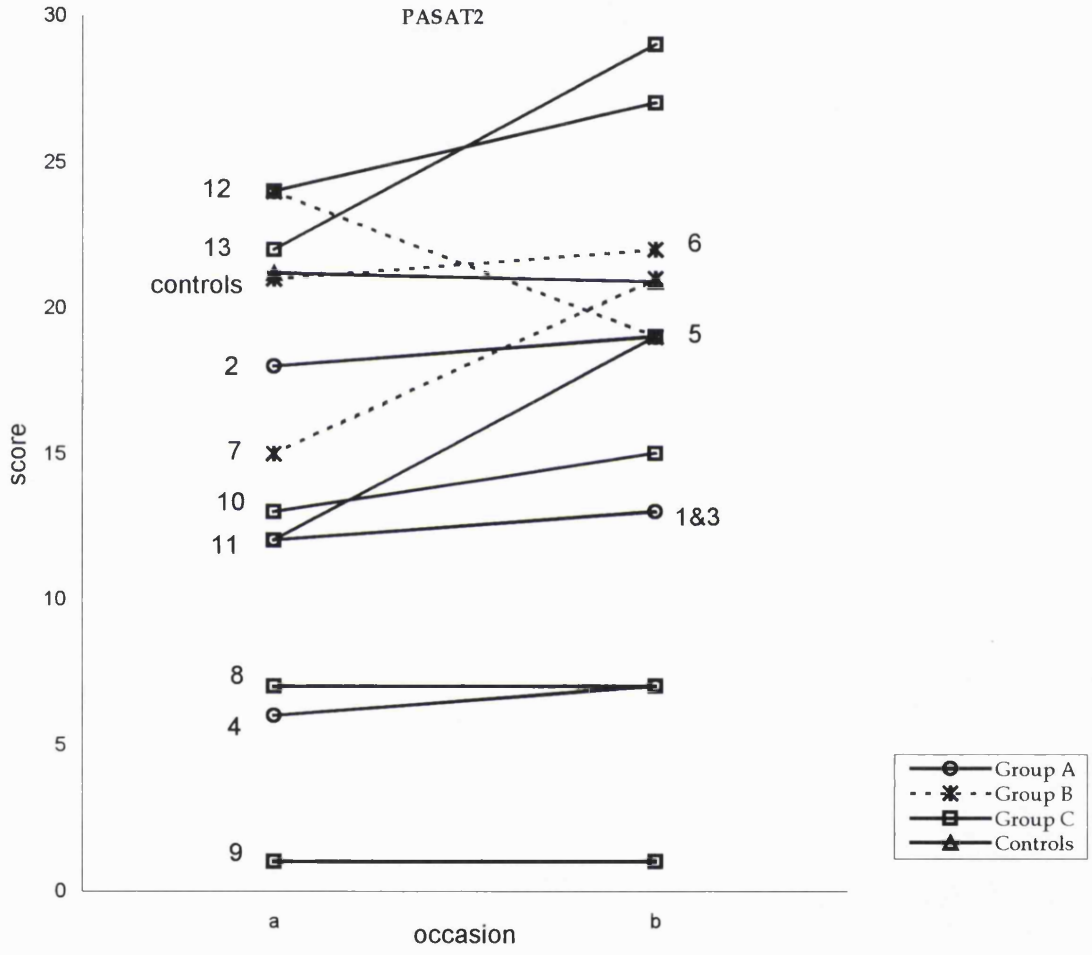


FIGURE 8. **INDIVIDUAL PATIENTS PERFORMANCE ON THE STROOP TEST**