PSYCHIATRIC, PSYCHOMETRIC AND MRI ABNORMALITIES IN MULTIPLE SCLEROSIS

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Thesis submitted to the University of London

for the degree of PhD.

1992

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ABSTRACT

Study 1. Forty two patients with acute optic neuritis were compared to matched, normal controls on tests of attention/information processing speed and anxiety/depression. Approximately half the sample had brain magnetic resonance imaging (MRI) abnormalities and were more impaired across a variety of psychometric tests compared to patients without brain lesions or controls. There were no psychometric differences between controls and optic neuritis patients without brain involvement. Total lesion area correlated significantly with some tests of attention. Psychiatric morbidity did not differ between optic neuritis patients, irrespective of the presence of brain lesions, and controls.

Study 2. Forty eight patients with clinically isolated lesions (eg. optic neuritis) were followed up after 4½ years with respect to MRI, psychometric and psychiatric abnormalities. Approximately half the sample had developed clinically definite multiple sclerosis (MS), with memory deficits becoming apparent. Attention deficits documented at initial assessment were present, but unchanged in those who remained with a clinically isolated lesion status. After dividing MS patients into a relapsing-remitting or chronic-progressive group, the latter were found to have significantly deteriorated on auditory attention tasks.

Study 3. Over 6 months, 5 patients with early relapsing-remitting MS and 5 with long standing, "benign" MS underwent serial psychometric testing and contrast enhanced brain MRI at 2 weekly/monthly intervals respectively. All patients were individually matched with healthy controls who completed the same psychometric procedure. As a group, MS patients made more errors and/or performed slower on all tasks. In patients with stable brain lesion scores, no consistent deterioration occurred in any test and the overall pattern was one of improvement over time.

However, patients with deteriorating lesion scores either showed a significant fall-off in performance on some psychomotor tasks or an impaired ability to improve performance with practice.

Study 4. Ten psychotic MS patients were assessed retrospectively with the Present State Examination and matched according to demographic and disease characteristics with 10 MS patients without psychosis. Both groups underwent brain MRI. There was a trend for the psychotic group to have a higher periventricular and total lesion score. This reached statistically significance for temporal horn scores. Clinical and MRI data pointed to an aetiological association between MS and psychosis.

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ACKNOWLEDGEMENTS

I would like to thank Dr. Maria Ron, who not only supervised this research, but also acted as mentor and friend. During the past 3 years, her ubiquitous red editing pen has exerted a profound influence over my existence, my initial apprehension of it giving way to respect and admiration.

I am indebted to Professor Ian McDonald and numerous members of his NMR research team at Queen Square, namely neurologists, Drs. David Miller, Alan Thompson and Bryan Youl; physicists, Drs. Paul Tofts, Gareth Barker and David Wicks; electrophysiologist Dr. Geoff Barrett and radiographers Dave MacManus and Sue Moore. They all gave freely of their time and expertise, without which this work could not have been completed.

My thanks also to Dr. Luke Kartsounis of the Department of Psychology, Queen Square, Dr. Richard Brown of the Human Movement and Balance Unit, Queen Square and to statisticians Peter Sacares (Queen Square) and Dr. Graham Dunn (Institute of Psychiatry) for their help and advice.

Sharing office space and friendship with Dr. Ian "Violets" Harvey was both stimulating and fun and one that contributed in no small measure to making this period such an enjoyable one.

This thesis could not have been so happily completed without the support of my wife Karen, whose knowledge, judgement and calming influence are so invaluable to me. For 3 years I further cluttered an already crowded existence only to receive patience, understanding and love in return.

*I am grateful to the **Wellcome Trust** for generously funding this research. Finally, the contribution of all the patients (and controls) who took part in this study is gratefully acknowledged. I had numerous occasion to witness courage, good humour, enthusiasm and perseverance for a task that frequently placed great demands on their time and energy.*

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The extent of my personal contribution

In accordance with University regulations. the extent of my personal contribution to the work of this thesis was as follows:

For a period of 3 years during which this work was completed, I was employed full time on a research grant funded by the *Wellcome Trust*. The grant holders were Dr. Maria Ron, Reader in Neuropsychiatry and Professor W. I. McDonald, Professor of Neurology, both from the Institute of Neurology, Queen Square. I was involved in planning both the design of the study and the details of data collection.

I undertook all psychiatric and psychometric assessments of patients and controls. The one exception in this regard was the study of patients with clinically isolated lesions, where Dr. L. Kartsounis of the Department of Psychology, Queen Square completed the follow-up cognitive battery.

With data obtained from Magnetic Resonance Imaging of the brain, I was responsible for devising a method to measure total lesion area and relaxation times in normal appearing frontal white matter. I personally analysed the MRI data from the acute optic neuritis and clinically isolated lesion studies. Dr. David Miller from the NMR unit at Queen Square made independent assessments of the MRI data from the latter study so that inter-rater reliability could be calculated. MRI data from the serial study was analysed by two neuroradiologists, Drs. Kendall and Kingsley, while Professor G. du Boulay completed the analysis of MRI data from the psychosis study.

The neurological examinations and completion of physical disability rating scales were carried out by two neurologists, Drs. A Thompson and B. Youl.

I personally performed the statistical analyses of all the data.

Anthony Feinstein

The above is a correct assessment of Dr. Feinstein's contribution to this thesis.

Dr. Maria A. Ron
Reader in Neuropsychiatry

INTRODUCTION

Multiple Sclerosis (MS) is the major cause of neurological disability among young and middle-aged adults. The observation that deficits also embraced cognitive and psychiatric abnormalities can be traced back to the French neurologist credited with naming the condition, Jean-Martin Charcot (1877), who noted patients may show "marked enfeeblement of the memory, conceptions are formed slowly and emotional faculties are blunted in their totality". Despite sporadic, albeit worthwhile attempts since then, it is only over the past decade that a concerted effort has been made to obtain accurate prevalence figures for cognitive and emotional dysfunction, document their nature and phenomenology and explore testable aetiological hypotheses. It is no coincidence that such an upturn in interest followed the introduction of Magnetic Resonance Imaging (MRI) in medicine, for the sensitivity this technique has in visualising MS lesions in the brain has enabled the in-vivo study of the pathogenesis of neurobehavioural dysfunction in a way seldom possible in other conditions.

There is now a sizeable body of knowledge devoted to cognitive and psychiatric dysfunction in MS and their relationship to variables such as disease duration, course and physical disability. The extent of brain involvement as viewed on MRI has been found to correlate significantly with cognitive deficits and while such a robust association at present eludes psychiatric abnormalities, there is tentative evidence suggesting the importance of the temporal lobes in this regard.

Despite these recent advances, a number of questions remain unanswered. The first concerns the natural history of psychiatric and cognitive abnormalities in MS. While there is evidence that the latter may be the earliest manifestation of disease, this finding needs replication with the benefit of improved imaging techniques and the elimination of previous methodological pitfalls. Longitudinal studies demonstrating how these early deficits progress over time in association with alterations in brain lesion load have yet to be undertaken. Similarly, no study has investigated the intriguing possibility that patients' emotional and cognitive state

may fluctuate as lesions in the brain wax and wane over weeks or months, the former perhaps proving a more sensitive indicator of changing brain involvement than alterations in neurological state elicited on physical examination. Finally, the relationship between MS and psychotic illness needs clarifying as a paucity of information exists regarding possible causes, phenomenology and outcome.

This thesis therefore comprises 4 studies that address these issues, each utilising MRI and psychometric and/or psychiatric assessments. The studies are:

1) Psychometric and MRI abnormalities in a homogenous sample of patients with acute optic neuritis, a condition that is frequently the harbinger of MS.

2) A psychiatric, psychometric and MRI follow-up study of patients with clinically isolated lesions of the type seen in MS (i.e. optic neuritis, brain stem and spinal cord presentations).

3) Serial psychometric, and MRI changes in patients with early relapsing-remitting and quiescent ("benign") MS.

4) Clinical and MRI abnormalities in MS patients with psychosis.

LITERATURE REVIEW

The literature review has been divided into 4 main sections. The first deals briefly with clinico-pathological aspects of MS and addresses issues such as diagnosis, definitions of disease related criteria, symptomatology, epidemiology, aetiology, laboratory findings and pathogenesis. In addition, a brief description is given of the relevant characteristics of patients with clinically isolated lesions of the type seen in MS, namely, optic neuritis, brain stem and spinal cord syndromes.

The second chapter is devoted to psychiatric aspects of MS and looks at the following conditions; euphoria, pathological laughing and weeping, depression, bipolar affective disorder and schizophrenia. The epidemiology and phenomenology of each are examined, factors pertaining to their possible aetiology reviewed and the natural history of psychiatric change discussed.

The third section deals with cognitive abnormalities and describes their prevalence, the individual functions affected and their relationship to such disease characteristics as duration, physical disability, exacerbations and course. The natural history of cognitive dysfunction is also reviewed.

The last review chapter is concerned with imaging procedures in MS. Mention is made of Computerised Axial Tomography (CT) and functional imaging, but the emphasis is on Magnetic Resonance Imaging (MRI). The importance of MRI as a research and diagnostic tool in MS is emphasised and a brief description of the underlying principles and relevant techniques is incorporated. Finally, the associations between pathological brain changes as determined by MRI and psychiatric and cognitive abnormalities are reviewed.

CHAPTER 1

Clinico-pathological aspects of Multiple Sclerosis

1 Multiple Sclerosis

The diagnosis of MS is essentially a clinical one and to sustain it, the physician must demonstrate that a patient has had at least two episodes of neurological disturbance involving distinct sites in the central white matter. To facilitate research the Poser criteria (1983) were introduced whereby terms pertaining to the disease process (eg. relapse, remission, exacerbation etc.) were operationally defined.

In the UK, the lifetime risk for MS is 1:800 which translates into ±60,000 people with the disease (Compston, 1990). Generally, MS is seen with greater frequency as the distance from the equator increases, in either hemisphere (Gonzalez-Scarano, 1986; Skegg et al. 1987). It is almost twice as common in women and although it may occur at any age, onset in early adult life is commonest. The course the disease runs is variable and initially impossible to predict. Approximately 5-10% of patients show a steady progression of disability from the onset of disease. The remainder run a relapsing-remitting course of which 20-30% never become seriously disabled and continue to function productively 20-25 years after symptom onset (Sibley, 1990). However, the largest group (almost 60%) enter a phase of progressive deterioration a variable number of years after disease onset.

Initial symptoms, which reflect the presence and distribution of the plaques, commonly involve numbness and tingling of hands, weakness of one or both legs, loss of vision or impaired visual acuity, facial numbness, vertigo, diplopia, dysarthria, ataxia and urinary frequency/urgency. The aetiology is unknown and both genetic and environmental influences are considered important. The 25% mono-zygotic concordance rate (Ebers, 1986) attests to the former while evidence for environmental influences comes from 3 main sources. Migration studies have

demonstrated that those who emigrate during childhood assume the risk of the country of adoption (Dean, 1967), disease epidemics have been reported in isolated communities such as the Faroe Islands (Kurtzke and Hyllested, 1979) and marked variations in prevalence have been found in genetically homogeneous populations (Miller et al. 1990).

Although the exact pathogenesis of MS is uncertain, there is little doubt that it is an inflammatory disorder of the central nervous system accompanied by severe immunological abnormalities (Lisak, 1986). The inflammatory response is important in the initiation of demyelination and affects the white matter, particularly adjacent to the lateral ventricles. The grey matter is usually spared. Plaques, which are the typical MS lesion, appear along the course of small veins and show infiltration of lymphocytes, plasma cells and macrophages during the early active phase. The axon is denuded of myelin, although left intact.

Imaging studies during an acute attack have shown leakage of contrast enhancing materials, indicative of a breakdown in the blood-brain-barrier (BBB). The compromised BBB results in oedema and the entry of immune mediators (viz. antibodies) which may contribute to myelin destruction. The leakage disappears spontaneously over 4-6 weeks (Miller et al. 1988a) and may be reversed temporarily by the administration of corticosteroids (Barkoff et al. 1991). Post mortem studies have confirmed that lesions visualised on MRI and Computerised Axial Tomography (CT)(Silberberg, 1986) correspond to MS plaques (Ormerod et al. 1987).

Diagnostic tests

Although the diagnosis of MS is essentially a clinical one, the Poser criteria (1983) allow 2 different forms of investigation to aid in the process. Results from imaging procedures, particularly MRI (see section on imaging) and evoked potential studies (delays in visual, auditory and somatosensory evoked potentials) are regarded as

para-clinical evidence of disease and if abnormal may assist in the diagnosis of "clinically definite MS".

Laboratory support for the diagnosis refers only to evidence from cerebro-spinal fluid of immunological abnormality in relation to the central nervous system, i.e. oligoclonal bands in the absence of such bands in the serum, and increased production of IgG (McDonald and Silberberg, 1986). The presence of such abnormalities is required for the diagnosis of "laboratory-supported definite MS".

2 Clinically isolated lesions (CIL)

Patients with CIL are of particular interest as they are frequently a forerunner of MS. In attempting to describe the natural history of psychiatric and cognitive abnormalities in MS, the study of such patients affords a valuable opportunity to document the earliest evidence of dysfunction before patients progress to "definite" disease status.

A Optic neuritis

Acute unilateral optic neuritis (ON) in adults is the presenting feature of MS in 20% of cases, over three quarters of patients going on to develop MS (Francis et al. 1987). It is characterised by the rapid development of visual loss, usually accompanied by pain with symptoms progressing for 3-4 weeks and then resolving over 2-3 months, recovery to 6/9 vision occurring in greater than 90% of patients (McDonald, 1983). Sixty percent of adults presenting with clinically isolated optic neuritis display one or more asymptomatic white matter lesions on MRI which appear indistinguishable from those seen in MS (Ormerod et al. 1987). The presence of such lesions is associated with a high risk of progression to clinically definite MS within 5 years (Miller et al. 1992), but MS should still not be diagnosed at presentation because the criterion of dissemination in space has not been satisfied.

B Brain stem and spinal cord syndromes

Acute brain stem disturbance eg.vertigo, diplopia is the presenting feature of MS in approximately 15% of patients while twice as many will present with spinal cord symptoms (sensory, motor and sphincter disturbance). The percentage that go on to develop MS is probably similar to that of optic neuritis (Miller et al. 1989a).

CHAPTER 2

Psychiatric Illness and Multiple Sclerosis

A wide array of psychiatric abnormalities have been described in association with MS, ranging in severity from transient adjustment disorders with mild anxiety and depression to bipolar affective disorder and schizophrenia. For many years euphoria was considered virtually pathognomonic of the abnormal mental state in MS and thought to occur in over two thirds of patients (Cottrell and Wilson, 1926). Depression was consequently thought of as rare, but over the years this opinion has substantially altered and the situation has now reversed.

1 Psychiatric Disorders

A Euphoria

Euphoria has proved difficult to define resulting in frequency estimates that have differed considerably (Rabins, 1990). The complexity of the task is illustrated by Cottrell and Wilson, (1926) who defined 4 states, namely "mental well being" or euphoria sclerotica characterised by a persistently cheerful mood; "physical well being" or eutonia sclerotica distinguished by unconcern over physical disability; pes sclerotica, an incongruous optimism for the future; and emotional lability. Although the validity of such an approach has never been adequately proven, the above criteria with the exception of emotional lability are still considered pathognomonic of the condition. Thus, as currently defined, euphoria bares some similarity to hypomania with regard to elevated affect, but lacks the associated motor hyperactivity and racing thoughts. The condition is fixed rather than fluctuating and may best be considered an organic personality change.

Few studies since Cottrell and Wilson have reported such high rates. Surridge (1969), comparing his case register of MS patients to a control group with muscular dystrophy (MD) found euphoria in 25.9% of the MS as opposed to none

in the MD group. Poser (1980) reported a 24% rate while Rabins et al. (1986) using Cottrell and Wilson's definitions noted a 48% point prevalence. A reason for the decline in frequency has been the recognition that many patients with emotional lability appear superficially euphoric but in reality have subjective evidence of depressed mood. In addition, those subjects with emotional incontinence (also termed "pathological laughing or crying") that were included in Cottrell and Wilson's rubric of emotional well being, are now considered a distinct entity (*see below*). Summarising the various studies to date, a median rate of 25% probably accurately reflects the true prevalence of euphoria (Rabins, 1990).

Euphoria is considered a manifestation of advanced MS commensurate with extensive cerebral damage. Studies demonstrating an association with greater physical disability and cognitive impairment (Surridge, 1969; Rabins et al. 1986), progressive disease course and enlarged ventricles on CT (Rabins et al. 1986) and widespread brain lesions on MRI (Ron and Logsdail, 1989) have all been reported.

B Pathological laughing and weeping

This refers to a patient's inability to control emotional responses that do not necessarily reflect subjective mood experiences. Attacks may follow slight provocation or may occur independently of such cues. Exact prevalence figures are not known, but clinical experience suggests a figure of approximately 10% (Minden and Schiffer, 1990).

The pathological mechanism underlying this symptom is not known. The fact that it responds to low doses of amitriptyline (Schiffer et al. 1985) or laevodopa (Wolf et al. 1979) points towards neurotransmitter abnormalities, although the differences in dosage requirements suggests an alternative pathogenesis to that of affective illness. It is also possible that demyelination disconnects "higher" cortical areas (eg. prefrontal) responsible for emotional control.

C Depression

i Prevalence

The frequency of depressive disorders has varied according to the cohort studied and the method used, for it is only in the 1980's that standardised psychiatric interviews and validated, reliable rating scales have been employed. In some studies, point and/or lifetime prevalence figures have been reported while others have used prevalence figures since the onset of MS, making comparisons across different studies problematic.

Conflicting evidence exists on whether there is an increase in depression prior to the onset of neurological symptoms in MS. While Whitlock and Siskind (1980) and Joffe et al. (1987a) are of the opinion there is, this has not been noted by Ron and Logsdail (1989) nor Minden et al. (1987), the latter finding that rates did not differ from those in a healthy community sample matched for age.

Data suggesting an absence of major depression and a low overall psychiatric morbidity early in the disease process (Logsdail et al. 1988) have come from studies of patients with clinically isolated lesions (optic neuritis, brain stem and spinal cord presentations). Prevalence rates for emotional distress in this group did not exceed those reported from normal community samples (Andrews et al. 1977) nor general practice attenders (Goldberg et al. 1970).

These figures contrast with those found in patients with established MS. A number of studies have used the life time version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) which enables Research Diagnostic Criteria (RDC) diagnoses to be made. Minden et al. (1987) noted a 54% lifetime prevalence while Schiffer et al. (1983), in a sample of 30 cases found a 37% prevalence of major depression since the onset of the MS. In a study of 100 consecutive attenders at an outpatient clinic, Joffe et al. (1987a) found a 47% lifetime prevalence of major depression and a 14% prevalence of current depression, with a further 13% of the

sample experiencing lesser degrees of depressive illness over their lifetime. Thus, pooling figures, the lifetime prevalence of major (unipolar) depression amongst hospital attenders is approximately 40-50% (Minden and Schiffer, 1990).

This figure is in accord with point prevalence figures obtained from self report questionnaires, of which the Beck Depression Inventory has been the most frequently used (Minden et al. 1987; Joffe et al. 1987a; Beatty et al. 1988; Beatty et al. 1989; Ron and Logsdail, 1989) although it should be noted that such an approach is not geared towards establishing a diagnosis. Scores have generally been in the mid to moderate range suggesting that depressive illness lacks the intensity of that encountered in depressed patients without MS.

Precise epidemiological figures on suicide in MS are not available. In the only study to date, Kahana (1971) reported that 3% of 295 patients committed suicide over a 6 year period. Whether this was due to the severity of depression or related to a combination of other factors, namely work and social, which in turn can contribute to depression, is not clear. This figure contrasts with a lifetime prevalence of approximately 1% reported for suicide attempts in a general population study, of which less than 1 in 10 would be expected to succeed (Paykel et al. 1974).

ii Phenomenology

Evidence suggests that symptoms differ in some respects from those seen in subjects with uncomplicated major depression, although there is considerable overlap. The typical picture commonly found in the latter, i.e. withdrawn and apathetic with feelings of guilt and worthlessness was not noted by Minden et al. (1987) who found that symptoms such as irritability, worry and discouragement predominated. A high frequency of irritability has also been confirmed by others (Ron and Logsdail, 1989).

To disentangle somatic symptoms due to mood disturbance from those directly attributable to physical disease is important in a disorder such as MS. This is highlighted by a symptom such as fatigue, which was one of the items most frequently endorsed by patients on the Clinical Interview Schedule (Ron and Logsdail, 1989), thereby raising the question whether it is a psychological or physiological symptom or a combination of both. Krupp et al. (1988) believe the fatigue of MS to be a distinct entity unrelated to neurological impairment, affective disorder or fatigue experienced by healthy subjects. Whether or not this is a valid assessment, this ubiquitous symptom is unlikely to exist in isolation and may influence other aspects of the mental state such as concentration, memory, irritability and sleep difficulties and in turn be aggravated by the coexistence of depression. The use of self rating scales for emotional dysfunction with somatic aspects removed, such as the Hospital Anxiety and Depression Scale (HAD)(Zigmond and Snaith, 1983), is particularly useful in this regard.

iii Aetiology of depression in MS

To what extent depressive disorders are due to brain damage or a reaction to a disabling, incurable disease has been the subject of contention. As most patients with definite MS have brain lesions, studies performed before the advent of MRI can only be seen as a rough guide to this relationship. Nevertheless, the finding of greater psychiatric morbidity in those with clinical or computerised tomographic (CT) evidence of brain involvement, point in this direction.

Two studies compared psychopathology in MS patients and a control group consisting of subjects with spinal cord injuries. Rabins et al. (1986) noted higher scores on the 28 item General Health Questionnaire (GHQ) in the MS group only if CT evidence of brain involvement was present. Dalos et al. (1983) also documented higher GHQ scores in their MS sample, but differences were due to higher scores on the somatic and social disability, not depression subscales. In addition, closer inspection of their data revealed that elevated subscale scores occurred more frequently in MS patients experiencing disease exacerbations, adding

to the difficulties of data interpretation. Modifying the above construct, Schiffer et al. (1983) compared 2 groups of 15 MS patients with either predominantly brain or spinal cord involvement based on clinical assessment. Despite being matched for age, duration of illness and degree of physical disability, the former had significantly more major depressive episodes. Although brain lesions will have been present in both groups, a greater brain lesion load is likely to have been found in those with a suggestive clinical picture.

Epidemiological data supporting the intrinsic role of brain pathology has come from Schiffer and Babigian (1984). Using a computer search of medical and psychiatric records in Monroe county, New York, they compared the psychiatric attendances of 3 groups of patients i.e. MS, temporal lobe epilepsy (TLE) and amyotrophic lateral sclerosis (ALS). TLE was chosen because of the strong association with psychiatric illness while ALS was included because of it's poor prognosis. Both MS and TLE patients had more psychiatric contacts than the ALS group (19.3 and 22.9% vs. 4.8% respectively) with the MS group having a significantly higher rate of depression than the other two groups. A similar conclusion was reached by Whitlock and Siskind (1980), who also found that MS patients experienced more depressive episodes than those with other neurological disorders without brain involvement, such as muscular dystrophy, motor neurone disease and dystrophica myotonica amongst others.

An alternative although potentially complimentary approach, emphasising the importance of psychological factors has been highlighted by several studies. Surridge (1969) did not find a significant difference in depression between samples of MS and muscular dystrophy patients and concluded depression in the MS group was largely reactive. There were however methodological flaws in his approach for the muscular dystrophy group was more socially and physically disabled and standardised assessment procedures were not used. More compelling evidence comes from those imaging studies that have failed to demonstrate a convincing relationship between the extent of lesions in the brain and depression. Apart from a single CT study that did show an association (Rabins et al. 1986), the trend

amongst MRI reports is to the contrary (*see section on imaging correlates of psychiatric illness*). Thus Logsdail et al. (1988), Ron and Logsdail (1989) and Anzola et al. (1989) all failed to find correlations between total lesion area and measures of psychological distress that included depression. In addition, Ron and Logsdail (1989) found that the MS subjects' perceived levels of social stress and support were the most important influences in the pathogenesis of their psychiatric morbidity.

There is no evidence to suggest a genetic link exists between MS and unipolar depression. Based on the family history method, Joffe et al. (1987b) did not find an excess of affective illness in the first degree relatives of patients with MS, a finding in agreement with that of others (Minden et al. 1987; Schiffer et al. 1988). However, with respect to depression occurring as part of a bipolar illness, the question is less clear (*see section on Bipolar Affective Disorder*).

iv Depression, physical disability and duration of illness

The questions of disease duration and physical disability are double edged swords when it comes to drawing aetiological inferences. An association between depression and greater physical disability could be interpreted as lending support to either a "cerebral" or "reactive" viewpoint and the same could be said for duration of illness. It is therefore not surprising that facts to date have been contradictory. While Whitlock and Siskind (1980) and McIvor et al. (1984) have reported a positive association between depression and disability, no such relationship between depression (Minden et al. 1987) and emotional dysfunction (Rabins et al. 1986; Ron and Logsdail, 1989) on the one hand, and disease duration, severity or course on the other has been noted.

The reason for the lack of a clear association between disease duration and psychiatric problems is likely to be due to the diversity in the course of MS. Thus, an illness with the same duration may involve either a few, mild relapses or follow a devastating chronic progressive course. It may also encompass patients with

either quiescent lesions or those with a rapidly deteriorating lesion load. Similarly, the degree of physical disability is determined by a combination of cerebral and spinal cord involvement, each of which may have a different influence on affect.

D Bipolar affective disorder

Case reports have appeared over the years describing the coexistence of MS and bipolar affective disorder (BAD) (Peselow et al. 1981; Mapelli et al. 1981), sometimes with rapid cycling (Kellner et al. 1984). Although rare compared to unipolar depression, there is some evidence to suggest that bipolar disorders occur with greater frequency in patients with MS than they do in the general population.

An epidemiologic study (Schiffer et al. 1986) found double the expected number of patients with both MS and BAD while Joffe et al. (1987a) in a consecutive sample of 100 out-patients found 13 times the expected rate of BAD. The increased rate in these studies was not attributable to treatment with steroids, although another study has reported that MS patients at high risk for BAD (i.e. previous episodes of depressive illness or a family history of affective illness) were more susceptible to develop hypomanic episodes whilst on steroids (Minden et al. 1988).

There is firmer evidence of a possible genetic link between MS and BAD than is the case with unipolar depression. Schiffer et al. (1988) in a study of 56 patients, demonstrated that bipolar MS probands had significantly more relatives with MS or affective disorders than unipolar MS probands and that females with MS were also at greater risk for developing an affective disorder. They further concluded that HLA-DR2 and HLA-DR5 may be markers of high genetic risk for the phenotype of MS with BAD. Others have however failed to replicate these findings (Joffe et al. 1987b).

E Schizophrenia and MS

Schizophrenia and MS are both common diseases with lifetime prevalences of 1:100 and 1:800 respectively. The possibility therefore exists that on the basis of chance alone, the two disorders may coexist. Although an epidemiological study addressing this question has not been undertaken, the consensus from numerous case reports appearing over the years, is that the association is infrequent (Schmalzbach, 1954; Parker, 1956; Geocaris, 1957; Mathews, 1979; Awad, 1983; Drake, 1984; Feinstein and Ron, 1990). A similar conclusion can be drawn from a study of 268 consecutive first admission schizophrenic patients thoroughly investigated for physical disease, none of whom had MS (Johnstone et al. 1987). Reasons for this may be twofold. First, MS is primarily a white matter disease while schizophrenia is mainly associated with cortical abnormalities and second, whereas evidence suggests schizophrenia may be a developmental disorder (Jones and Murray, 1991) with perinatal influences such as trauma (McNeil and Kaij, 1978) or infection (Crow, 1983) proving important, the same cannot be said for MS.

Conversely, similarities between the course of the two conditions and certain common epidemiological features such as age of onset, unimodal age distribution and geographical clustering have led some (Stevens, 1988) to postulate that the two may share an infectious or immunological cause. In a series of 39 published cases collected by Davison and Bagley, (1969) both conditions had started simultaneously in a third of cases, while in a further 25% the psychosis began within 2 years either side of the onset of neurological symptoms and the temporal link was interpreted as signalling an aetiological connection. The association between brain damage secondary to other aetiologies and schizophrenia has been documented (Feinstein and Ron, 1990) and MS may follow a similar pattern that suggested the link between the two conditions was causal rather than a chance occurrence.

Individual patients with evidence of coarse brain disease and schizophrenia are phenomenologically indistinguishable from those with schizophrenia alone and only when group comparisons are made are the former likely to differ by having a higher percentage of persecutory delusions, preservation of affective responses and a later age of onset of psychosis (Slater et al. 1963; Davison and Bagley, 1967; Feinstein and Ron, 1990). The association of the two conditions is of potential interest in that further light may be shed on the localisation of cerebral structures considered important in the pathogenesis of psychosis. In their review of numerous central nervous system disorders associated with schizophrenia like psychoses, Davison and Bagley (1969) noted the importance of limbic and diencephalic structures in the pathological processes. However, a study of 65 patients with psychosis and demonstrable brain disease such as Parkinson's and Huntington's disease, cerebro-vascular and infective pathology (Feinstein and Ron, 1990) failed to identify a specific site of cerebral pathology. A study of psychosis co-existing with MS may help clarify the issue for MS plaques are highly sensitive to detection by MRI and their anatomical location can be accurately established. Although no imaging study has specifically looked at psychosis and MS, there is tentative evidence of an association between thought disorder/delusions and temporal lobe pathology (Ron and Logsdail, 1989).

Despite these pointers, the pathogenesis of schizophrenia concurrent with MS remains unclear and the relationship of onset of psychosis to the duration and course of MS and degree and site of brain involvement has yet to be resolved.

2 Natural history of psychiatric change in MS

There are no long term follow-up studies of psychiatric morbidity in MS. However, the lack of psychopathology in those with clinically isolated lesions (Logsdail et al. 1988) contrasts with that seen in established MS (Ron and Logsdail, 1989). Only 2 studies have investigated the natural history of emotional change in response to fluctuations in physical condition. Dalos et. al., (1983) administered the 28 item GHQ at monthly intervals to 64 MS patients and 23 spinal cord injured patients

matched for age, sex, duration of symptoms and physical disability. Exacerbations in the MS group were associated with significant increases in GHQ scores, a conclusion that replicated the earlier finding of Cleeland et al. (1970) who used the Minesota Multiphasic Personality Inventory. While exacerbations appear linked to emotional distress, the same does not apply to the course of disease, i.e. relapsing-remitting or chronic-progressive (Rabins et al. 1986; Minden et al. 1988).

Minden et al. (1987) have attempted to explain the apparent contradictory finding of an association between increased psychopathology and exacerbations in the disease, but not with physical disability. The sudden unexpected nature of an exacerbation accompanied by emotional turmoil has been contrasted with the relatively constant level of overall functioning during the stable phase of the disease, which allows time for necessary adjustments to be made.

3 Psychiatric presentations of multiple sclerosis

Although some cases of MS presenting with psychiatric symptoms have been reported (Young et al. 1976; Mathews, 1979; Whitlock and Siskind, 1980), the evidence from epidemiological studies suggests that this is uncommon and may be a chance finding. A comparison of the rates of psychiatric illness in large samples of patients with MS and temporal lobe epilepsy (TLE) (Schiffer and Babigian, 1984) revealed that although 17% of the MS group were initially diagnosed as having a psychiatric illness, this was significantly less than the 29% reported for TLE. This figure is similar to the 19% reported by Stenager and Jensen (1988) who found the onset of MS coincided with psychotic disorders and transient situational disturbances, but not with neurotic disorders. While both these studies make the point that psychiatric illness may predate neurological symptoms (often by years), no unequivocal conclusions can be drawn concerning a shared pathogenesis as it is possible the two disorders may have coexisted purely by chance given the fact that both commonly occur. In addition, it can be notoriously difficult to document retrospectively the first, often subtle neurological symptoms, which makes interpretation of data such as these potentially hazardous.

Nevertheless, in a well defined regional population, Skegg et al. (1988) were able to identify 91 patients with MS (a point prevalence of 0.08%) of whom 16% had been referred to a psychiatrist between the onset of their symptoms and the diagnosis of MS. Although neurological symptoms were present at the time in the majority of patients, these had been overlooked by the psychiatrists in all but 2 cases. Instead, patients were given diagnoses such as hysterical personality disorder or conversion disorder.

The reverse situation, namely psychiatric illness masquerading as MS can also present the clinician with diagnostic difficulties. A follow-up of 400 patients referred to neurologists and subsequently found not to have MS, revealed 14 with primarily psychiatric problems (Murray and Murray, 1984). Such patients were more likely to be female, hospital employees or have a friend with MS, and suffer from anxiety, depression and hysteria.

4 Psychological precipitants of onset/relapse

The data concerning the role of psychological factors in either triggering the onset of MS or producing exacerbations in already established disease is unclear. A positive association between stress and the onset of MS has been reported by Warren et al. (1982, 1991) and Grant (1986), but not Pratt (1951) or Baldwin (1952). This area is beset with methodological difficulties such as determining the precise onset of MS, retrospective nature of recall and the use of inadequate instruments to measure stress. This was illustrated by Rabins et al. (1986) who found that patients retrospectively reporting an association between stress and exacerbations were significantly more anxious than those who did not.

Summary

1. Psychiatric morbidity is common in MS, particularly unipolar depression where a lifetime prevalence of ±50% has been recorded in hospital attenders.

2. There is no genetic evidence to support this association with depression and at present no definitive conclusions can be drawn concerning the relative importance of cerebral involvement or social factors in the pathogenesis of mood change. It may therefore be best to consider an interactional model in which the presence of brain lesions creates a vulnerability, enhanced by environmental factors uniquely attributable to the disease.

3. Bipolar Affective Disorder may occur more frequently than expected in MS patients and tentative evidence suggests a link via the HLA system.

4. Euphoria is uncommon and associated with cognitive impairment, extensive brain involvement on MRI and usually, greater physical disability.

5. Psychotic episodes indistinguishable from schizophrenia have also been reported. The age of onset and some clinical features suggest a causal link between the two, while the association of temporal lobe pathology and psychosis may also be of significance.

CHAPTER 3

Cognitive dysfunction in multiple sclerosis

1 Prevalence

Prevalence figures for cognitive dysfunction have varied considerably, ranging from over 50% in patients in a tertiary hospital setting (Peyser et al. 1991) to 17% in subjects with mild physical disability residing in the community (van den Burg et al. 1987). A study that assessed cognition as part of a bedside neurological examination using brief testing, reported the lowest estimates, viz 13% (Peyser et al. 1980). The reason for this variability can thus be traced to differences in patient selection, methods of assessment and interpretation of the results. In the most representative study to date, Rao et al. (1991a) studied 100 randomly recruited community based MS patients and a similar number of demographically matched healthy control subjects. Thirty one different cognitive tests were administered and impairment on 4 or more was considered indicative of cognitive dysfunction, resulting in 43% of the MS group being rated as impaired.

2 Clinical significance and nature of dysfunction

There is a general consensus that MS affects numerous aspects of cognition embracing attentional processes, memory, abstract/conceptual reasoning and visuospatial functions (Peyser et al. 1990). These deficits differ however from those in dementias involving cortical substrates, such as Alzheimer's Disease. Filley et al. (1989) controlling for differences in age, sex and education, compared 42 patients with chronic-progressive MS and an equal number with Alzheimer's Disease using a comprehensive psychometric battery. They found that MS subjects were more impaired with respect to attention and psychomotor functions while the Alzheimer group had greater deficits in learning, memory and language skills. Thus

agnosia, apraxia and language difficulties are absent or mild in MS, often resulting in a more subtle clinical presentation and one easily missed.

Slowed information processing speed characterises the performance of MS subjects on a variety of cognitive tasks (Litvan et al. 1988a) and is independent of motor speed (Rao et al. 1989a). This cognitive slowness is part of a constellation of signs and symptoms often seen in dementias with predominantly subcortical pathology, other features including forgetfulness, mood changes, psychomotor slowing and motor abnormalities (Cummings, 1986). However, comparisons between MS and other postulated "subcortical dementias" have highlighted important differences. Caine et al. (1986) compared the cognitive deficits of MS with those of Huntington's disease and found the latter to have greater deficits encompassing verbal and non-verbal memory, language usage and calculating ability. In addition, evidence of cognition as a function of widespread neural networks involving multiple brain areas argues against a strict cortical-subcortical dichotomy (Mesulam, 1990).

The clinical significance of these cognitive findings has been demonstrated by Rao et al. (1991b) in a well controlled study comparing 52 cognitively impaired and 48 intact MS patients matched with respect to age, premorbid occupation and IQ, marital status, percentage taking medication, duration of illness, disease course and degree of physical disability. The former were found to have experienced greater difficulties with work, sex, social activities and performing routine household tasks in addition to exhibiting increased psychopathology.

A more detailed review of the salient aspects of cognition in MS follows. As attentional processes and the natural history of cognitive change are the focus of the cognitive studies in this thesis, these subjects receive special emphasis.

A General Intelligence

As a group MS patients have IQ's within the normal range when examined cross sectionally and when premorbid IQ is inferred from educational and employment records. However, this broad generalisation risks overlooking significant, albeit mild degrees of deterioration. Evidence of decline in IQ accrues from studies comparing current IQ measures with estimates of premorbid intelligence obtained from reading tests purported to be resistant to deterioration and from the few available longitudinal studies. Using the first approach, Ron et al. (1991) obtained an estimate of premorbid IQ using one such reading test in 58 MS patients and a matched sample of disabled control subjects having an array of disorders without brain involvement. When these values were compared to current IQ scores based on a shortened version of the WAIS, the MS patients exhibited a significantly greater decline than the controls. Longitudinal data from earlier studies are however equivocal, both supporting (Canter, 1952) and refuting (Fink and Houser, 1966) this view.

A decline in motor skills is unlikely to fully account for the fall in IQ noted by Ron et al. (1991) and Canter (1952), for there is little doubt that deficits in memory, abstracting ability and numerous other cognitive functions exert a deleterious effect on the verbal component of IQ usually measured in these studies.

B Memory impairment

The most comprehensively studied aspect of cognition to date has been memory (Rao et al. 1984; Beatty et al. 1988; Litvan et al. 1988b). Patients with MS have impairment in memory compared to normal control subjects (Beatty and Gange, 1977; Rao et al. 1984), physically disabled but non-brain damaged patients (Staples and Lincoln, 1979; Ron et al. 1991) and psychiatric patients (Jambor, 1969). Evidence of primary (short term) deficits have begun to emerge and could explain some of the well described deficits in secondary (long-term) memory involving both verbal and non-verbal modalities, recall tasks being more adversely affected

than those of recognition (Grafman et al. 1990). The latter finding suggests that difficulties may not lie with encoding new information, but with retrieval processes.

Memory difficulties may begin early in the disease process. Using a cohort, the majority of whom had MS of less than 5 years duration, Grant et al. (1984) noted disturbances in delayed recall which were associated with disease exacerbations. This finding was confirmed by Lyon-Caen et al. (1986) who found that almost two thirds of a sample with MS of less than 2 years duration had deficits on the Wechsler Memory Scale when compared to a matched control group with other neurological disorders. Problems were experienced with information presented both verbally and visually and could not be accounted for by the presence of depressed mood. Although common in MS, low mood does not appear to significantly affect memory ability. Schiffer and Caine (1991) addressed this specific issue by undertaking psychometric testing while MS patients were depressed and then retesting them after they had become euthymic, on average 7 months later. While they noted an improvement in verbal memory tests that did not reach statistical significance, the small sample size (n=11) together with difficulties in controlling for the effects of practice make interpretation of these results problematic.

MS patients also show dysfunction in metamemory (an individual's knowledge about his/her own memory) and are therefore likely to under report symptoms of memory loss (Beatty and Monson, 1991). The figure of 40% quoted by Rao et al. (1984) for subjects with MS and subjective complaints of memory impairment is therefore liable to be an underestimate.

However, the situation regarding MS patients who spontaneously complain of subjective memory impairment differs from that noted with metamemory. Evidence suggests such complaints are associated with depression rather than psychometric evidence of memory dysfunction (Fisher, 1989), a situation analogous to that in patients positive for the human immunodeficiency virus (Wilkins et al. 1991). Fisher (1989) also demonstrated that relatives opinions as to the cognitive and

everyday difficulties experienced by patients were more accurate than those expressed by the patients themselves, a view confirmed by Rao et al. (1991b). The extent of frontal lobe involvement in MS patients (Taylor, 1990) may account for this discrepancy.

C Abstracting Ability

A variety of tests have been employed to assess abstracting ability such as the Grassi Block Substitution Test, the Halsteid Category Test and the Wisconsin Card Sort Test. Results have shown MS patients have mild (Reitan et al. 1971) or more marked (Rao et al. 1984; Heaton et al. 1985) deficits in relation to healthy control subjects. Their performance is also inferior to those of subjects with physical illness sparing the brain (Parsons et al. 1957) and approximates those of other brain damaged patients (Ross and Reitan, 1955; Goldstein and Shelley, 1974). In addition, Rao et al. (1987) using the Wisconsin Card Sort Test demonstrated greater deficits in patients with chronic-progressive as opposed to relapsing-remitting MS.

D Attention

Deficits in both auditory and visual attention have been found in CIL patients (optic neuritis, brain stem and spinal cord syndromes) (Callanan et al. 1989) compared to disabled patients without brain involvement. In turn, patients with definite MS have greater visual attention deficits relative to CIL patients (Ron et al. 1991). These findings apart, the area of attention has been relatively unexplored in MS research to date, a fact acknowledged by the cognitive study group of the National MS Society (New York)(Peyser et al. 1990) who have recommended the inclusion of 4 attention tests (Symbol-Digit Modality Test, Paired Auditory Serial Addition Task, Stroop and Auditory Trails A) in future batteries.

The exploration of attention is an important part of this study and to set the problem in the appropriate context, a discussion of the various neural networks involved in the process of directed attention now follows.

An attempt at cerebral localisation of function can make use of 3 different approaches. The centrist approach states that complex functions may be localised to specific cortical areas that are exclusively devoted to that function. At the other end of the spectrum is the concept of cerebral equipotentiality, which minimises the role of such centres and assumes that complex function is widely represented in cortex. The third and intermediate approach implies the presence of widespread neural networks in which complex function is considered in terms of several component processes, each of which has a distinct localisation that is richly interconnected with other sites subserving that particular function. Each of these approaches to localisation may have validity according to the function considered, with evidence from studies in monkeys and humans suggest that directed attention is organised according to the network approach (Mesulam, 1981).

A network for spatially directed attention

Attention refers to a subjects ability to attend to a specific stimulus without being distracted by extraneous environmental stimuli while vigilance describes the ability to sustain attention over an extended period of time (Strub and Black, 1980). Attentional selectivity is a necessary system limitation imposed when the processing resources/capacity of the brain become insufficient. The attention system is independent from data processing systems (Posner and Petersen, 1990) and is carried out by a separate neural network.

In cognition, unattended processing of sensory stimuli is called "automatic" to distinguish it from the special processing that becomes available with attention. In automatic processing, searching can take place in parallel without much effect from distracters. However, when a target is defined in terms of certain attributes and

distracters incorporated into the background, the search becomes slow, attention demanding and serial (Duncan and Humphreys, 1989).

Four distinct contributions to the overall organisation of directed attention have been identified, namely sensory association, motor, limbic and reticular, all richly interconnected. Attention is thus a balance between ascending (reticular-cortical) activation and cortical (cortico-reticular) modulation, the limbic system adding emotional importance to the object of attention and conscious voluntary effort being supplied by the frontal lobes (Mesulam, 1981).

i Sensory representation

A pivotal cortical area in integrating sensory input is the dorsolateral portion of the posterior parietal cortex. However, sensory afferents must first be processed in other cortical areas before reaching here. The initial cortical relay for the 3 major sensory modalities occurs in the supratemporal plane (auditory), occipital lobe (visual) and postcentral gyrus (somatosensory). These primary sensory areas connect to surrounding **unimodal** association areas; auditory cortex to superior temporal gyrus, visual cortex to peristriate and inferotemporal cortex and somatosensory cortex to the superior parietal lobule. Connections from more than one type of **unimodal** area then converge within cortical areas designated **polymodal**, eg. superior temporal sulcus. The dorsolateral parietal area therefore receives inputs not from primary sensory cortex and unimodal association areas, but from the polymodal areas and only after sensory information has been extensively processed. This area thus contains an elaborate sensory representation of extrapersonal space, a prerequisite for distributing attention.

ii Motor representation

The frontal cortex, particularly the frontal eye fields (Brodman area 8) and surrounding regions (Brodman area 6) assist in efferent integration that initiates or inhibits motor mechanisms involved in attentive behaviour. Damage to this area

results in neglect encompassing auditory, visual and tactile stimuli and manifests as a failure to orientate, manipulate and explore perceptual representations.

The dichotomy between sensory and motor components is not however complete. Some sensory representation occurs in frontal cortex and vice versa, an arrangement shown to improve functional efficiency (Mesulam, 1981).

iii Cingulate region.

The cingulate region (Brodman areas 23-24) has extensive connections with limbic structures (i.e. hippocampal formation, presubiculum, amygdala) in addition to polymodal association areas, and therefore assists in limbic integration within the attention network. It gives motivational relevance to sensory events which may then receive more extensive representation in the dorsolateral parietal cortex, thereby enhancing activation of frontal mechanisms for orienting, reaching and fixating.

In addition to the above 3 cortical areas, other subcortical structures form an integral part of the network. In the case of visual directed attention, the superior colliculus, striatum and thalamic pulvinar nucleus are all functionally important. The superior colliculus is more closely associated with the frontal eye fields while the pulvinar nucleus and striatum are allied to all 3 cortical components (Mesulam, 1990).

iv Reticular structures

An intact reticular formation is essential to maintain arousal without which attention (and vigilance) becomes impaired. In the monkey reticular input to cortical areas involved in attention originates in the intralaminar thalamic nuclei, the locus coeruleus and the midline raphe nuclei and similar connections are thought to exist in the human brain.

The network described above is relevant for spatially directed attention. The distribution of object specific attention requires additional components, eg. for visual attention, association areas in the temporal lobes, in particular the inferior temporal cortex are functionally important. Neurones here are concerned with the features of an object such as colour, orientation, texture and shape (Wise and Demisone, 1988).

A single lesion occurring anywhere within a particular network may therefore disrupt it's functional integrity through a process of disconnection (Geschwind, 1959). As MS is predominantly a white matter disease, lesions are unlikely to impinge directly on the cortical areas mentioned above, but rather disrupt the many connections between them. The deficits that result are not of seeing, hearing, feeling or moving, but of looking, listening, touching and exploring (Mesulam, 1981).

3 Cognition and clinical features of MS

A Physical disability

The study of the relationship between cognition and physical disability has yielded contradictory findings (Heaton et al. 1985; Rao et al. 1991a). In a study designed specifically to address this relationship, Marsh (1980) found that disability as measured by the Kurtzke scale (KDS)(1970) correlated only with duration of illness but not with either verbal, performance or full scale IQ on the WAIS. She did however note that scores on performance subtests with a large motor component were lower than the verbal subsets. A failure to find any association between KDS (Kurtzke, 1970) scores and cognitive dysfunction has also been reported by others (Peyser et al. 1980; Rao et al. 1985; Lyon-Caen et al. 1986). Alternative procedures for assessing physical disability such as the Activities of Daily Living Test (Howarth and Hollings, 1979) have given similar results (Ron et al. 1991).

There are however exceptions to the above (Huber et al. 1987; Stenager et al. 1989). Indirect support has also come from Beatty and Gange (1977) who used 5 tests of motor impairment and found a correlation with memory deficits while an epidemiological study investigating the frequency, patterns and predictors of cognitive dysfunction (Rao et al. 1991a), found a weak albeit significant correlation with disability.

Failure to find an association may be an artefact of research methodology that relies on a biased rating assessment procedure. Thus, while cognitive deficits are attributable to plaques in the cerebral hemisphere white matter, physical disability as measured by currently used rating scales such as the KDS (Kurtzke, 1970), predominantly reflects the presence of lesions in the spinal cord, posterior fossa and cerebellum, causing mainly motor deficits.

A further problem in interpreting these data is that physical disability is often linked to variables such as age, exacerbation, disease duration and disease course. Thus, more disabled patients have tended to be older with disease of longer duration and a chronic-progressive course. To separate these potentially confounding effects, Beatty et al. (1990) undertook a longitudinal study whereby disease type was only assigned after a two year period during which patients underwent neurological examination every 6 months. Using multiple regression techniques, they failed to find any demographic or clinical predictors of cognitive performance.

B Duration of illness

The majority of studies have failed to find an association between disease duration and cognitive dysfunction (Ivnik, 1978a; Rao et al. 1984; Rao et al. 1985; Rao et al. 1991a). Marsh (1980), although finding a link between disease duration and disability, found that neither correlated with cognition. The reason for this can be traced to the fact that patients with illnesses of similar durations may differ greatly with respect to disease activity, ranging from quiescent ("benign") to rapidly

progressive. Controlling for confounding effects such as age and disease course, Beatty et al. (1990) also failed to demonstrate such an relationship.

Two studies have however reported different results. Ron et al. (1991) found a positive association with a modest correlation co-efficient (r=0.30), albeit significant at a 1% level while Grant et al. (1984) showed that disturbances in short term memory, learning and recall of verbal and non-verbal information were associated with the number of years of "active disease". They defined this concept as "number of years in which the patient reported at least one weeks duration of symptoms", which is open to criticism as MRI studies have shown that clinical relapses do not often mirror the development of new brain lesions, the latter occurring 7 times more often (Thompson et al. 1992)

C Disease course

There is some evidence to suggest that cognitive deficits appear to be more severe in patients with chronic-progressive MS than in those who follow a relapsing-remitting course, although not all studies are in agreement. Heaton et al. (1985) studied 100 patients with either relapsing-remitting (RR)(n=57) or chronic-progressive (CP)(n=43) MS who were consecutive admissions to a neurological ward and a similar number of healthy controls. Patients were clinically stable at the time of testing. Both MS groups were more cognitively impaired than the controls and the CP patients were in turn significantly more impaired than the RR group on all measures (memory, abstracting ability, visuospatial functions, attention) except the WAIS verbal IQ. These differences were not related to greater sensory or motor impairment in the CP group and persisted when the duration of disease (longer in the CP group) was controlled for.

These results were confirmed by Rao et al. (1987) who compared the performances of RR and CP patients and a control group of back pain sufferers using the Wisconsin Card Sort Test. Whilst no differences were apparent between the RR group and control subjects, CP patients differed from both in terms of the number

of perseverative errors and fewer categories achieved. A stepwise regression analysis suggested that these differences were independent of physical disability or disease duration.

Indirect evidence supporting disease course as an important predictor of cognitive dysfunction has also come from studies that confined themselves to one of the subgroups. Thus, in a study of RR patients, Anzola et al. 1990 reported very mild overall cognitive impairment while Beatty et al. (1989) observed that cognitive deficits in their RR patients were less severe than those previously documented in subjects with a CP course. Studies limited to CP patients have reported that three quarters were impaired on tests of rapid information processing speed (Beatty et al. 1988) and that memory was significantly compromised in over half (Rao et al. 1984).

Assumptions that the course of MS runs true once established have been questioned by a recent study demonstrating clinical course may be more variable than previously acknowledged. In a 1 to 5 year follow-up study of 254 patients with definite MS (mean 2.6 years), Goodkin et al. (1989) found that approximately a third of CP patients became stable while slightly less (20%) RR patients deteriorated to a CP course. It should be noted however that no patients reverted from a CP to a RR course. Nevertheless, such data questions whether a clear cut relationship between disease course and cognitive impairment exists. Beatty et al. (1990), using the same patient data base reported on by Goodkind and colleagues, assigned disease course to patients only after a minimum two years observation. Forty two and 43 patients with RR and CP MS respectively were then selected to undergo psychometric assessment. Using multiple regression techniques, disease course was an excellent predictor of physical disability (accounting for greater than 50% of the variance), but no variable was found to be a significant predictor of cognitive dysfunction. Failure to find such an association has also been noted in a recent community based study (Rao et al. 1991a).

4 The natural history of cognitive change in MS

Rapidly progressive dementia in which patients experienced profound physical and mental deterioration over the course of a few months has been described (Bergin, 1957). This clinical picture is however highly unusual and for the majority of patients cognitive impairment occurs over a period of years.

It's onset may nevertheless take place soon after the disease begins, often predating the development of the multifocal neurological symptoms. This conclusion has been reached from studies of patients with clinically isolated lesions (CIL) of the type seen in MS, the majority of whom will develop MS in time (Francis et al. 1987; Miller et al. 1989a). Thus, Callanan et al. (1989) noted deficits in auditory and visual attention in 48 patients with optic neuritis, brain stem and spinal cord syndromes, compared to a matched, disabled control group with illnesses sparing the brain. No differences were apparent on other aspects of cognition tested i.e. decline in IQ, abstracting ability, visual and verbal recognition memory and naming ability. However, evidence that early deficits may extend beyond the attention system has come from Lyon-Caen et al. (1986) who documented memory deficits in a small number of patients with optic neuritis and MS of less than 2 years duration.

Two main approaches have been adopted to study the natural history of cognitive function in MS. The first has been cross sectional with samples stratified for duration of illness, while the second and preferred method has been to undertake longitudinal studies, of which to date there has been very few.

A Cross sectional studies

Cross sectional studies have found little evidence to support a progression of deficits. Ivnik (1978a) studied 36 patients with MS divided into triads on the basis of the number of years they had MS symptoms (i.e. 1-5; 6-10 and >10 years). The three groups were matched for sex, education and age of onset. No cognitive

differences were found between the three groups and only in tests dependent on intact tactile perception did the group with a longer duration perform more poorly. In a similar study, Halligan et al. (1988) divided 60 MS patients into 3 equal groups with different durations of illness (<5; 5-15 and >15 years) and found that a mild decline in abstracting and memory functions was present in the group with the longest duration of illness. However, other cognitive functions were intact and occupational or social functioning appeared unaffected.

B Longitudinal studies

This method is to be preferred and although studies are few in number, they have given a clearer picture concerning cognitive change. Significant deterioration over time was described in an early longitudinal study by Canter (1951). He studied a group of 23 servicemen whose intellectual ability had been tested using the Army General Classification Test, when they first joined the army. The subjects had subsequently developed MS and when retested using the same test 4 years after their original assessment, showed a drop of 13.5 points. In a second study Canter, (1951) compared the test-retest IQ (with a 6 months interval) of 47 MS patients and 37 control subjects and noted that whereas the control group improved their performance (probably as a result of practice effects), the MS group showed a slight deterioration in scores. Earlier studies have also pointed towards a differential progression of cognitive deficits, with preservation of verbal skills being documented by Fink and Houser (1966). Ivnik (1978b), while noting that purely cognitive skills remained relatively unchanged after an interval of approximately three years, found motor skills had in some cases deteriorated.

These studies made no mention of whether patients were in exacerbation at the time of testing, used a limited psychometric battery and failed to control for the possible effects of medication, disease course and mental state. Nevertheless, recent studies with improved methodology have generally confirmed these early findings. Filley et al. (1990) undertook a follow-up of the sample originally described by Heaton et al. (1985). Patient were divided into stable relapsing-remitting (n=18),

exacerbating relapsing-remitting (n=18) and chronic-progressive (n=10). The mean duration of follow-up for all patients was 19 months, although the time between assessments was significantly longer for the stable than the exacerbating RR group. All patients were tested using the expanded Halsted-Reitan battery which comprises cognitive, cognitive/sensorimotor and sensorimotor tests. No deterioration was noted in either the exacerbating RR or CP groups on any of the purely cognitive measures, but the CP group had deteriorated significantly more than the stable RR on two of 15 cognitive/sensorimotor tests, both indicative of information processing speed. In the sensorimotor category, performance in the CP group had declined significantly more than both RR groups on 3 out of 5 indices. Thus, limiting the results to purely cognitive measures, virtually no decline had taken place. Unfortunately, the short follow-up period, a high sample attrition rate (only 46% of the sample were followed-up) and small sample size detract from the value of the study.

In a more comprehensive study, Jennekens-Schinkel et al. (1990) completed a 4 year follow-up of 33 patients (85% of the original sample) and 18 healthy control subjects using a wide array of cognitive tasks. Over three quarters of the MS sample had shown no decline at follow-up. Cognitive change was not related to disease course and when it occurred was characterised by considerable individual variation. Longitudinal deterioration in relation to healthy control subjects was most noticeable on motor related tasks such as finger tapping, but also occurred for immediate recall of a visually presented word list. The authors concluded that the majority of MS patients were functioning at their estimated premorbid level both at their initial and follow-up assessments.

Summary

1. Cognitive impairment affects a substantial number of patients with MS, the prevalence figures varying according to the sample studied. Documenting these deficits is important because they exert a detrimental effect on patients daily occupational and social functioning.

2. Cognitive deficits differ from those in diseases primarily involving a cortical substrate such as Alzheimer's and include abnormalities in attention, memory, abstracting ability and overall speed information of processing.

3. Attentional deficits in MS have not been well studied to date. This is an important omission, given the fact that the numerous lesions scattered throughout the cerebral white matter are likely to disconnect the neural network subserving attention.

4. Cognitive dysfunction does not appear related to duration of illness nor degree of physical ability, while the relationship with disease course is equivocal.

5. The natural history of cognitive change is characterised by extensive individual variation and medium term follow-up results suggest that only in a minority of patients does further decline occur.

CHAPTER 4.

Imaging correlates of neurobehavioural dysfunction

This section reviews evidence from structural and functional imaging studies and their attempts at correlating observed abnormalities with evidence of both cognitive and psychiatric dysfunction. The emphasis is on Magnetic Resonance Imaging, as this technique has great sensitivity in visualising MS plaques in the brain. Comparisons between Magnetic Resonance Imaging (MRI) and Computerised Axial Tomography (CT) in MS have shown that the former detects almost 10x as many lesion (Young et al. 1981) and in cases where the diagnosis cannot be made with clinical criteria alone, MRI increases the diagnostic yield over CT by between 3-5 fold (Paty et al. 1988). Although offering potentially exciting possibilities, Magnetic Resonance Spectroscopy in MS has yet to be utilised in the search for neurobehavioural correlates.

1 Computerised Axial Tomography

Abnormalities on Computerised Axial Tomography (CT) in the brains of patients with MS were first reported in the mid 1970's (Warren et al. 1976; Glydensted, 1976). Although high resolution scanners, contrast enhancement and delayed scanning have all led to greater sensitivity in detecting MS lesions (Spiegel et al., 1985), the yield is still low compared to that of MRI (Young et al. 1981). It is nevertheless of value in demonstrating sulcal widening and ventricular dilatation, usually present in well established, severe disease. Depending on the sample under study, these abnormalities have been found in 20 to 60% of MS subjects (Rao, 1990).

Given the lack of sensitivity of CT in detecting specific MS pathology, it is not surprising that correlations between imaging and cognitive measurements have been weak. No study has attempted to correlate the extent of lesion involvement in the brain with cognitive/psychiatric abnormalities, preferring to concentrate on parameters of cerebral atrophy instead. Brooks et al. (1984) estimated intellectual decline as the discrepancy between present full scale IQ (WAIS) and a premorbid estimate based on reading test scores. They found in their 13 patients, a strong association between IQ deficits and generalised cerebral atrophy. Rabins et al. (1986) similarly noted an inverse relationship between ventricular-brain ratio (VBR) and scores on the Mini Mental State Examination, a coarse estimate of cognitive impairment. In addition, they found that euphoria was associated with increased ventricular enlargement and the presence of brain lesions. The significantly higher depression scores in their MS group compared to matched control subjects with spinal cord injury was also attributed to the presence of brain lesions.

In a larger study of CT and cognition, Rao et al. (1985) investigated 47 patients with chronic-progressive MS on tests of verbal and visual spatial learning and memory. Sulcal measurements were discarded as unreliable and attention focused on the ventricular system. Variable degrees of ventriculomegaly were found in 60% of subjects and correlated with indices of cognitive decline. In particular, third ventricular width was the most sensitive CT indicator of intellectual and memory deficits. However, subsequent re-analysis of their data using improved measurement techniques failed to replicate this finding and led Rao (1990) to conclude that generalised ventricular enlargement and not just third was associated with cognitive decline.

2 Magnetic Resonance Imaging

Monographs on magnetic resonance imaging (MRI) are available (Young, 1984; Andrew et al. 1990) and a detailed description of the principles and techniques falls

outside the scope of this thesis. Only a brief explanation is included to set in place the clinico-MRI correlations that follow.

Technique

MRI is a technique whereby images of objects such as the brain, are created using nuclear magnetic resonance. In body tissues, before the application of a magnetic field, the magnetic moments of the protons (^1H) are randomly aligned and have zero net magnetisation (M_o). When an external field is applied (viz. produced by the magnet of the MRI imaging system), the individual magnetic moments align parallel or anti-parallel with the applied magnetic field. There are slightly more parallel than anti-parallel protons resulting in a slight net magnetisation.

In a static magnetic field, the energy required to stimulate or excite the low energy parallel protons to higher energy anti-parallel protons is supplied by electromagnetic radiofrequency (RF) waves. When radio waves of the right frequency are passed through the sample, some parallel protons will absorb energy and be excited to a higher energy state in the anti-parallel direction. The amount of energy required to flip a proton from a parallel to anti-parallel orientation (and thus a higher energy state) is dependent on the strength of the magnetic field. The high energy protons are then observed as they return (relax) to their low energy state. In doing so, they emit electromagnetic energy of the same frequency as the RF source and which is detected using a sensitive radio receiver. This is the signal that eventually generates the image to be viewed. The size or magnitude of the signal is proportional to the number of protons (proton density) in the tissue under study (Young et al. 1984).

The procedure is confined to those nuclei that possess an odd number of either protons, neutrons or both, eg. ^1H, ^{13}C, ^{19}F, ^{23}Na and ^{31}P, although imaging is usually carried out on ^1H nuclei (protons) because of their high concentration (principally in water) and high nuclear magnetic resonance sensitivity.

Relaxation times

Three principle properties of a substance can be measured, namely density of nuclear species and 2 relaxation times (T_1 and T_2). "Relaxation Time" refers to the time required for the net tissue magnetisation vectors to come to equilibrium in a static external magnetic field. In the absence of an applied radiofrequency, transverse magnetisation decays exponentially towards zero with a time constant T_2 and the longitudinal magnetisation returns exponentially towards the equilibrium value M_o with a characteristic time constant T_1. Relaxation times supply valuable information concerning the physical state of a sample and detect pathological changes in tissues that appear macroscopically normal. Their values increase as the amount of free water in the sample increases, as in oedema.

A Magnetic Resonance Imaging in MS

Magnetic Resonance Imaging (MRI) is a highly sensitive technique for demonstrating brain lesions in patients with MS. Abnormalities are present in virtually all patients with clinically definite MS (Miller et al. 1988a), the position of MRI lesions correlating with plaques seen at post mortem (Ormerod et al. 1987). The characteristic pattern is one of multifocal white matter lesions, the majority situated adjacent to the lateral ventricles.

Prolonged T_1 and T_2 relaxation times in MS patients compared to healthy controls (Ormerod et al. 1986) or those with systemic lupus erythematosus (Miller et al. 1989b) have been noted, while CIL patients tend to occupy an intermediate position between MS patients and healthy controls (Ormerod et al. 1986). The reasons for these changes are not entirely clear, but probably reflect the presence of microscopic abnormalities, such as perivascular inflammation, in the normal appearing white matter (Allen et al. 1981).

Although MRI has proved invaluable in providing a window to the brain in MS, it is not without limitations. Small demyelinating lesions may escape detection because of restrictions on spatial resolution. On an individual basis, there is difficulty distinguishing MS plaques from lesions in patients with vascular disease (Ormerod et al. 1984) and in those with vasculitides, namely Systemic Lupus Erythematosus and Behcet's disease amongst others (Miller et al. 1987). In addition MRI cannot differentiate high intensity signals occasionally seen in healthy individuals (Hachinski et al. 1987; George et al. 1986) from MS plaques.

The lack of unwanted effects has made serial studies with MRI possible (Isaac et al. 1988; Miller et al. 1988a; Willoughby et al. 1989). Together with the use of contrast compounds such as Gadolinium-DTPA (Gd-DTPA), new light has been shed on the pathogenesis of lesion formation, for the presence of enhancement signifies a breakdown of the blood-brain barrier (BBB)(Hawkins et al. 1990) and is a consistent finding in new lesions (Miller et al. 1988a; Thompson et al. 1989)(*fig. 1*). Serial MRI studies with Gd-DTPA have also demonstrated that disruption of the BBB can precede other MRI abnormalities and clinical evidence of a new lesion (Kermode et al. 1990a+b). In over two thirds of patients, the duration of enhancement is less than 6 weeks (Miller et al. 1988a; Thompson et al. 1991).

The progressive nature of brain involvement is further illustrated by the changes in lesion load over time. While approximately 60% of CIL patients have lesions on MRI at initial presentation (Ormerod et al. 1987), this progresses to virtually 100% by the time they develop definite MS (Miller et al. 1992). Fluctuations in both lesion size and number, particularly in those with a secondary progressive type of illness has been documented (Thompson et al. 1991). The dynamic pattern of the lesions explains the poor correlation between it and the degree of physical disability (Isaac et al. 1988; Thompson et al. 1991) reported in many studies.

B Relationship between MRI and cognitive abnormalities

The strength of the association between cognitive dysfunction and MRI lesion load is influenced by the method used to quantify lesions. Two approaches have been followed, the use of rating scales to estimate the size and number of lesions and direct quantification of each lesion area/volume using computerised methods. The majority of early studies have relied on the former method which is considered inferior as it is prone to human error and produces a range of artificially restricted values (Rao, 1990).

Direct quantification however is not without problems. In this method, individual brain slices are displayed on a computer monitor and using a cursor, their outline manually traced by the rater. The software then calculates the total number of pixels included within the trace, which can be converted to an area (cm^2) or volume (cm^3) measurement. However, partial volume effects often make it difficult to distinguish where a lesion ends and healthy brain begins, thereby lowering inter and intra rater reliability. With improvements in software capabilities, it is now possible for direct quantification of lesions to be undertaken solely by computer without introducing human error (Wicks et al. 1992). The validity of such techniques have not however been firmly established and their use in searching for cognitive correlates has not been attempted.

i Lesion load and cognitive dysfunction.

The computerised method of detecting total lesion area has produced more significant correlations with cognitive dysfunction than a rating scale approach, although results remain modest. The reason probably relates to the difficulty MRI has in clearly delineating pathological lesions from normal brain and the problem of deciding which lesions are relevant in terms of their localisation and ability to interrupt associated neural networks. In addition, other abnormalities such as T_1 and T_2 relaxation times may be present in the macroscopically normal appearing white matter, but would not be detected on routine scanning. While an association

between abnormal relaxation times and cognitive dysfunction has not been investigated in MS, such a relationship has been found in Alzheimer's disease (Besson et al. 1990).

Using a rating scale approach for MRI assessment, most studies have reported positive, albeit weakly significant associations between total lesion score and global estimates of cognitive dysfunction. Thus, Medaer et al. (1987) found that MRI lesion score could differentiate between MS patients without and those with either moderate or severe cognitive deterioration. Total lesion scores could not however distinguish between moderate and severe cognitive impairment, which may have reflected the arbitrary way in which the degree of impairment was defined or the limitations of the method of lesion quantification. Similarly, Franklin et al. (1988) in a study of 60 patients with chronic-progressive MS found a modest albeit significant correlation between total brain lesion load and a score representing overall cognitive ability, while in a sample of patients with mild physical disability, a significantly higher periventricular lesion score was present in patients with cognitive impairment as opposed to those without (Pozzilli et al. 1991). Similarly, Ron et al. (1991) found that patients with clinically definite MS had more extensive MRI and cognitive deficits than those with clinically isolated lesions and total lesion area correlated with an estimate of global cognitive dysfunction.

A minority of studies on the other hand have failed to find such an association. Huber et al. (1987) studied 32 patients with clinically definite MS using a battery of psychometric tests of language, memory, praxic and visuospatial skills. Dementia was defined as impairment on any 3 areas tested and was present in approximately a quarter of subjects. Comparing demented to non-demented subjects revealed no differences with respect to number or distribution of MRI lesions or generalised cerebral atrophy. However, atrophy of the corpus callosum was significantly more extensive in the dementia group. The failure of Anzola et al. (1989) to detect a significant correlation may reflect a serious flaw in their methodology in that some patients were scanned as long as 6 months prior to psychometric testing.

In addition to investigating global associations, some studies have also looked at correlations between total lesion load and specific cognitive indices. Results have been mixed with associations for (Callanan et al. 1989; Ron et al. 1991) and against (Franklin et al. 1988) being reported.

The yield of significant, positive correlations is however considerably strengthened when direct computerised quantification of total brain lesion area is used. In the only study of its kind reported to date, Rao et al. (1989b) used a comprehensive battery of psychometric tests covering a range of parameters that minimised reliance on visual acuity and motor dexterity. In their analysis they also controlled for age and education, something others (Huber et al. 1987; Franklin et al. 1988) had failed to do. In addition to directly measuring total lesion area, a mid-sagittal slice was used to visualise the corpus callosum, the outline traced on a computer console and the area obtained using the necessary software.

An association was sought between 34 different cognitive indices and 3 MRI parameters, namely total lesion area, size of corpus callosum and ventricular-brain ratio. The latter was not associated with a single cognitive index, but total lesion area correlated significantly with 25 and corpus callosum atrophy with 8 cognitive measures respectively. The authors concluded that when total lesion area exceeded a particular cut-off point, the probability of cognitive impairment was high.

ii Localised brain abnormalities and cognitive dysfunction

Attempts at linking pathology in specific anatomical areas and cognitive deficits have so far been confined to studies of the corpus callosum and a number of positive findings have already emerged. Both Huber et al. (1987) and Rao et al. (1989c) noted an association between corpus callosum atrophy and cognitive dysfunction, the latter finding deficits with dichotically presented verbal stimuli and postulating that this may account for the difficulties experienced by some MS patients on tests of laterality and sustained attention and vigilance. In addition, speed of information processing and rapid problem solving ability has also been

found to correlate with corpus callosum size (Rao et al. 1989b). While these 3 studies have all provided convincing evidence linking certain specific cognitive deficits to a reduction in the size of the corpus callosum, Pozzilli et al. (1991) using similar quantification techniques found no correlation with any psychometric variable. The discrepancy between their finding and that of Rao and colleagues may be due to differences in sample composition, the former excluding any patients with chronic-progressive MS whilst the latter included patients with a wider range of disability and variable disease course.

The frequency and severity with which the corpus callosum is affected in MS has not been systematically investigated, although post-mortem studies suggest involvement is common and occasionally extensive (Barnard and Triggs, 1974). However, abnormalities seldom occur in isolation and attributing particular deficits to a single anatomical area is not without risk.

iii Longitudinal studies

There are no longitudinal studies of MRI and cognitive abnormalities in MS, but indirect evidence of change over time can be gleaned from a study comparing patients with MS, clinically isolated lesions and disabling illnesses sparing the brain (Ron et al. 1991). MS patients were more cognitively impaired than those with CIL who were in turn more impaired than the physically disabled control group. Co-efficients of concordance between total lesion score and individual/global cognitive indices were stronger in the MS as opposed to the CIL group which suggests that deterioration in cognitive ability accompanies the decline from clinically isolated lesion to definite MS status. It is however difficult to infer causality from cross sectional data and longitudinal studies are needed to address this question.

C Relationship between MRI and psychiatric abnormalities

This area has received relatively little attention in comparison with cognition. Those MRI studies that have looked for correlations between brain lesion score and lesion localisation on the one hand and psychopathology on the other have generally found a weaker association than for cognition. This contrast with findings from other neuropsychiatric disorders such as stroke, where a putative association between depression and left sided, anterior lesions has been reported (Robinson et al. 1983). The inability to produce similar conclusions in MS may be related to differences in disease characteristics, namely the acute onset of stroke with a well demarcated brain lesion as opposed to the often insidious onset, chronic course and diffuse white matter involvement of MS.

The firmest evidence implicating specific brain areas in the pathogenesis of psychiatric disorders has come from Honer et al. (1987) using direct, computerised lesion detection. They compared the MRI findings in 8 patients with MS and abnormal mental states with those of 8 control patients matched for age, sex, duration and disability, but without psychiatric impairment. DSM-111 (American Psychiatric Association, 1980) diagnoses were major depression (3), bipolar affective disorder (2), organic hallucinosis (1), organic affective syndrome (1) and organic personality disorder (1). Although the two groups did not differ with respect to total lesion load, the psychiatric group had significantly more temporal lobe involvement.

Similarly, Reischies et al. (1988) in a study of 46 patients with MS found that periventricular and discrete frontal lesions were associated with psychopathology, but the absence of a standardised psychiatric assessment limits the value of this study.

These positive findings are however offset by a number of negative ones. Logsdail et al. (1988) found few psychiatric abnormalities in a sample of 76 subjects with clinically isolated lesions and when present, were equally common in those controls

without brain lesions. Social factors appeared more important in the pathogenesis of psychiatric morbidity, a similar conclusion being reached by the same research group (Ron et al. 1989) in a sample of 116 patients with definite MS. Although psychiatric morbidity was a lot higher than in the CIL sample, no relationship was found between MRI total lesion area and global measures of psychiatric impairment.

An absence of any association has also been reported by those rating exclusively depressive symptoms (Huber et al. 1987; Anzola et al. 1989). The equivocal findings to date thus highlight the multifactorial nature of mental illness in MS, which by implication will always be likely to produce at best, modest imaging correlates.

There are no reports in the imaging literature of studies specifically addressing the question of psychosis and MS. Tentative evidence from a study of psychiatric morbidity in MS (Ron et al. 1989) suggested that flattening of affect, thought disorder and delusions were more common in MS patients with more severe temporo-parietal involvement on MRI, but numbers were too small to reach statistical significance. This would be in keeping with data from other sources implicating the presence of limbic structures in the pathogenesis of schizophrenia with (Torrey and Petersen, 1974) and without (Suddath et al. 1990) evidence of coarse brain disease.

3 Positron Emission Tomography and Single Photon Emission Computerised Tomography

In comparison with CT and MRI, the limited ability of positron emission tomography (PET) to localise areas of brain dysfunction has curtailed it's use in MS. The role of functional imaging in MS has therefore largely been to demonstrate evidence of widespread cerebral blood flow and metabolic

abnormalities, and this it has successfully achieved. Given this fact, the positive association between global estimates of cognitive impairment and cerebral involvement becomes easier to understand.

In the most comprehensive of 3 published studies, Brooks et al. (1984) compared 15 MS subjects in remission to 13 normal controls, looking at regional cerebral oxygen utilisation, oxygen extraction, blood flow and blood volume. Significant global reductions in cerebral oxygen utilisation and blood flow were found both in the white and cortical grey matter of the MS patients. These deficits were associated with cortical atrophy on CT and evidence of intellectual decline as assessed by the Wechsler Adult Intelligence Scale. No regional abnormalities were found and they failed to find a correlation between the functional abnormalities displayed on PET and either disease duration or severity.

Herscovitch et al. (1984) in a single case report of a 24 year old patient with aphasia, apraxia, left sided hemiparesis and sensory changes, demonstrated a lesion in the right cerebral white matter on CT while PET showed a reduction in regional cerebral blood flow (rCBF) in the fronto-parietal cortex superficial to the lesion. Subsequent improvement in rCBF was associated with clinical remission. Although the association between the structural and functional abnormalities would have been improved by MRI as opposed to CT, to date no such study has been undertaken.

In the only published report, Pozzilli et al. (1991) undertook Single Photon Emission Computerised Tomography (SPECT) using 99m (99mTc) hexamethyl-propyleneamine oxime (HMPAO) in a sample of 17 MS patients and 17 matched, healthy control subjects. A ratio of regional to whole brain activity measured by SPECT demonstrated a significant reduction in the frontal lobes and left temporal lobe of the patient sample. Deficits in verbal memory and verbal fluency correlated with a reduction in left temporal 99mTc-HMPAO uptake.

A potentially useful avenue for future exploration is highlighted by the study of Sheremata et al. (1984), who used a word learning activation task in a case control study involving 3 MS subjects and 3 normal matched controls. They found reduced metabolism in both temporal, and to a lesser extent, frontal lobes. Although information was not presented on all brain areas, the authors concluded that their results were indicative of generalised cortical hypometabolism.

Summary

1. The majority of MRI brain studies in MS have demonstrated an association between total lesion load and cognitive impairment (either isolated cognitive indices or an overall index of cognitive impairment).

2. The correlation between localised brain abnormalities and specific cognitive deficits is largely unexplored so far. Atrophy of the corpus callosum, but not an increase in ventricular-brain ratio has been found to correlate significantly with cognitive dysfunction.

3. There is evidence suggesting the association between imaging and cognitive abnormalities begins early in the disease process, but how this progresses over time has yet to be investigated.

4. The poor correlation between physical disability and extent of brain involvement on MRI has raised the possibility that cognitive change may be a more sensitive marker for brain involvement and may reflect lesion fluctuation over time.

5. The relationship between psychiatric symptoms and imaging abnormalities is less robust than that for cognition, reflecting the multifactorial nature of mental illness in MS. A closer association appears to be present between temporal lobe pathology and the presence of delusions/thought disorder.

6. The association between psychiatric/cognitive dysfunction and functional imaging indices has received scant attention, but there is a suggestion that cerebral blood flow/metabolic deficits may be more widespread than structural abnormalities.

SECTION II: The studies

Aims

The overall aim of the thesis was to investigate cognitive and psychiatric dysfunction in MS and their relationship to MRI brain abnormalities. Three of the studies were linked by a further aim, namely to delineate the natural history of change in these three parameters and to explore their inter-relationship. The fourth study utilised MRI to explore a neglected aspect of research, namely the association between MS and psychosis.

Approval was obtained from the Ethics Committee of the National Hospital for Neurology and Neurosurgery, Queen Square for these studies.

CHAPTER 5

STUDY 1. Acute optic neuritis

The aim of this study was to ascertain the prevalence of psychometric deficits in a homogeneous sample of patients with clinically isolated lesions of the type seen in MS, i.e acute optic neuritis (ON). A further aim was to investigate correlations between these deficits and the extent of brain abnormalities discernable on MRI.

Deficits in attention constitute the focus this study as previous results (Callanan et al. 1989) suggested that other cognitive abnormalities such as memory, while characteristic of patients with definite MS, were not impaired in patients with optic neuritis or other clinically isolated lesions.

1 Methodology

A Subjects

i Patients with a first episode of acute, unilateral optic neuritis of less than 5 weeks duration were selected for the study. Those with vision of less than 6/6 in the unaffected eye were excluded as were those with a history of alcohol/drug abuse, head injury leading to loss of consciousness or systemic disease. The sample comprised consecutive referrals to Moorfield's Eye Hospital where all subjects were screened by a neurologist to ensure inclusion criteria were met. In addition to recording demographic details, note was also made of any loss of colour vision and orbital pain. All subjects had a normal neurological examination except for signs of optic neuritis.

ii A group of 36 healthy controls, drawn from friends and relatives of the ON patients and staff from the Institute of Neurology, were used as controls. They were matched as a group to the ON patients with regards age, sex, premorbid IQ

(NART)(*see below*) and number of years of schooling. Patients and controls underwent a battery of psychometric tests presented in the visual and auditory mode, designed largely to detect deficits in attention and speed of information processing. All subjects and controls were tested in the morning to ensure uniformity of test conditions.

A second, separate control group of healthy volunteers (n=30) matched for age and sex were scanned over the same period as the patient group to provide normative data for MRI relaxation times. The validity of these measurements was checked using phantoms which controlled for machine drift over time. This group did not receive psychometric testing.

B Psychometric Assessment

i) The National Adult Reading Test (NART)(Nelson, 1976). This reading test has been shown to be resistant to the effects of cognitive decline and is considered a sensitive index of premorbid IQ. Subjects were required to read aloud 50 words, proceeding in increasing order of difficulty of pronunciation. Failure to pronounce the word correctly was scored as an error and a full scale IQ score was obtained from the number of errors made.

ii) Advanced Raven's Progressive Matrices (Set 1)(Raven, 1958) This test was used to assess reasoning in the visuospatial modality. Raw scores were converted to an age adjusted scaled score with a mean of 10.

iii) The Purdue Pegboard Test (Purdue Research Foundation, 1948) This is a test of manual dexterity. Subjects were instructed to place the pegs in holes with each hand and then both hands simultaneously for periods of 30 seconds. The total number of pegs correctly placed over 90 seconds was taken as the score.

iv) The Stroop Colour-Word Test (Stroop, 1935) A computerised version of this test was used to measure the ability to focus attention on one attribute of a

compound stimulus (the colour in which words are written) and to ignore another competing attribute (the meaning of the word). A *control condition* was established prior to the Stroop test itself, measuring the speed and accuracy of identifying colours. Subjects were thus asked to name the colours of squares shown on the screen and speed of response was recorded. In the *test condition*, the names of colours written in different colours were presented. The subject was asked to say the colour the word was written in and not the colour named by the word. The time to complete this task and the number of errors made were recorded.

v) The Symbol-Digit Modalities Test (SDMT)(Smith, 1968) A computerised version of this test was used whereby 9 different symbols each associated with a number were presented visually to the subject. Nine symbols at a time were shown to the subject in various orders and the subject had to respond by naming the number that corresponded to each symbol according to the original code. This approach minimised a sensorimotor component to the procedure. Eight consecutive trials were administered at a constant time interval and presentation times for symbols and trials were the same for patients and controls. A total time for all 8 trials and a mean time per individual trial were obtained. In addition, the total number of errors was also recorded.

vi) The Paced Auditory Serial Addition Task (PASAT)(Gronwall, 1977). The task requires subjects to perform serial additions and to shift attention from old and no longer relevant items to new items. In the version used here, subjects were required to add 31 pairs of randomised digits presented in an auditory fashion so that each was added to the digit immediately preceding it. Two levels of difficulty were employed, with items being presented at 4 and 2 second intervals. The number of errors for both trials were recorded.

vii) The Paced Visual Serial Addition Task. As above, but items were presented visually on the computer monitor.

viii) Speed of Letter Counting (Willison et al. 1976). The subject was presented

with an A4 size sheet of paper on which a number of capital letter A's were interspersed (in rows) with capital letters B, C, D and E. The time taken to count the number of A's was used as a measure of visual attention.

ix) Auditory Attention Test (Callanan et al. 1989). Subjects were asked to listen to an auditory presentation in which letters of the alphabet in random order were read out at one second intervals. Embedded amongst these letters was the alphabet in the correct order and subjects had to respond by identifying these particular letters. The total number of false positives and omissions was taken to represent a measure of auditory attention.

x) Simple Reaction Time (SRT) This gave an index of basic psychomotor speed. The test comprised 60 trials for each hand. The imperative stimulus to which the subject had to react was the filling of a square either to the left (for the left hand) or the right (for the right hand) of a central blank square on the computer monitor. The subject reacted by either pushing the left or right button on a button box. The right hand responses were completed before proceeding to the left hand ones. Prior to the imperative stimulus, an arrow appeared in the central square pointing in the direction of the square to be filled. The arrow appeared 1.6 seconds, 0.8 seconds or 0.2 seconds before the imperative stimulus respectively, each for 25% of the time. For the remaining 25% the arrow appeared simultaneously with the imperative stimulus. The order of the interval was randomly assigned to prevent the subject anticipating the exact occurrence of the stimulus. The interval between the end of one trial and the appearance of the arrow for the next trial was also randomly assigned between 1 and 4 seconds.

xi) Choice reaction time (CRT) The test comprised 80 trials. As in the SRT, the imperative stimulus to which the subject had to react was a filling of a square either to the left or right of the central blank square. A mixture of *warned* and *cued* choice reaction time trials was used. In the *warned* trials, a cross appeared in the central square prior to the imperative stimulus. This indicated that the stimulus was about to appear but not which side. In the *cued* trials, the arrow appeared in the

central square pointing in the direction of the square to be filled. The 80 trials were equally and randomly divided between warned and cued responses. Within each 40, half the responses were right and half left. The timing for the cross or arrow to appear prior to the imperative stimulus was the same as in the SRT and also randomly assigned to prevent anticipation.

In addition to the above psychometric battery, mental state was assessed using the *Hospital Anxiety and Depression Scale* (Zigmond and Snaith, 1983). This self report scale has subscales for anxiety and depression (range of 0 - 21 for each) and attempts to avoid the influence of somatic complaints in rating the severity of emotional distress. Scores greater than or equal to 10 on either the anxiety or depression subscales were taken as indicative of psychiatric "caseness".

The Social Stress and Support Interview (Jenkins et al. 1981) was used to determine the amount of social stress or support as perceived by the subject. Scores of +1 for support, 0 if neither support nor stress were evident and -1 for stress were assigned to the following areas; work, finances, housing, social contacts, marriage and family relationships. High scores therefore indicated little stress and good support, while the converse applied to low scores.

All subjects were tested and scanned on the same morning. The psychometric battery took approximately one hour to administer.

C MRI assessment

Subjects underwent multislice MRI of the brain with a 0.5 Tesla Picker superconducting system. Contiguous, axial (transverse) slices with a 5mm thickness were obtained using a $SE/_{1500/60}$ sequence.

A procedure to detect total lesion area was derived from in-house software. All lesions were identified and marked on the hard copy. The images from the

magnetic tape were then viewed in the Picker SUN workstations (SUN Microsystems Inc., Mountain View, CA) and each of the 24 individual brain slices enlarged to full screen size. Using the hard copy to confirm the presence and site of lesions, the interface window was adjusted to improve contrast between lesion and surrounding brain tissue. A trace was then manually drawn around individual lesions and their anatomical location recorded. The area within the trace corresponded to the area in pixels occupied by that particular lesion. Having analysed all 24 slices in this manner, the individual lesion areas were summed to give a total lesion area. Intra-rater reliability (test-retest) revealed a variance of approximately 3% for patients with a high lesion load (in excess of 20 lesions) and 6% for those with a more moderate load.

T_1 and T_2 relaxation times were calculated from algorithms supplied by the manufacturer. Problems with machine reliability meant that the first 12 consecutive patients could not have their relaxation times accurately computed and as a result T_1 and T_2 data were only obtained for the remaining 30 of the 42 ON subjects. A single slice of normal appearing frontal white matter was chosen for this purpose using 2 spin echo ($SE/_{1500/40}$, $SE/_{1500/120}$) and an inversion recovery ($IR/_{150/40/500}$) sequence. Analysis was undertaken using the automated programme "ANALYZE" (Mayo Foundation Biodynamic's Research Unit, 1986). A manual trace was used to outline the area of frontal white matter, delineating it from cortical grey matter and cerebrospinal fluid. The interface window on the T_1 weighted images was adjusted to give maximum tissue contrast for this purpose. The anatomical trace thus obtained was superimposed on the T_2 weighted image, which had greater sensitivity in demonstrating the presence of MS plaques, and the interface window again adjusted to maximise the contrast between lesion and normal appearing white matter. With the additional help of the printed MRI pictures, the outline of the lesions (if present) was traced manually. The aim of this procedure was to define the largest possible area of normal appearing frontal white matter demarcated from cortex, CSF and lesions, from which T_1 and T_2 relaxation times could be obtained (*fig. 2*).

D Statistical analysis

Both parametric and non-parametric analyses were used depending on the distribution of the particular variables. Thus, for demographic comparisons 2 sample t-tests or chi-squared tests were utilised, the median and range being quoted for all non-parametric analyses. 2-tailed p values are reported throughout.

Comparisons between 3 groups (i.e control and ON subjects with and without brain lesions) were undertaken using either Oneway analysis of variance (ANOVA) or Kruskal-Wallis ANOVA, depending on variable distributions. To reduce the experimentwise error, only those variables significant at the 5% level were further analysed with the Tukey-Kramer multiple comparisons method to ascertain where specific group differences lay. The Tukey-Kramer method was preferred as it is the method of choice for dealing with unequal sample sizes and is more powerful than methods such as the Bonferroni for pairwise comparisons. For post-hoc analysis of statistically significant Kruskal-Wallis tests, Mann-Whitney comparisons were done.

Correlations between variables were assessed with either the Pearsons or Spearmans Rank correlation co-efficient, depending on the distribution of the variables concerned.

The software package used for this and subsequent data analysis in this thesis, was the Statistical Package for the Social Sciences, version 3.1 (SPSS)(Norusis, 1986).

2 Results

Forty two consecutive patients met the selection criteria and were matched to 36 controls with respect to age, sex, number of years of education and premorbid IQ (*Table 1*). Seven of the patients and 4 of the controls were left handed. The mean duration of symptoms was 14.5 days (range 3-35 days). Thirty three patients had experienced loss of all or part of the visual field in the affected eye while 30 had experienced orbital pain. Twenty four patients reported their symptoms were improving at time of testing, 11 thought symptoms had remained constant since presentation while 7 noted deterioration. Aggravating factors such as exercise were reported by 14 subjects. Apart from symptoms of optic neuritis, the neurological examination was entirely normal for all the patient sample.

A MRI

i) Lesion area

Twenty three subjects (55%) had high signal abnormalities on MRI. The lesion area in pixels and cm^2 is given in *Table 2*.

ii) Relaxation times

There were no significant differences in either T_1 or T_2 times between the ON group and 30 matched control subjects (*Table 3*).

Comparing relaxation times in those subjects with (n=19) and without (n=11) high signal intensity lesions on MRI revealed the former to have higher T_1 values (mean 421.7 vs. 416.9 msecs.) but this did not reach statistical significance. Total lesion area did not correlate significantly with either T_1 or T_2 relaxation times.

B Psychometric performance

Comparisons using Analysis of Variance (ANOVA) were undertaken between control subjects (n=36) and ON subjects with (n=23) and without (n=19) brain MRI abnormalities. There were no significant differences between the 3 groups with respect to demographic details and premorbid IQ. There were no differences in the number of patients from the two ON groups who were experiencing orbital pain or had impaired visual acuity at the time of testing.

A number of differences emerged between the 3 groups when psychometric test performances were compared, ON patients with normal MRI generally occupying an intermediate position between that of the control subjects and that of the ON patients with observable brain lesions. The main differences between the groups were observed in the performance of the following tests (*see Table 4*):

i) Pegboard Test

No differences were present between the two ON groups who both performed significantly worse than the normal control group. Post-hoc analysis confirmed a significant (p=0.05) difference between the control and both ON groups.

ii) Stroop Test

A 0.5 second difference between the ON group with and without brain lesions in the *control* condition (speed of colour recognition) had increased to 3 seconds for the *full* Stroop paradigm, but did not prove statistically significant due to a larger standard deviation in the brain lesion group. Re-analysis using non-parametric statistics gave a similar result. There was no significant group × condition interaction ($F(4,150)=1.48$; $p=0.2$:ANOVA), group referring to either of the two ON or control groups and condition to the *control* and *full* Stroop paradigm.

iii) Symbol Digit Modalities Test (SDMT)

The patients with observable brain lesions were slower than the other 2 groups on total time taken to complete the 8 trials. A significant time effect, independent of group was apparent across the 8 trials ($F(7,525)=16.1$; $p=0.0001$:ANOVA) indicating that all subjects got progressively quicker through trials 1 to 8. There was however no significant group × time interaction ($F(14,525)=1.47$; $p=0.12$:ANOVA), implying that changes in speed across the 8 trials were consistent for all 3 subject groups (*Fig. 3*). Post-hoc analysis failed to demonstrate significant differences between any two groups.

iv) Paced Auditory Serial Addition Task (PASAT).

Differences across the three groups were apparent for the 4 and 2 second test stimuli. Post-hoc analysis revealed that with a 4 second stimulus, the ON group with brain lesions made significantly more errors than either the control subjects or those with ON and a normal MRI. At the 2 second stimulus test however, a significant difference was only apparent between the healthy control subjects and those with ON and brain lesions. There was no significant group × time (4 or 2 second stimuli) interaction ($F(2,75)=1.08$; $p=0.34$:ANOVA).

v) Paced Visual Serial Addition Task (PVSAT).

Differences across the three groups were present at the 2, but not 4 second stimulus. Post-hoc analysis demonstrated that this difference lay between the ON group with brain lesions and the healthy control subjects, the former making more errors. The group × time interaction was however significant ($F(2,75)=3.29$; $p=0.04$:ANOVA), with more errors being made on the 2 second trial particularly by those patients with an abnormal MRI. In general, both patient and control subjects considered the auditory tasks to be the more difficult irrespective of whether the stimulus was 4 or 2 seconds and this is reflected in the increased number of errors on the PASAT as opposed to the PVSAT.

vi) Reaction Time Tests.

The scores for the simple and choice reaction times are shown in *Table 5*. There were no group differences for the simple or choice reaction time (warned or cued) tests. There was a significant group × time (warning signal interval) interaction for the simple reaction ($F(6,222)=2.66$; $p=0.02$:ANOVA), but not the choice reaction tests. This was due to the optic neuritis group without brain lesions reacting slower than the other two groups to stimuli presented without warning. This group then proceeded to get progressively quicker as the warning interval increased while the other two groups reached a plateau after 0.8 secs.

Analysis of variance was performed to investigate the interaction between group (control or optic neuritis patients with or without lesions), modality (simple or choice reaction time; warned and cued), side of response (right or left) and time (0, 0.2. 0.8 and 1.6 seconds). The group × modality × side × time interaction was not significant ($F(12,444)=0.95$; $p=0.5$:ANOVA). The only significant interactions were modality × time ($F(6,444)=12.7$; $p=0.0001$:ANOVA), side × time ($F(3,222)=3.8$; $p=0.01$:ANOVA) and modality × time × side ($F(6,444)=2.4$; $p=0.03$:ANOVA), indicating that all subjects irrespective of control or optic neuritis status were quicker on simple reaction time tasks as opposed to choice and that right hand responses (dominant side in the majority of cases) were quicker than left.

No group differences were present for the remaining psychometric tests, namely the Raven's Matrices, Visual Attention (letter counting speed) and Auditory Attention Task (alphabet discrimination).

C Mental State

Five ON subjects had a premorbid history of psychiatric illness and received out-patient treatment. These disorders comprised adjustment disorders (n=3) and minor affective disorders (n=2). None of the controls had a past psychiatric history.

At interview, there were no differences in scores on the HAD between the ON subjects and the matched control group, nor were any differences apparent when those subjects with an abnormal MRI were compared to the rest (*Table 6*). Five subjects with ON met the criteria for psychiatric "caseness" as opposed to 7 control subjects. The 5 ON patients were classed as psychiatric "cases" by virtue of their scores on the anxiety subscale exceeding the threshold and none were significantly depressed. A similar situation existed for the control group with 6 of the 7 psychiatric "cases" exceeding the cut off point for anxiety only.

ON subjects, with or without brain involvement on MRI were not more likely to perceive their lives as being more stressful or their social support less adequate than the control group (*Table 6*).

D Relationship between cognition and MRI abnormalities

Correlations between total lesion area and psychometric/psychiatric tests were undertaken and two statistically significant results were obtained with respect to mean time for the symbol-digit modalities test and the number of errors on the 4 second paced auditory serial addition task (*Table 7*).

E Sensitivity of psychometric tests in detecting brain damage

Starting with the premise that those ON subjects who had deficits on psychometric testing were more likely to have brain involvement, the various tests were re-examined to investigate which were the most sensitive and specific predictors of cerebral involvement. A discriminant function analysis was used for this purpose. The following variables were selected on the basis of results from the analysis of variance across control and patient groups (see *Table 4*); Stroop test, SDMT (total time), PVSAT (4 and 2 second stimuli), PASAT (4 and 2 second stimuli) and the Raven's Matrices. Scores were dichotomised about their mean or median depending on their distribution and entered in the analysis. A combination of 3 variables were found to predict with a 76% accuracy whether subjects would have brain lesions on

MRI or not. These were the SDMT (total time), PASAT (4 second stimuli) and the PVSAT (4 second stimuli). Of the three, the SDMT was the most powerful predictor, correctly grouping almost 70% of cases.

3 Discussion

Comparisons between optic neuritis patients with and without brain lesions and healthy controls revealed a number of differences. These however only reached statistical significance for 3 tests, the PVSAT (2 secs.), PASAT (2 secs.) and the PASAT (4 secs.) and only the latter could distinguish between optic neuritis patients with and without an abnormal MRI. In terms of raw scores, patients with optic neuritis and a normal MRI occupied a position intermediate between healthy control subjects and optic neuritis patients with an abnormal MRI. Patients who present with optic neuritis and brain lesions on MRI are likely to develop MS (Miller et al. 1988b) and even at the early stages of clinical manifestation, attentional deficits are already present. The present study thus confirms the earlier findings of Callanan et al. (1989) whose sample of patients with clinically isolated lesions was more heterogeneous and had been ill for much longer periods.

A Psychometric performance

There was no MRI evidence (either visible lesions or abnormal relaxation times) to suggest brain abnormalities in approximately half the optic neuritis sample. Differences between this group and control subjects on the pegboard test could not be attributed to impaired motor speed given the former's slightly superior performance on the simple reaction time test and this left impaired visual acuity in the optic neuritis group as the likely explanation. The absence of brain abnormalities in the optic neuritis subgroup was further reflected by their similar performance to the control group on all remaining psychometric tests.

There were no differences between the two optic neuritis groups regarding visual acuity and this is supported by their almost identical performances on the pegboard

task. There was however evidence to suggest that the patients with an abnormal MRI had additional deficits directly related to the presence of brain pathology. In comparison with the optic neuritis group with a normal brain, they made significantly more errors on a slower test of auditory attention (4 second PASAT). The two groups did not differ with respect to errors on the 4 second PVSAT, but differences became apparent with a 2 second stimulus. As visual acuity in the groups was the same, this finding suggests the role of cerebral mechanisms.

The fact that in this sample psychometric differences between groups were present on some (serial addition tests), but not other tests (letter counting, alphabet task) within the same sensory modality could be due to the greater sensitivity and complexity of the former. Thus, failure by the optic neuritis group with brain lesions to perform adequately on the serial addition tasks may also reflect abnormalities in speed or efficiency of information processing, a function noted to be slowed in patients with definite MS (Rao et al. 1989a) and considered anatomically distinct from that of attention (Posner and Petersen, 1990). Tasks like the PASAT which tap a number of different cognitive processes including retrieval from short term memory, make it a sensitive discriminator of cognitive speed between brain damaged patients and controls, particularly when stimuli are presented more quickly (Litvan et al. 1988a). A similar effect was noted in this study where a group × time interaction was present for the PVSAT. Tests that were not time dependent, viz. the Raven's Matrices, failed to distinguish between the groups lending indirect support to the above explanation. In interpreting these results however, caution is advocated for while post-hoc Tukey-Kramer analyses controlled for multiple comparisons, the possibility remained that at the 5% level of significance, one of the significant findings may have been due to chance alone.

No group differences were found between the optic neuritis and control subjects on reaction time tests other than a group × time effect for the simple reaction tasks which cannot be readily explained given the pattern of results from the other tests. In definite multiple sclerosis, abnormalities in reaction time are most marked in those patients with a chronic-progressive course (Elsass and Zeeberg, 1983), longer

disease duration and greater physical disability (Jennekens-Schinkel et al. 1988a). It is therefore not surprising that in a sample of patients with acute optic neuritis, representing early demyelinating disease, delayed reaction time were not apparent. Increasing task complexity (i.e. changing from a simple to choice paradigm) did not lead to a differential increase in reaction time in the optic neuritis group, something also noted by Jennekens-Schinkel et al. (1988b) in subject with definite MS.

B Association between MRI and psychometric abnormalities

At presentation, 55% of the optic neuritis patients had brain lesions almost exclusively confined to hemispheric white matter, a figure in agreement with previous reports (Ormerod et al. 1987). As attention is subserved by large scale neurocognitive networks dependent on fibre bundles linking various cortical and subcortical structures (Mesulam, 1990), it follows that lesions scattered widely throughout the white matter can cause considerable disruption to the functioning of these systems. This is reinforced in this study by the association between extent of the lesion area and degree of psychometric deficits.

The robust correlation between cognitive deficits and total lesion area on MRI has not been previously reported in patients with clinically isolated lesions, the reasons being twofold. First, this study used more sensitive tests of attention than those employed previously (Callanan et al. 1989), the SDMT being particularly noteworthy in this regard (Beatty and Goodkin, 1990) and second, improved methods of MRI analysis were used with quantification of total lesion area proving superior to a rating scale approach (Rao et al. 1989b). This positive correlation refutes the myth of the "silent" MS lesion and demonstrates cognitive dysfunction to be a sensitive marker of brain involvement, often preceding other neurological signs and symptoms (Jacobs et al. 1986; Thompson et al. 1990). The ability of 3 psychometric tests to discern accurately the presence of brain lesions in over three quarters of the optic neuritis sample, while of obvious limited value in individual

cases, provides support for the role of brain pathology in the production of the observed attentional deficits.

C Mental State

Irrespective of the presence of brain abnormalities, the optic neuritis group was characterised by a low psychiatric morbidity no different from that of the control group and similar to that reported in general population studies (Andrews et al. 1977). This is in agreement with a previous study that found a low psychiatric morbidity in a mixed group of patients with CIL (Logsdail et al. 1988).

D Disability

While there is evidence from studies of patients with definite MS that cognitive dysfunction affects a wide variety of occupational, social, sexual and basic activities of daily living (Rao et al. 1991b), it seems unlikely that the same applies to this sample given the mild severity of their deficits. The majority of patients were still working and had not experiencing social or occupational difficulties other than that related to impaired visual acuity.

Summary

1. Deficits in attention and/or information processing speed were present in patients with acute optic neuritis provided there was evidence of brain lesions on MRI.

2. Deficits in tests such as Symbol-Digit Substitution and Paced Auditory Serial Addition correlated significantly with the extent of lesion involvement on brain MRI.

3. Patients with acute optic neuritis, irrespective of the presence of brain lesions, had no increase in anxiety and /or depression relative to healthy controls.

CHAPTER 6

STUDY 2. Clinically isolated lesions

A 4½ year follow-up study of patients with clinically isolated lesions of the type seen in MS was undertaken. The aim of the study was twofold, first to chart the progression of cognitive, psychiatric and MRI abnormalities and their relationship with clinical features and second, to explore the nature of these deficits still further, in particular memory impairment. It was thereby hoped to throw light on the evolution of these changes early in the demyelination process.

1 Methodology

A Subjects

Forty eight patients with clinically isolated lesions (CIL) underwent concurrent Magnetic Resonance Imaging (MRI), psychometric and psychiatric examination at the National Hospital, Queen Square between 1985 and 1987 (Callanan et al. 1989; Logsdail et al. 1988). This group was recalled an average of 54 months (range 42 to 67 months) after their original assessment. The group initially comprised 14 patients with optic neuritis, 16 with brain stem and 18 with a spinal cord syndromes. The sample at follow-up was reduced to 44 as the passage of time and re-examination of medical records made it clear that 4 subjects had been incorrectly diagnosed. Thus one patient was re-diagnosed as having motor neurone disease and another a presenile dementia of the Alzheimer type. The other two subjects were re-assessed as having had MS at the time of inclusion into the study. Of the remaining 44 subjects, 35 (80%) were prepared to take part in the study.

At a single follow-up examination, a history covering the intervening period was

obtained and each patient underwent thorough neurological examination. Present physical disability was rated on a scale of 1 to 10 according to the Expanded Disability Status Scale (EDSS)(Kurtzke, 1983) and a note made whether the patient was in exacerbation or not (defined as symptom or symptoms of neurological disturbance with or without objective confirmation, lasting more than 24 hours)(Poser et al. 1983). In addition, hospital case notes and general practitioner records kept during the follow-up period were obtained to supplement the above information. On the basis of all information obtained, the Poser Criteria (Poser et al. 1983) were used to classify the patients clinical status at follow-up (i.e. CIL or clinically definite MS). In those who had developed MS, the course of the illness was defined as either relapsing-remitting or chronic-progressive. Relapsing-remitting (RR) patients had experienced a variable number of relapses during the follow-up period, but remained clinically stable (i.e. non-progressive) between such episodes. Those with chronic-progressive (CP) disease had developed a steady increase in disability for at least 6 months prior to follow-up and were further divided into a primary and secondary group. The former referred to a steady decline without remissions since disease onset while the latter indicated that there had been a relapsing-remitting course prior to the onset of steady progression.

B Psychometric assessment

The same cognitive battery used in the initial study (Callanan et al. 1989) was re-administered at follow-up. The battery comprised the following tests:

i) Wechsler Adult Intelligence Scale (WAIS)(Wechsler, 1955). A shortened version which gives measures of verbal, performance and full scale I.Q.'s. was used. The subtests administered were Arithmetic, Similarities, Digit Span, Vocabulary (verbal I.Q.), Picture Completion, Picture Arrangement and Block Design (performance I.Q.). The subtests were administered according to the standard procedure (Wechsler, 1955)

ii) Recognition Memory Tests for Words (Warrington, 1984). This test consists of

50 frequently encountered words as stimuli and 50 distracter words. The task calls for the subject to read the recognised word from a list of stimulus words paired with the distracter words. An age corrected, scaled score based on the number of words correctly recognised was obtained.

iii) Recognition Memory Test for Faces (Warrington, 1984). The test stimuli consists of 50 black and white photographs of unfamiliar male faces and 50 distracter male face photographs. In the retention task, the subject was required to indicate recognition by pointing to the appropriate photograph. As in 2 above, an age corrected, scaled score based on the number of photographs correctly recognised was obtained.

Parallel versions of both verbal and visual recognition memory tests were used to minimise practice effects.

iv) The Wisconsin Card Sorting Test (WCST) (Nelson, 1976). A shortened version of the WCST was used and scored according to the procedure recommended by Nelson (1976). Four stimulus cards and two sets of 24 response cards were presented to the subject who had to sort the latter according to a consistent stimulus attribute (i.e. colour, number or shape). The total number of errors was considered indicative of abstracting ability.

v) Speed of Letter Counting (Willison et al. 1980) The time taken to count the number of A's interspersed with other letters was used as a measure of visual attention.

vi) Auditory Attention Test (Callanan et al. 1989) From an auditory presentation, subjects were required to identify in correct order the alphabet which was embedded in a random collection of letters. The total number of false positives and omissions were taken to represent a measure of auditory attention.

vii) Graded Naming Test (McKenna and Warrington, 1983). This test assessed

language function and consisted of 30 black and white line drawings presented to the subject in a graded order of difficulty. The number of objects correctly named was used as a measure of word retrieval ability.

Recall memory had not been tested in the original assessment. As research has shown a dissociation between the process of memory retrieval, involving recall and recognition (Delbecq-Derouesne et al. 1990), two additional tests of recall memory were included to examine this effect in the present sample.

viii) Paired-Associate Learning Test (Warrington and Weiskrantz, 1982). The test material consisted of 3 groups of 10 paired-associate noun-verb and 3 groups of 10 semantically related words. The test stimuli were written on cards and subjects required to read each paired-associate at a rate of one per 2 seconds. Retention was immediately tested by presenting the first item of each pair (in the same order as in the learning trial), the subject being required to recall the missing item.

ix) Story Recall Test (Caughlan and Hollows, 1985). Subjects were read a short story and their recall tested immediately after the reading and again after an interval of 30 minutes. Correct, approximate and incorrect or additional responses were scored as 2, 1 and 0 respectively. Results were age-corrected to yield an **immediate** and **delayed** recall score. Scores were subdivided into percentiles according to published normative data, namely <5hth, 5-10th, 10-25th, 25-50th, 50-75th, 75-90th and >90th and given values 1 to 7 respectively.

As the *Paired Associate Learning Test* and *Story Recall* had not been used in the initial assessment, no comparisons over time could be carried out. Scores from these tests were only used in comparisons between the various subgroups at follow-up (ie CIL, RR or CP).

An estimate of premorbid IQ had been obtained at the initial interview using the National Adult Reading Test (*NART*)(Nelson, 1982) and *Schonell Graded Word*

Reading Test (Nelson and O'Connell, 1978). These reading tests have been shown to be resistant to cognitive deterioration and the values obtained at initial assessment were used to determine the decline in IQ by comparing them with the full scale IQ (*WAIS*) obtained at follow-up. This difference was termed the *IQ deficit.*

Psychometric testing therefore examined the following functions: IQ deficit, verbal and visual recognition memory, verbal recall memory, abstracting ability, visual and auditory attention and naming ability.

C Psychiatric Assessment

The *Clinical Interview Schedule (CIS)*(Goldberg et al. 1974) was used in the initial assessment and was thus repeated to record change in psychiatric status over time. The schedule which includes sections for rating both subjective complaints and objective evidence of psychopathology on a 0 to 4 scale, measures predominantly neurotic symptomatology but has 2 items for recording psychotic features. Scores greater than or equal to 14 were again taken as the cut-off point indicating "caseness". Scores were separately analyzed with and without the fatigue item to reduce the influence of physical symptoms on the overall score. Patients were in addition asked to complete the *Hospital Anxiety and Depression Scale (HAD)*(Zigmond and Snaith, 1983) designed for use in hospital populations and less dependent on physical symptoms of anxiety and depression.

To gauge the influence of social factors as perceived by the subject, the *Social Stress and Support Interview (SSSI)*(Jenkins et al. 1981) was used. This instrument had been used in the initial study (Callanan et al. 1989; Logsdail et al. 1988). For details of scoring, see *chapter 5.*

D MRI Assessment

All but one subject (n=34), who had a phobia of confined spaces, underwent multislice MRI of the brain ($SE/_{1500/60}$) with the same 0.5 Tesla Picker superconducting system used originally. Upgrades to the software during the follow-up period had resulted in a reduction of slice thickness from 10mm to 5mm. The method used to quantify the total amount of visible MRI abnormality followed that of Ormerod et al. (1987) and was as follows: the size and presence of lesions were recorded independently by 2 raters in the following periventricular areas: body of the ventricles, frontal, temporal and occipital horns, trigone, third and fourth ventricle. In addition 8 discrete areas of brain parenchyma were also examined, namely internal capsule, basal ganglia, frontal, parietal, temporal and occipital lobes, brain stem and cerebellum. In each area the largest lesion was scored according to the longest diameter measured, using a 4 point scale (0 = 1mm, 1 = 2-5mm, 2 = 6-10mm, 3 > 10mm). A total lesion score was obtained by adding scores from all the areas and a periventricular score by adding the scores of the periventricular regions. A kappa of 0.96 was obtained for inter-rater reliability.

T_1 and T_2 relaxation times, which had not been obtained in the original study were calculated from algorithms supplied by the manufacturer. A single slice of normal appearing frontal white matter was chosen for this purpose using two spin-echo ($SE/_{1500/40}$, $SE/_{1500/120}$) and an inversion-recovery ($IR/_{1500/40/500}$) sequence. Analysis was undertaken on a Picker SUN station using the automated programme "ANALYZE" (Biodynamic Research Unit: Mayo Foundation, 1986) and the procedure followed that outlined in the previous chapter.

Healthy controls (n=30) were scanned over the same period using the above sequences and results of their T_1 and T_2 relaxation times compared to the subjects'. The validity of these measurements was checked using phantoms which controlled for machine drift over time. These controls did not complete psychometric or psychiatric testing.

All investigations were completed the same day, in the same order, namely history and physical examination, MRI, psychometry and psychiatric assessment. The entire procedure took 4 hours and was completed before midday in each subject.

E Statistical Analysis

Both parametric and non-parametric statistics were used depending on whether the data distribution was considered normal or not. Thus, in comparing the initial and follow-up samples, paired t-tests or Wilcoxon Matched-pairs Signed-rank Tests were used. In the case of non-parametric analysis, the median and range are quoted.

Comparisons between 2 independent samples were undertaken with 2-sample t-tests and Mann-Whitney U tests. 2-tailed p values are reported throughout. One-way Analysis of Variance (ANOVA) and Kruskal-Wallis ANOVA were used in analysing differences between 3 subgroups, depending on distributions. To reduce the experimentwise error, only those variables significant at the 5% level were further analysed with the Tukey-Kramer multiple comparison method to delineate inter group differences more clearly. For non-parametric post-hoc analysis, Mann-Whitney comparisons were undertaken. Correlations between variables were assessed with either the Pearsons or Spearman Rank correlation co-efficients depending on their distribution.

2 Results

The sample (n=35) comprised 22 female and 13 male subjects. Nineteen subjects (54%) had developed clinically definite MS while 16 (46%) remained in the isolated lesion category. The percentage of patients at follow-up with optic neuritis, brain stem or spinal cord presentations, relapsing-remitting or chronic progressive MS is shown in *fig. 4*. The chronic-progressive group comprised 6 with a secondary and one with a primary progressive course. Of the 19 patients with MS, 3 were experiencing exacerbations on the day of examination. The mean EDSS for

the MS group was 3.5 (range 0 to 8.0; median=3.0). In 2 patients, their neurological status precluded the full psychometric battery of tests being completed.

A Cognitive change at follow up

i The whole group

The initial and follow-up performance of the whole group (n=35) on psychometric testing was compared (*Table 8*). The only function that declined significantly at follow-up was visual memory.

ii Clinically isolated lesion vs. multiple sclerosis group

The follow-up group was divided into those with clinically definite MS and those remaining clinically isolated lesions and the two groups compared across all parameters. The 19 patients with definite MS did not differ from the 16 CIL subjects with respect to mean age (40 vs. 41 years), duration of symptoms (79 vs. 76 months) or age of symptom onset (33.6 vs. 34.8 years). They were however more physically disabled with higher EDSS scores (3.0 vs 1.3; Z=-2.4; p=0.02: Mann-Whitney U). They also had a significantly higher median lesion score on MRI (19.5 vs. 2.0; Z=-3.82; p=0.0001: Mann-Whitney U). No CIL subjects were taking psychotropic medication but 5 with MS were doing so (3 on benzodiazepines, 2 on tricyclic antidepressants).

Despite these differences, the MS group performed as well on all psychometric tests except for visual memory where their median scores were significantly lower (10.0 vs. 7.5; Z=-1.93; p=0.03: Mann-Whitney U).

The differences between the MS and CIL were further explored by dividing the MS group into Relapsing-Remitting (n=12) and Chronic-Progressive(n=7). The demographic and disease related characteristics of the three groups are shown in

Table 9. There were no age differences between the 3 groups and while the CP group had a slightly earlier age of symptom onset accounting for an extra year duration of symptoms, this difference was not statistically significant.

However, the CP group was found to differ from the CIL and RR groups on several measures of psychometric testing including story recall (immediate and delayed), paired-associate learning and auditory attention (*Table 10*).

B Psychiatric change at follow-up

i Entire group

Psychiatric status based on median CIS scores showed a significant increase in morbidity over time for the group as a whole (median 4.0 vs. 11.0; Z=-2.3; p=0.02; Wilcoxon Matched-pairs). Thus, 8 subjects had become "cases" at follow-up as opposed to one improving to "non-caseness", the rest remaining unchanged (Z=-2.1; p=0.04: McNemar Test). Overall, 14 subjects were classed as "cases".

Analysis of the CIS without the fatigue item still showed a significant difference between the initial and follow-up scores (4.0 vs. 10.0; Z=-1.92; p=0.05: Wilcoxon Matched-pairs). However, when change in "caseness" over time was reanalysed with fatigue removed from the scoring, the significance was no longer apparent with 5 patients becoming "cases" and one improving to "non-caseness".

Analysis of individual items on the CIS showed preoccupation with physical complaints (such as fatigue) and concentration difficulties to be significantly more common at follow-up with a trend for depressive and obsessive symptoms to be more prevalent.

No subjects were psychotic at follow-up although in the interim one had been admitted to hospital with a paranoid psychosis that lasted 10 days and responded

well to chlorpromazine. Euphoria had developed in 2 subjects, both markedly disabled and with a chronic-progressive disease course.

ii Psychiatric change: clinically isolated lesion vs. MS

There was a trend for the MS group to have higher CIS scores (7.5 vs 11.0; Z=-1.69; p=0.09; Mann-Whitney U) than those with CIL, but they were equally likely to be classed as "cases". This non-significant trend was also present for the HAD scale with the MS group having higher mean anxiety (5.3 vs. 6.3; t=-0.77; p=0.45) and depression (3.7 vs. 5.6; t=-1.44; p=0.16) scores.

More marked differences became apparent when the MS group was subdivided into relapsing-remitting and chronic-progressive. The CP subgroup had scores on the clinical interview schedule double those of the CIL subgroup and while all 3 subgroups had similar results on the HAD anxiety scale, the CP's HAD depression ratings were three times those of the other two (*Table 10*).

iii Change in Social Stress and Support

For the group as a whole scores on the SSSI did not show a deterioration over time i.e. subjects did not perceive themselves to be under more stress or receiving less support (3.8 vs. 3.6; Z=-0.26; p=0.79: Wilcoxon Matched-pairs). However, when the group was split into CIL and MS, the latter were experiencing greater social stress (4.4 vs 3.0; Z=-1.99; p=0.05; Mann-Whitney U). Further subdivision of the MS group into RR and CP illustrated significant differences between the CIL and CP subgroups (*Table 10*). The SSSI correlated significantly with the degree of physical disability (r=-.42; p=0.01: Spearman's Rank). Thus, more disabled patients perceived themselves as receiving less overall support.

C Interaction of cognitive, psychiatric and social variables

To investigate the possible confounding effects of psychiatric and social variables on significant differences in cognition between the CIL, RR and CP groups, analyses of co-variance were performed on the 4 cognitive variables where ANOVA had demonstrated subgroup differences. Thus, Story Recall (immediate and delayed), PALT (noun-verb) and Auditory Attention were entered as the dependent variables and social stress and support, physical disability and psychiatric state (CIS scores) chosen as the co-variates. This removed the statistically significant differences between the groups with respect to recall memory tests although non-significant trends remained for all three. Significant differences however persisted for the auditory attention task ($F=3.6$; $p=0.04$)(see *Table 11*).

With regard to psychiatric measures, differences in depression scores on the HAD between the 3 subgroups were re-analysed with social stress and support, physical disability and gender as the co-variates. Significant differences between the 3 subgroups were no longer apparent. Most of the variance was accounted for by the social stress variable, with the remaining two having a negligible influence (see *Table 10*).

An attempt was made retrospectively to identify features that may have predicted a chronic-progressive or relapsing-remitting course at the initial examination. The 7 CP patients (3 of whom presented with cord, 3 with brain stem syndromes and one with optic neuritis) did not differ from the RR or CIL groups in terms of demographic, psychometric or psychiatric variables, although they already had a significantly higher MRI lesion score than the rest of the group at the initial assessment (14.0 vs. 5.0; $Z=-2.3$; $p=0.02$: Mann-Whitney U).

D MRI changes at follow-up

Only 4 patients had normal scans at follow-up, as opposed to 8 in the initial study. Comparisons between the initial and follow-up MRI scans were not possible because of differences in slice thickness. At the follow-up assessment, differences in total lesion score between the 3 groups were apparent with the CIL subjects differing from both the RR and CP groups respectively (*Table 9*).

No significant correlations were found between total lesion score and psychiatric status. Of the individual cognitive functions, visual (recognition) memory was the only one significantly related to MRI total lesion score (r=-.47; p=0.01: Pearson's product-moment correlation co-efficient), the negative sign implying lower memory scores associated with higher lesion scores.

Although the T_1 and T_2 relaxation times of the patients were higher than those of the controls, this difference was not statistically significant (mean T_1: 430.2 vs. 425.4; mean T_2: 78.6 vs. 77.5 respectively). When the CIL values were excluded and only the definite MS compared to normal controls, a trend was observed for higher T_1 values in the MS group (mean 434.3 vs. 421.9; t=2.13; p=0.06). T_1 values correlated with total lesion score (r=.51; p=0.01: Spearman's Rank correlation co-efficient).

Significant correlations were found between elevated T1 relaxation times and naming ability (r=-.43; p=0.01: Pearson's correlation co-efficient), abstracting ability (r=.43; p=0.01; Spearman's Rank correlation co-efficient) and visual memory (r=-.50; p=0.01: Spearman's Rank correlation co-efficient). The negative sign for the visual memory correlation was in the expected direction. i.e elevated relaxation times associated with lower memory scores.

3 Discussion

In the initial study, the CIL group was found to be significantly more cognitively but not more psychiatrically impaired than a group of physically disabled controls matched for age, sex and premorbid IQ. After a 4½ year follow-up approximately half the sample had developed clinically definite MS, a rate in agreement with previous reports (Bradley and Whitty, 1968; Francis et al. 1987; Miller et al. 1988b). As a group, an increase in psychiatric morbidity was apparent (CIS scores, but not "caseness") and performance in tests of visual memory had deteriorated. When subdivided according to disease course, those with a chronic-progressive pattern were found to have further deteriorated on tests of auditory attention.

A Cognitive change

While longitudinal studies are necessary to determine the natural history of cognitive decline, they are in turn bedeviled by the difficulties of controlling for practice effects. In this study, the use of parallel forms of memory tests and the long period that elapsed between the two examinations are likely to have minimised this problem. The possibility nevertheless remains that the extent of cognitive decline may have been slightly underestimated, but this could not account for the differences between the various subgroups emerging at follow-up.

Memory impairment has often been described in patients with definite MS (Litvan et al. 1988b) and indirect evidence from cross sectional studies suggest that memory functions deteriorate over time (van den Burg et al. 1987; Ron et al. 1991). The only available follow-up study (Jennekens-Schinkel et al. 1990) on patients with MS suggests considerable individual variation in memory deterioration after an interval of 4 years. This study confirms that finding and documents for the first time the natural history of cognitive deficits from the time the first neurological manifestations of the disease (CIL) occurred. It also demonstrates visual memory to be more vulnerable to advancing disease than other types of memory.

There was a large degree of overlap in cognitive performance between the CIL and RR groups despite the latter being more physically disabled. One possible explanation could be that only 1 of the 12 RR subjects was in exacerbation, which has been shown to have an adverse effect on cognition (Bieliauskas et al. 1980; Grant et al. 1984). Although these results confirm the presence of cognitive impairment in patients with relapsing-remitting MS noted by previous authors (Beatty et al. 1989; Anzola et al. 1990) these deficits appear to remain relatively mild and constant over time provided the disease remains in remission.

The MRI, psychometric and psychiatric abnormalities were consistently more severe in the CP compared with the CIL and RR groups, although they only reached statistical significance with respect to auditory attention and MRI lesion score. The failure to demonstrate more widespread impairment in the CP subgroup may represent a type II error given the small number of CP patients. Nevertheless, their performance is broadly in keeping with results from other studies (Heaton et al. 1985; Rao et al. 1987) and suggests that in definite MS, disease type is a more sensitive marker of cognitive decline than either disability or duration, variables found to be unrelated to cognitive impairment in this sample. Cognitive impairment thus appears to relate directly to more severe degrees of brain pathology, which in turn results in greater physical disability. Reports of positive correlations between impaired cognition and duration of illness (Grant et al. 1984) and physical disability (Marsh, 1980) may therefore have obscured a more fundamental relationship between cognitive impairment and course of MS.

While as a group patients with chronic-progressive disease had a more impaired cognitive performance, their scores were not homogeneous and a degree of individual variability was present. A division of CP subjects into primary and secondary has been recommended (Thompson et al. 1991) on the grounds that they differ widely with respect to brain imaging. However, the small number of CP patients in the present sample precluded determining whether cognitive impairment was less marked in those with a primary progressive course in whom MRI abnormalities are also less severe.

B MRI abnormalities and cognition

The only significant correlation between total MRI lesion score and a cognitive variable was with visual memory. In this regard, these results are comparable to those of Franklin et al. (1988) who employed a similar procedure in assessing lesion involvement on MRI and reported a correlation with an index of overall cognitive impairment, but differ from others (Rao et al. 1989) who found an association between total lesion area and a large number of cognitive variables. Differences in methods of estimating lesion volume are likely to account for this discrepancy and the use of more precise quantitative methods may reveal significant correlations in future studies.

This study is the first to describe a significant correlation between white matter relaxation times and focal cognitive deficits in MS, although such associations have been reported in Alzheimer's disease (Besson et al. 1989). An increase in T1 relaxation times reflects the presence of microscopic abnormalities (perivascular inflammation, myelin breakdown and astrocyte hyperplasia)(Allen et al. 1981) in the MRI normal appearing white matter and is likely to be a sensitive indicator of the presence of brain pathology responsible for the detectable cognitive impairment.

C Psychiatric change

The assessment of psychiatric morbidity in physically ill patients is not without problems as it is difficult to separate somatic symptoms (eg. fatigue) that occurred in the context of a physical disease from those which are an integral part of depression. Notwithstanding this, it was considered important to apply standard psychiatric instruments to these patients if their psychiatric phenomenology was to be understood. In a previous study (Ron et al. 1989) the CIS proved able to distinguish psychiatric symptoms in patients with MS from those directly attributable to their physical disability by comparing their results to a matched control group, also physically disabled, but without brain involvement. In the present study, these confounding effects have been minimised by excluding fatigue,

a common MS symptom, and by using a self report questionnaire (the HAD) designed specifically for use in a hospital population and therefore less reliant on physical symptoms.

When the patients were first examined over 4 years ago, they had a low prevalence of psychiatric morbidity, not greater than that encountered in the general population (Logsdail et al. 1988). At follow-up 40% had become psychiatric cases, a figure higher than that for subjects without MS in community (Andrews et al. 1977) or general practice samples (Goldberg and Blackwell, 1970). However, when the effects of fatigue were removed from the analysis, the change in "caseness" over time was not significant. Nevertheless, total CIS scores (even with fatigue excluded from the follow-up figures) showed a statistically significant increase over time. This increase in psychiatric morbidity was further confirmed by the high depression scores in the CP group on the HAD scale.

Observing the phenomenology of psychiatric change more closely, somatic complaints including fatigue, concentration difficulties and obsessional thoughts were the commonly endorsed items and as previously reported (Minden et al. 1987) the typical picture of depression associated with social withdrawal and guilty ruminations was rarely encountered. Euphoria was rare and confined to 2 subjects both of whom had a chronic-progressive course and were severely physically disabled. This supports the view that euphoria is closely associated with the severity of brain pathology (Rabins et al. 1990). The degree of physical disability was not related to psychiatric morbidity, but correlated well with the degree of perceived social stress and support and when the effect of this variable was controlled for, differences in depression between the 3 subgroups disappeared. The subjective perception of stress and support (SSSI) as measured in this study is likely to be coloured by the presence of depressed mood and therefore not wholly independent of psychiatric assessment. However, the many adverse changes experienced by these patients as their disability progresses, also reflected in this index, have a clear role in the pathogenesis of psychiatric morbidity (Ron et al. 1989).

Summary

1. Approximately 50% of patients with clinically isolated lesions had developed clinically definite MS after 4½ years.

2. Deficits in attention noted at initial cognitive assessment remained unchanged if patients had not progressed to definite MS.

3. In those patients who developed MS, memory impairment had become apparent. In addition, MS patients with a chronic-progressive course also showed a further, significant decline in auditory attention.

4. Some cognitive deficits correlated significantly with MRI abnormalities, i.e. total lesion score and raised T_1 relaxation times, thus confirming the central role of brain pathology in the pathogenesis of cognitive decline.

5. At follow-up, psychiatric morbidity had increased in the entire sample with depression being more prominent in chronic-progressive MS.

6. No correlations were found between any MRI and psychiatric indices.

CHAPTER 7

STUDY 3: Serial study

Little is known about possible short term fluctuations in cognitive ability and mental state in MS patients who experience clinical relapses. The aim of this study was therefore to investigate whether aspects of cognitive function, i.e. attention and speed of information processing, fluctuate over weeks or months in association with changes in brain involvement as visualised on MRI. A similar relationship was sought for anxiety and depression.

1 Methodology

A Subjects

i Two patient groups entered the study:

Group A: 5 patients with "active", early RR disease were included in this group. The mean age was 30 years with a mean Expanded Disability Status Score (EDSS)(Kurtzke, 1983) of 3.1 and a mean duration of illness of 4 years (range=2-8 years).

Group B consisted of 5 patients with longstanding "stable" MS. Their mean age was 46 years, with a mean EDSS of 2.8 and a mean duration of illness of 22 years (range=14-34 years).

ii Each patient was individually matched with a healthy control in terms of age (within 3 years), sex and premorbid IQ (within 7 points on a reading test). The subjects' characteristics are shown in *Table 12*.

B MRI assessment

T_2-weighted MRI of the brain was performed (Picker 0.5T, $SE_{2000/60}$, 5mm contiguous slices, 128 × 256 image matrix). Thereafter, Gadolinium-DTPA (Gd-DTPA) 0.1 mmol/kg. was injected intravenously and T_1 weighted scans of the brain were obtained ($SE_{500/40}$, 128 × 256 image matrix). Scanning plan was determined by 4 oblique pilots (transverse, coronal, sagittal and a final check transverse pilot) to ensure consistency throughout the study.

The scans were examined by two neuro-radiologists who were blind to the patient's disease pattern. The lesions were counted and measured in 7 periventricular (body of the lateral ventricles, frontal horns, trigones, temporal and occipital horns, third and fourth ventricle) and 9 other areas (corpus callosum, brain stem, cerebellum, internal capsules, basal ganglia, frontal, parietal temporal and occipital lobes) sites. A scoring system similar to that used in study 2 was used; lesions were weighted according to size and individual scores summed to estimate total lesion load. Thus, 1 point was given for lesions between 2-5 mm in diameter, 2 points for 6-10 mm and 3 points for greater than 10 mm. The degree of lesion enhancement was assessed using the same system and an enhancement score (range=0-10.0) thus obtained.

C Psychometric Assessment

The psychometric testing was primarily aimed at exploring attention and information processing speed and tests selected were those thought least likely to be influenced by the effects of practice. Details of these tests have been described in *Study 1: Chapter 5.*

i) The Purdue Pegboard Test (Purdue Research Foundation, 1948).

ii) The Stroop Colour-Word Test (Stroop, 1935).

iii) The Symbol-Digit Modalities Test (SDMT)(Smith, 1968).

iv) The Paced Auditory Serial Addition Task (PASAT)(Gronwall, 1977).

v) The Paced Visual Serial Addition Task.

vi) Simple Reaction Time (SRT).

vii) Choice reaction time (CRT).

viii) An estimate of premorbid IQ was obtained using *The National Adult Reading Test (NART)*(Nelson, 1976). This test was only used at the initial session.

ix) The Advanced Raven's Progressive Matrices (set 1)(Raven, 1958) was used to assess reasoning in the visuospatial modality and undertaken at the final test session.

x) In addition to the above psychometric tests, the patient and control group's mental state was documented using the *Hospital Anxiety and Depression Scale (HAD)*(Zigmond and Snaith, 1983). Scores greater than or equal to 10 on either the anxiety or depression subscale were indicative of psychiatric "caseness". The HAD scale was completed by the subject at the end of each cognitive/MRI examination.

xi) Finally, the *Social Stress and Support Interview (SSSI)*(Jenkins et al. 1981) was used to determine the amount of stress or support as perceived by the subject. The SSSI was completed at the final testing session and related to stress/support present during the previous 6 months. Together with the NART and Raven's Matrices, the SSSI was only given once.

D Testing protocol

Patients were examined neurologically and psychometrically on the same day. Neurological examination was performed by a neurologist and psychometric testing was undertaken without knowledge of whether patients had deteriorated in the interval between tests. A cursory observation however made it clear that in some patients a decline in motor ability had occurred. A relapse was defined in terms of the Poser (1983) criteria (*see study 2, chapter 6*). In order to minimise practice effects in the interpretation of the results, all patients were tested twice (referred to as P_1 and P_2 in figures 7 to 15) before starting serial MRI. The control subjects completed the same battery of tests as the patients under the same testing conditions, but did not undergo MRI. Having completed the two practise sessions, Group A with their matched control subjects were seen two weekly over 6 months while Group B and their controls were seen monthly. Thus, the former were seen 12 times and the latter 6 times in addition to the 2 practice sessions for each. An attempt was made to keep the time and place of testing constant throughout the trial. Thus all participants were tested before midday and patients underwent MRI either immediately before or after cognitive testing. While there was individual variation in the order of psychometric/MRI investigation, this remained constant for each patient for the duration of the study.

E Statistical Analysis

Sample sizes placed limitations on the way the data could be analysed. Group A's results were analysed separately from those of Group B given the differences in both the number of times they were seen and intervals between testing. With an effective sample size of 5, the probability of obtaining a type II error was high. This was illustrated by results of the Wilcoxon Matched-pair Signed-rank Tests undertaken on summary measures such as a mean score for individual psychometric measures. To obtain a statistically significant result at the 5% level all 5 patients with MS had to have lower scores (ranks) than their matched controls. Such an occurrence would have resulted in a significance value of $p=0.04$

and it would only have needed one of the 5 patients to achieve a better score than his/her control for the significant result to disappear.

With the above limitations in mind, it was decided to concentrate on descriptive measures. Graphs representing individual and group performances for all tests were completed, the graph for each patient and matched control appearing on the same set of axes. The axis calibrations were standardised for each test and kept identical for all 10 case-controls thereby facilitating comparisons between them. The fact that testing took place at a fixed interval of either 2 or 4 weeks meant that the area under the curve for each subject for each test corresponded closely to their mean performance for that test over the 6 months. Thus, visual inspection of the graphs gave a clear indication of these mean differences. For the Reaction Time Tests, the graphs represent a mean time for all the stimuli combined.

Individual patient's clinical condition and performances on psychometric testing were compared to their MRI results (both lesion and enhancement scores). To avoid multiple correlations, the graphs of their MRI scores were visually inspected and only those in which an increase in lesion load had occurred were included in the analysis. Thus patients 4,5,8 and 9 were not studied further. If an increase in MRI scores occurred without a corresponding change in the performance of a given test, it was concluded that the test in question was insensitive to these changes.

The number of missing values was small and dealt with as follows: Two control subjects (*no. 14 and 20*) could not complete their final testing session and values from their previous session were substituted instead. A single patient (*no.3; Group A*) developed bilateral colour blindness during sessions 11 through 13 (with full recovery by session 14) and was unable to do the Stroop paradigm for these 3 sessions. Values were substituted by taking the average of her scores from sessions 11 and 14. A temporary software fault resulted in Simple Reaction Time data being lost for *patient 1* and *control 4* at their 10^{th} test session and an average based on times from sessions 9 and 11 was substituted.

2 Results

In Group A, 4 of the 5 patients experienced a total of 8 clinical relapses and two patients (nos. 1 and 2) deteriorated substantially, the former entering a chronic-progressive phase. Both patients were unwilling to receive steroids. In Group B, a single patient had 2 relapses (patient 10) and developed a chronic-progressive course during the study. There was no overall neurological improvement in any patient during the 6 months although 1 patient from Group A (no. 4) and 4 patients from Group B (nos. 6, 7, 8 and 9) remained stable. Thus, in relation to their level of physical disability at which they entered the study, no patients experienced a remission in their MS.

A MRI

Total lesion and Gadolinium enhancement scores

Group A: The mean lesion score on entry to the study was 30. Over the 6 months a further 44 new lesions developed, largely due to changes in patients 2 and 3 as lesion scores for patients 4 and 5 remained constant while patient 1 only showed a small, initial rise. Three lesions disappeared during the study. The individual total lesion scores over time are shown in *fig. 5a*.

Following injection of Gd-DTPA, 34 (77%) of the new lesions enhanced, all but one occurring in patients 2 and 3 (*fig. 5b*). Enhancement scores generally increased when total lesion score went up, but the relationship became ill defined when total lesion score stayed constant. Four chronic lesions also showed enhancement.

Group B: Changes in lesion score were less marked than in Group A, although the Group's mean lesion score at entry to the study was higher (i.e 44). However, less lesions (20) developed over time, the majority occurring in patient 10 who had the highest lesion load of any patient at entry to the study. As in Group A, three

lesions disappeared and no decrease of more than 2 points in the lesion score occurred in any single patient. Individual lesion score changes are shown in *fig. 6a.*

Changes in lesion enhancement scores were again less marked than in Group A (*fig. 6b*) and only 7 (33%) new lesions enhanced. Patient 10 had the highest enhancement score and transient enhancement occurred in patients 7 and 8.

B Psychometric and psychiatric change

The mean and median results with standard deviations and ranges for all psychometric tests are displayed in *Table 13.* Individual and group patient-control comparisons for all psychometric tests and the HAD are shown graphically in *figures 7a* to *15a* for Group A and *figures 7b* to *15b* for Group B. The performances of all subjects on the Cued Choice Reaction Time Task were similar to those on the Warned paradigm and therefore only the latter are represented graphically.

Patients as a group performed worse than controls on all psychometric tests, although both groups tended to improve over the 6 month period at a comparable rate. Patients from Group A were more depressed than their control subjects and for the second half of the study, also more anxious, but HAD scores for depression and anxiety fell below the psychiatric "caseness" cut off point throughout the study. Patients from Group B were neither more anxious nor depressed than their matched controls and both were also under the threshold score for "caseness". Group A perceived their lives as having less stress and more support than their control subjects and the situation was reversed for Group B.

Inspection of *figures 7* to *15* reveals that patients in whom lesion load had remained relatively constant during the study showed no significant change in test performance other than that attributable to practice effects. On the other hand, those (patients 2, 3 and 10) in whom lesion load had significantly increased also exhibited clear changes in test performance.

C A detailed description of patients in whom clear MRI changes occurred during the study

i Patient number 2

A 29 year old, single, female nursing auxiliary had a 3 year duration of symptoms. She was one of a pair of dizygotic twins discordant for MS and had a second degree relative with the condition. During the study she had 3 relapses, the first from sessions P_2 to 2 with marked leg weakness and ataxia (followed by an almost full recovery), the second from sessions 6 to a week after 7, characterised by leg stiffness, right sided weakness and blurring of vision (with subsequent substantial improvement) and the third from sessions 9 to 12 with right sided weakness, mainly of the leg, and tingling in both arms from which she made a slow improvement.

The patient started with the lowest total lesion score in Group A, which after a moderate early increase, escalated more rapidly from the sixth session onwards (second relapse) and nearly doubled (22 to 43) by the end of the study. Changes in the patient's MRI lesion and enhancement scores correlated significantly ($r=0.69$; $p=0.01$). During the test period she developed a total of 19 new lesions and her EDSS deteriorated from 3.5 to 5.0, but two weekly Kurtzke ratings failed to correlate with the MRI results ($r=0.04$). Her lesion load was almost evenly distributed between periventricular and discrete brain sites including the corpus callosum, with the frontal lobes predominantly affected.

Details of her test performances are shown in *figures 7a* to *15a*. Although the patient's MRI showed the greatest decline from session 6 onwards, deterioration in her pegboard performance only occurred at session 10, a delay of 2 months (*fig. 7a*) and 2 weeks after her third relapse. Thereafter her pegboard results continued to deteriorate until the end of the study, her performance over the 12 trials correlating significantly with a changing lesion score over the same period ($r=-0.64$; $p=0.03$).

Her performance in the remaining tests fluctuated more than her control's, but failed to parallel the continuous increase in her total lesion score. Performance on tests such as the Stroop (*fig. 8a*), SDMT (*fig. 9a*), and serial visual (PVSAT)(*fig. 10a*) and auditory (PASAT)(*fig. 11a*) addition tasks, but not the simple (*fig. 12a*) and choice (*fig. 13a*) reaction time tests showed overall improvement (clearly due to practice effects) for both patient and control.

An increase in anxiety was noted at session 6 (*fig. 14a*) which coincided with the second relapse and the onset of her sustained rise in total lesion score, while a corresponding increase in depressive symptoms began 2 weeks later (*fig. 15a*). MRI changes correlated significantly with changing anxiety ($r=0.66$; $p=0.02$) and depression ($r=0.60$; $p=0.04$) scores. Despite her deteriorating scores in both subscales, these did not exceed the threshold point for psychiatric "caseness", thus suggesting emotional dysfunction was relatively mild.

ii Patient number 3

The patient was a 29 year old female, single nurse with an 8 year duration of symptoms. Six months previously, she had started amitriptyline 150 mg. and carbamazepine 600 mg. per day for relief of limb pain and continued this throughout the study. Her EDSS remained unchanged at 4.0 and correlated neither with psychometric nor MRI results at any point in the study. She experienced two relapses, the first from sessions P_2 to 3, consisting of right sided sensory disturbances more marked in her leg, fatigue, Lhermitte's symptom and occasional nausea and vertigo. The second relapse occurred from sessions 9 to 11 and consisted of blurring of vision in the right eye with mildly decreased acuity and bilateral loss of colour vision. Minimal right sided weakness was present throughout the study.

The patient started with a high lesion load that increased significantly before reaching a plateau at session 7 that lasted for 4 sessions (2 months) before increasing again (35 to 50). The periods of most marked deterioration occurred

from sessions 1 to 3 and 4 to 6, the former coinciding with a clinical relapse. Changes in magnitude for lesion and enhancement scores correlated significantly (r=0.80; p=0.002). The majority of lesions were periventricular and confined mostly to the body of the lateral ventricles and trigones, although discrete frontal lesions (8 lesions of less than 5 mm.) were present throughout. There were also more than 8 discrete frontal lesions (of < 5mm) throughout the study.

Performance on the pegboard task began to deteriorate at session 3 and showed a steep decline from sessions 4 to 5, thereafter remaining fairly constant (*fig. 7a*). The time scale of this deterioration matched the period of greatest increase in MRI lesion load, the respective changes in the two indices correlating significantly (r=-0.74; p=0.006). Further evidence of a fall-off in motor performance during this period could be seen in the simple (*fig. 12a*) and choice reaction (*fig. 13a*) time tests where a precipitous decline occurred at session 4 and continued for 2 months (until session 8). Thus, deterioration continued for a month after MRI lesion score had reached a plateau. However, taken over the 6 months, SRT and CRT performance correlated significantly with MRI lesion scores (r=0.77; p=0.004 and r=0.83; p=0.001 respectively). To investigate whether this decline in reaction times was primarily motor or indicative of deteriorating cognitive speed, the SRT was subtracted from the Warned CRT result and this difference compared to those for the remaining 4 patients in Group A. The CRT-SRT values were roughly similar for all 5 patients and thus suggested the sudden deterioration in reaction times for patient 3 was essentially a motor effect.

Interpretation of the Stroop test results (*fig. 8a*) were more difficult as her performance times started to deteriorate at session 7 in association with failing colour discrimination (bilateral). By session 9, coincidental with her second relapse, this had progressed to complete bilateral colour blindness that persisted for 6 weeks and precluded her completing the full paradigm. By the time colour vision had returned at session 12, her performance had become considerably slower. Her period of colour blindness was associated with no increase in lesion score from

session 7 to 10 and thus no significant correlation (r=0.49; p=0.10) was present between Stroop and MRI scores.

The patients performance on the SDMT (*fig. 9a*), PVSAT (*fig. 10a*) and PASAT (*fig. 11a*) was either inferior to or fluctuated more than her control. There was no sudden, consistent fall-off in her performance and overall she showed a tendency to improve with time, as did her control.

The patient also showed evidence of emotional disturbance during the study. Her anxiety symptoms (*fig. 14a*) exceeded the threshold for "caseness" on two occasions and showed a tendency to increase from session 4 onwards, but overall these scores did not show a significant correlation with her MRI lesion score (r=0.26; p=0.42). The rising depression scores (*fig. 15a*) were however significantly associated with the increasing lesion scores on brain MRI (r=0.73; p=0.007) and exceeded the "caseness" cut-off score from session 3 until the end of the study.

iii Patient number 10

The patient was a 43 year old, single English teacher with a 19 year duration of symptoms. She had a relapse at session 2 lasting one month with increasing ataxia and difficulty in walking. This was followed by a partial recovery and a second relapse at session 4 with a further increase in ataxia, leg weakness and bladder symptoms from which she did not recover. Her illness therefore entered a chronic-progressive phase with a deterioration in her EDSS from 3.0 to 6.0 over the course of the study.

She had the highest lesion score of all patients to begin with and this increased steadily over 6 months (60 to 70)(*fig. 6a*). The greatest lesion load was in the frontal lobes where 13 discrete lesions of less than 5mm were initially present. During the course of the study some frontal lesions enlarged and new lesions of less than 5mm appeared. Changes in contrast enhancement (*fig. 6b*) did not follow those of total lesion score, peaking at session 2 and thereafter declining slightly

over the remaining 5 months (r=0.48; p=0.33). MRI and EDSS changes did however correlate significantly (r=0.92; p=0.01).

Her cognitive performance differed from patients 2 and 3 in not demonstrating a sudden and consistent fall-off in performance on any of the tests. She was however the most cognitively impaired of all 10 patients and showed a unique inability to benefit from practice on the Stroop (*fig. 8b*) and 2 second PASAT (*fig. 11b*). While her overall performances were generally poor, this was most noticeable on tests without a motor component, i.e. the Stroop (*fig. 8b*), SDMT (*fig. 9b*), PVSAT (*fig. 10b*) and PASAT (*fig 11b*).

Her performances on motor oriented tasks, while inferior to her control, were relatively less impaired and demonstrated improvement over time (*figs. 7b, 12b, 13b*). The CRT minus SRT values exceeded those of the other 4 patients from Group B and pointed towards slower cognitive speed as the likely explanation for the difficulties she experienced with the choice reaction time paradigm.

This patient illustrated a paradoxical situation in that she deteriorated physically throughout the trial, had the highest lesion load and poorest cognitive performance of any patient and yet endorsed few anxiety (*fig. 14b*) or depressive (*fig. 15b*) items on the HAD. At no stage did her scores exceed the "caseness" threshold. Her lack of anxiety and depression were part of a mental state that could best be described as euphoric, demonstrating an inappropriate lack of concern for her obvious disabilities.

3 Discussion

The aim of this study was not to demonstrate differences in psychometric test performance between MS patients and controls, but rather to explore changes in cognition and mental state over time in response to changes in brain pathology as revealed by MRI. While serial imaging studies in MS have been undertaken and an association sought with neurological change (Willoughby et al. 1989; Thompson et

al. 1991), this is the first serial study trying to document concomitant psychometric and MRI changes.

A Methodological issues

This study presented a number of major methodological difficulties. The first was posed by the correct patient selection. The two MS groups were chosen with a view to highlighting longitudinal differences in cognitive performance between patients with "active" brain disease and another group with a relatively static picture, but only 2 patients in the first group followed the predicted course, which may explain the failure to find a consistent fall-off in group performance on any psychometric test. In addition, by confining one group to patients with early relapsing-remitting disease, this may have further minimised the chances, for cognitive deficits in such patients have previously been characterised as mild (Anzola et al. 1991).

A further problem in serial testing of this kind was to control for practice effects. It was therefore decided to use only tests of attention and reaction times and exclude functions such as memory, where the learning component may have been more prominent. Deficits in performance on the SDMT (Beatty and Goodkind, 1990), Paced Serial Addition Tasks (Litvan et. al. 1988a) and Reaction Time Tests (Jennekens-Schinkel et. al. 1988a+b) have previously been demonstrated in MS patients and it was therefore not surprising that patients in the present study made more errors or proved slower on timed tests. As improvements due to practice may have obscured any deteriorations or fluctuations attributable to the effects of brain disease, close individual matching with healthy control subjects was undertaken in an effort to distinguish these competing influences. With no normative serial data being available over so many trials, it also was initially unclear for what duration practice effects would continue to be evident. Working on the premise that these would be most noticeable early on and that a plateau would rapidly be reached beyond which limited or no improvement would occur, each patient was given two practice sessions before they entered the scanning protocol. This number was

limited by the logistics of carrying out such a study, which called for a high degree of compliance from both patient and control groups. From the graphic representation of group performances, it can be seen that although practice effects were most marked during these early sessions, results from tests such as the Pegboard, Stroop and Symbol-Digit Substitution Test continued to improve throughout the study. This was noticeable in both patient and control groups, which although differing in terms of speed of response and/or number of errors made, often ran a roughly parallel course. It would thus appear that patients with MS, although cognitively impaired in relation to healthy controls, have a similar ability to improve with practice.

B Psychometric change

The group performances did however obscure two important findings, namely individual differences between patients and controls and the variability in the performance of some MS patients. The latter was previously noted by Jennekens-Schinkel et al. (1990) and best illustrated in the present study by patients 4 and 5 who had virtually identical MRI results and widely different psychometric performances. The variability between ***and*** within MS patients over time could not have been due to test conditions as patients (and controls) were always tested in the same room and at approximately the same time of day. Differences in longitudinal performance for individual patient-control pairs were most apparent where MRI changes were greatest, namely patients 2,3 and 10 who all increased their contrast enhancing lesion load by more than 10 points over the 6 months. Tests with an important motor component proved most sensitive in detecting the deterioration noted on brain imaging, their sensitivity in follow-up studies having previously been noted by Ivnik, (1978b). While the remaining tests have detected group differences in cross sectional studies, they mostly proved insensitive for serial testing, performances tending to improve despite an increasing lesion load. Although practice effects could account for this, the possibility remains that other tests may have been more sensitive in mirroring the brain changes, or that newly

observed lesions did not further compromise cognition because of their localisation and/or size.

The exception to the above was patient 10 for while patients 2 and 3 primarily demonstrated a fall-off in sensorimotor tasks, she performed poorly on tests of pure cognitive ability, revealing an impaired ability to benefit from practice. This may have reflected her predominantly frontal lesion distribution and/or the presence of more subtle brain abnormalities, eg. T_1 and T_2 relaxation times in macroscopically normal appearing white matter. These were not measured in this study, but as demonstrated in the follow-up study (*chapter 6*), correlations with cognitive dysfunction have been found, particularly in patients with a chronic-progressive disease course.

C Association between MRI, psychometric and neurological abnormalities

This study also provides an illustration of the frequently observed discrepancies between neurological abnormalities on the one hand and MRI and psychometric abnormalities on the other. In patient 1, substantial physical deterioration compatible with a chronic-progressive disease course, but without an increasing brain lesion load suggested prominent spinal cord involvement, hence psychometric performance being spared. Conversely, patient 3 had an unchanged EDSS throughout the study, but lesion load went up and psychometric performance deteriorated. Patient 10 however with a steady, moderate rise in lesion score, doubled her EDSS and performed poorly on most psychometric tests. The extent of brain involvement often, but not necessarily more marked in patients with chronic-progressive illness, would therefore appear to be the crucial factor in determining psychometric performance.

D Change in mental state

Psychiatric morbidity was low in the patient group, who like their controls scored well below the "caseness" cut-off point. However, those in whom increasing MRI

abnormalities and relapses occurred during the study (patients 2 and 3) showed an overall increase in their levels of anxiety and depression, patient 3 becoming clinically depressed despite taking a tricyclic antidepressant. Whether the worsening depression was due to an increasing lesion load or a subjective response to deterioration in physical well being, or a combination of the two is difficult to discern. The only data which is roughly comparable comes from Dalos et al. (1985) who serially studied a sample of MS patients and found that clinical exacerbations were associated with increased psychiatric morbidity. Brain imaging was not however part of the protocol and no inferences could be made as to the pathogenesis of the emotional disturbance.

Patient 10 was again the exception, for despite progressive physical and MRI deterioration and consistently poor psychometric performance, she endorsed few anxiety or depressive symptoms at any stage. Her inappropriate cheerfulness and sense of physical well being suggested euphoria and persisted unabated throughout the study. This serial account thus supports the idea that euphoria in MS is a fixed, altered mental state akin to an organic personality disorder (Minden and Schiffer, 1990).

4 Implications

A study of this kind placed extensive demands on patients and controls in addition to utilising considerable financial resources. These facts limited sample size which in turn precluded any meaningful statistical analysis of the data. The difficulties of correct patient selection and controlling for practice effects over many test sessions also contributed to what was largely a negative result. Nevertheless, the idea of exploring whether short term fluctuations in cognition mirror those observed on brain MRI needed to explored and the difficulties inherent in such an undertaking exposed. The findings thus have clear implications for future research, which are to find practical, alternate methods of demonstrating cognitive and mental state change in MS, within a useful clinical context.

The fact remains that cognitive and mental state abnormalities are associated with brain involvement on MRI even in the absence of neurological signs. These subtle changes may prove valuable in comparing the effectiveness of different treatments or in monitoring responses to a specific treatment by testing patients before and after they receive it. Such protocols would be simpler than the above serial design and allow greater numbers of patients to take part.

In the present study, the data uniquely demonstrated how subjects have the ability to improve performance over 14 sessions (6 months), even on tests as straight forward as a Pegboard task. It is thus clear that practice effects will bedevil any longitudinal study and attempting to control for this with a few sessions before testing does not work. Parallel forms of tests may help in this regard.

Summary

1. As a group, patients with MS either made more errors or had slower response times than healthy controls on serial tests of attention and/or information processing speed.

2. Psychometric data in both patient and control ***groups*** *demonstrated that practice effects persisted for at least 6 months (14 sessions).*

3. As individuals, it was only the three MS patients with an increasing brain lesion load who showed either a fall-off in performance on certain psychomotor tasks or an inability to improve with practice on tests devoid of a motor component.

4. In two patients with an increasing lesion load, a significant correlation was found between MRI changes and increasing anxiety and/or depression scores.

5. Euphoria was demonstrated in a single subject with chronic-progressive MS, the highest brain lesion load and the greatest psychometric deficits.

CHAPTER 8

STUDY 4: Psychosis study

The aim of the study was first to analyse the clinical presentation, course and symptomatology of psychosis in patients with MS and second, to attempt a clinico-pathological correlation by studying the size and location of brain lesions detected by MRI in comparison with a matched group of non-psychotic MS patients.

1 Methodology

A Subjects

i Ten patients with definite MS who had experienced psychotic symptoms and had MRI scans were included in the study. This represents the total number of such patients referred to the psychiatric department of the National Hospital for Neurology and Neurosurgery over the past 6 years. The criteria of Poser et al. (1983) were used to define clinically definite MS while the term psychosis implied the presence of delusions and/or hallucinations in the absence of dementia or delirium. This allowed for the inclusion of patients with both schizophrenia and affective psychosis. Levels of physical disability were rated from case notes using the Expanded Disability Status Scale (EDSS) as in the previous studies.

ii A control group of MS patients who had not experienced a psychotic illness was used for comparison. Attempts were made to match each subject individually with a control in terms of age (± 5 years), sex, EDSS (± 1.0) and duration of M.S. (± 3 years). In one case the age difference was 7 years and in another the difference in duration of illness was 6 years. Controls were drawn from a large group of MS outpatients attending a clinic at the same hospital. Although cognitive assessment was not part of this study, no gross cognitive impairment had been clinically observed in any of the psychotic group and in all but one of the control subjects.

B Psychiatric assessment

In the psychotic group, mental state was assessed retrospectively using a symptom checklist (SCL) derived from the Present State Examination (Wing et al. 1974). From the SCL computerised Catego subclasses, classes and diagnoses were generated. Of these, the subclasses were preferred as they give the most information concerning the phenomenology of the disorder i.e. "nuclear schizophrenia" implying the presence of Schneiderian first rank symptoms.

C MRI assessment

Subjects and controls underwent contiguous, multislice axial MRI of the brain (Picker superconducting system) using a group standard transverse imaging plane (MacManus et al. 1989). All scanning protocols included T2 weighted images that optimised lesion detection. Thus a spin echo $(SE)_{2000/60}$ was used with a field of view of 30 cm. The number of excitations were 2, the matrix 128 × 256 pixels and the phase encoding gradient horizontal. Patients and controls had been scanned over a period of 6 years during which time changes to the MRI scanner and software upgrades were made to improve the quality of images. Thus, soon after installation the strength of the magnet was increased from .25 to .5 Tesla and slice thickness reduced from 10mm to 5mm. Despite these changes, the imaging protocols and slice thickness were the same in all patient and control groups. It was not however possible in one case to match the patient/control images for strength of magnetic field. The EDSS and MRI were performed when the patients were psychotic in 8 cases. In the remaining 2 cases, MRI was undertaken 1 and 3 years after the psychotic episode with a normal mental state at the time.

Subjects were compared to controls with respect to site and extent of lesions. MRI analysis was undertaken by a neuro-radiologist blind to psychiatric diagnosis. In assessing the MRI, a system devised by Ormerod et. al., (1987) and described previously in *chapter 6* was followed. The percentage of the total lesion score in

each particular area was obtained by dividing the score for each area by the total lesion score and multiplying by 100. This was termed the "percentage score".

D Statistical Analysis

Comparisons between patients and controls with respect to individual brain areas were undertaken with non-parametric statistics because of the ordinal system of rating the MR images. However, t-tests were used for total lesion score comparisons.

2 Results

Despite the demographic differences between two of the patients and their controls, the overall group matching was very close.(*Table 14*). The psychotic group was equally divided into either relapsing-remitting (RR) or chronic-progressive (CP) MS while the control group had 6 CP and 4 RR patients. Eight patients from each group had been treated with steroids at some stage, but in only a single psychotic subject had steroids been given prior to the onset of psychosis.

A Psychiatric features

The mean age of onset of psychosis was 36.6 years (range 26-52 yrs.). Using the SCL, 4 subjects obtained a Catego subclass of mania (*MN*), 2 of nuclear schizophrenia (*NS*), 2 of schizo-affective psychoses (*NSMN/NSPD*) and one each of paranoid disorder (*DP*) and psychotic depression (*PD*). The schizo-affective and paranoid patients were incorporated into the schizophrenic rubric which assumes primacy in a hierarchical classification system. Thus, two broad categories of schizophrenia and affective psychosis each with 5 subjects were obtained. There were no differences between the two subgroups with respect to any demographic variables, duration of MS symptoms or age of onset of the psychosis. They did however differ in physical disability where the affective subgroup had a

significantly higher EDSS (median of 6.0 vs. 2.5; Z=-2.1, p=0.04: Mann-Whitney U).

The mean duration of neurological symptoms prior to the onset of psychosis was ±8½ years (range 0 to 19 years). In all cases neurological symptoms preceded psychosis, but in one case the diagnosis of MS was made at the time of the onset of psychosis. Steroids were possibly implicated in the aetiology of 1 manic episode. Six patients were neurologically stable at the time of the psychosis while 4 were in exacerbation.

A breakdown of the frequency of individual psychotic symptoms is shown in *Table 15*. The commonest were persecutory delusions (70%) followed by less well defined symptoms designated by the PSE as "non-specific evidence of psychosis" (60%). This included heightened or changed perception, "minor" hallucinations (music, voices calling a name), suspicion, perplexity etc. Thirty percent experienced passivity phenomena and sexual/fantastic delusions while 20% had thought disorder, second person auditory hallucinations, delusions of reference and grandiose delusions. Lack of insight was common to all psychotic patients.

Six of the 10 psychotic patients had only one episode of psychosis, while 3 had two episodes and 1 had three. The median duration of psychosis was 5 weeks (range 1 to 72 weeks). Eight of these patients required psychiatric in-patient treatment and the remaining two were treated as out-patients. Neuroleptic medication was used in 8 subjects. In 9 cases the psychosis remitted, but in one a chronic, paranoid course ensued.

Two of the psychotic group had a positive psychiatric history prior to the onset of neurological symptoms, diagnosed as a phobic and antisocial personality disorder respectively. One control had been treated for a premorbid major depressive illness. Two control subjects had been treated for depressive disorders following the onset of demyelination. A positive family history was present in one subject with a depressive psychosis and another with "nuclear schizophrenia" who both had a

relative with a major depressive disorder. It was not possible to obtain this information from the case notes of the controls.

B MRI abnormalities

Comparisons between the MRI scans of the psychotic and control groups are shown in *Table 16*. The psychotic group had a greater total lesion and a total periventricular lesion score, but this was not statistically significant. Trends emerged for a higher lesion score in the psychotic group in the areas surrounding the temporal horns bilaterally (*fig. 16*). A similar result was also obtained in the left trigone and the area surrounding the third ventricle. Combining the left temporal and adjacent left trigone area scores resulted in differences between the psychotic and control groups reaching statistical significance (Z=-2.04; p=0.04: Mann-Whitney U).

A clearer picture of the difference in distribution of lesion scores between the psychotic and control MS patients was demonstrated by observing what percentage of the total lesion score was present in each particular area. In the controls, the total lesion score was distributed equally between periventricular and other brain areas while in the psychotic patients the periventricular lesion score contributed more than 60% to the total lesion score. This difference was not however statistically significant. The most marked differences were present in the area around the temporal horns where the "percentage score" in the psychotic patients was almost double that of the control group (*fig. 17*). Thus, not only did the psychotic patients have a greater lesion score but lesions were differentially distributed in periventricular areas and in particular around the temporal horns of the lateral ventricles.

The various brain areas were also analysed to determine whether the presence or absence of lesions as opposed to their size was the crucial factor, but no differences were found between the two groups.

There were no differences between the schizophrenic and affective psychosis subgroups in relation to any of the MRI parameters examined. In the psychotic group, lesion scores between the right and left hemispheres did not significantly differ. In addition, there were no significant correlations between individual psychotic symptoms and site of MRI lesions.

3 Discussion

There was a trend for the psychotic MS patients to have a higher total lesion score than a matched control group of MS patients without psychosis. This was due to higher scores in periventricular areas, in particular the area around the temporal horns of the lateral ventricles. The presence or absence of lesions in a particular site was not sufficient to discriminate between patient and control groups and lesion score was the critical variable in this regard.

A Methodological issues

Some limitations of MRI need to be considered in interpreting these results if the differences in temporal lobe pathology are to be considered causal. The anterior parts of the temporal lobes are more subject to artefact on MR images, namely carotid artery and CSF pulsation than other regions of the cerebrum. Although no motion suppression MR sequences were employed, the greatest care was exercised in distinguishing lesion from artefact and the blinded observation of subjects and controls throughout helped control for any bias in this regard.

B Phenomenology and clinical details of psychosis

The frequency of persecutory delusions and relative preservation of affective responses in the psychotic cohort confirms these features as the hallmark of psychosis associated with coarse evidence of brain disease (Slater et al. 1963; Davison and Bagley, 1969; Feinstein and Ron, 1990). However, there was also a broad degree of symptom overlap between the present patients and those reported

in the International Pilot Study into Schizophrenia (WHO, 1973) thus emphasising that on an individual basis patients with and without coarse brain disease are indistinguishable. Phenomenological reports of mania (Peselow et al. 1981), rapidly cycling bipolar disorder (Kellner et al. 1984), paranoid psychosis (Drake, 1984) and schizophrenia (Schmalzbach, 1954; Parker, 1956) in association with MS confirms this.

The late age of onset of psychosis in this sample contrasts with the findings of studies of schizophrenia and mania without demonstrable brain disease. Thus, the World Health Organisation's (1973) study of schizophrenia reported a mean age of onset of 28 years as opposed to 36 years in this sample and Winokur et al. (1969) reported a median of 25 years for the onset of mania. This age difference argues in favour of a specific causal link between the presence of MS pathology and psychosis.

C MS and psychosis: onset of symptoms

It is often notoriously difficult to determine the precise onset of demyelination and that may obscure the relationship between duration of neurological symptoms and onset of psychosis. Moreover, MRI has shown the frequency of widespread "silent" lesions of unknown age at the time of the first clinical manifestation (reference to *study 1; chapter 5*) and the association between size/presence of lesions and neurological status is often poor (Thompson et al. 1990). The present finding of psychosis occurring after MS symptoms had been present, often for many years, may have been subject to a referral bias as the sample was selected from a neurological hospital. Nevertheless, it is likely that this pattern is the rule as no MS cases were detected among a large group of first episode schizophrenic patients thoroughly screened for physical disease (Johnstone et al. 1987). Discrepancies with Davison and Bagley's (1969) data may be due to shortcomings in their series which was made up of heterogenous, published case reports. The above finding, together with the late onset of psychosis argues for the role of longstanding as well as strategically placed MS lesions in the pathogenesis of psychosis.

D MRI correlates of psychosis

The evidence that exists in the literature regarding the relationship between MRI and psychiatric abnormalities in MS tends to support the present finding of an association between psychosis and temporal, periventricular pathology. Thus, Reischies et al. (1988) have reported a connection between periventricular involvement and psychopathology although it is unclear what percentage of their patients were psychotic. In a study that comes closest to the present one, Honer et al. (1987) undertook MRI comparisons between 8 MS patients with and without psychiatric disorders, matched across relevant parameters, 3 of whom were psychotic. No differences were found with respect to total lesion area, although the psychiatric group had a greater lesion area in the temporal lobes.

The importance of temporal lobe pathology in schizophrenia has been demonstrated in a number of studies. Crow et al. (1989) found enlargement in the left temporal horn at post-mortem while MRI evidence of reduction in temporal lobe (Suddath et al. 1989) and in particular hippocampal volume (Suddath et al. 1990) is the most sensitive in-vivo evidence to date implicating these areas. Similar findings in patients with schizophrenia secondary to brain disease have been reported by some (Slater et al. 1963; Davison and Bagley, 1969), but not others (Feinstein and Ron, 1990), the latter including patients with heterogenous pathologies. In the present study however, the uniformity of the sample allowed more specific conclusions about clinico-pathological correlates to be drawn.

The fact that only 10 cases were available for study over a 6 year period in a tertiary setting, illustrates the rarity of psychosis occurring in MS. A possible explanation may be that although periventricular pathology is important in the pathogenesis of psychosis, it is an age linked phenomenon and lesions acquired in adult life have a lesser chance of producing psychosis than those acquired in utero or during the perinatal period.

The situation concerning anatomical correlates of affective psychosis has not been

researched so thoroughly. Results from CT studies are equivocal and only a single MRI study has focused on structural brain abnormalities of patients with bipolar affective disorders (Swayze et al. 1990). Here, ventricular enlargement was less than in schizophrenic patients and confined to males. The present results point to pathological changes in temporal periventricular areas as a non-specific marker for psychosis and implies that in these patients other factors may be relevant in determining the type of psychosis. The fact that affective patients were significantly more disabled than their schizophrenic counterparts despite similar brain involvement on MRI, suggests that greater physical disability, caused by spinal cord involvement and independent of brain pathology, may have acted as an important aetiological factor in this group.

Although psychosis in general was more likely to be associated with abnormalities in the left temporal horn area as opposed to the right, there was no difference in this regard between schizophrenic and affective patients. This may have been due to the use of the Catego classification which includes all patients with first rank symptoms under a "nuclear schizophrenia" grouping, even if up to 20% of manic patients may exhibit them (Carpenter et al. 1973). However, the lack of correlation between lesion side and individual psychotic symptoms argues against this.

Summary

1. Psychosis associated with MS is an unusual occurrence. On an individual basis, psychotic MS patients are phenomenologically indistinguishable from schizophrenic or manic patients without demonstrable brain disease. However, as a group they have a later mean age of onset of psychosis.

2. Compared to controls, the psychotic MS patients had a greater lesion load in periventricular areas, particularly in relation to the temporal horns.

3. The homogeneous composition of the present sample, later age of onset of psychosis and MRI findings all suggest that psychosis in MS is not a chance occurrence, but rather a consequence of the disease process.

CONCLUSION

The aim of three of the studies in this thesis was to delineate the natural history of cognitive and mental state abnormalities in MS and their correlation with a changing lesion load of the brain as visualised by MRI. The acute optic neuritis study demonstrated deficits in both visual and auditory attention within weeks of symptom onset, provided brain lesions were present. There was however little associated anxiety or depression.

The 4½ year follow-up of patients with clinically isolated lesions found that roughly half had gone on to develop clinically definite MS and that deficits in attention had spread to involve memory as well. A subgroup of patients whose MS had become chronic-progressive also showed evidence of further decline in attentional processes. However, the main factor that determined whether cognitive decline took place was the extent of lesion formation in the brain, which is often though not necessarily associated with a chronic-progressive disease course. This helps to explain the discrepant findings in the literature with regard to the association between disease course and cognitive decline. In contrast to cognition, a more complex association was found between psychiatric state and lesion load. While psychopathology was more evident in patients with greater brain involvement, patients' perceived social stress and support and their degree of physical disability also appeared to be aetiological important.

The question of whether cognitive deficits and mental state abnormalities fluctuate from week to week in association with alterations in lesion load was largely left unanswered by the third study, owing to the methodological problems inherent in such studies. Evidence did however emerge in two patients of a fall-off in psychomotor ability accompanied by increasing anxiety and depression, as the number and size of brain lesions increased.

The fourth and final study investigated the relationship between MS and psychosis. The clinical and MRI data suggested the association was not a chance phenomenon

and that MS was causally implicated in the psychosis. Periventricular temporal lobe lesions were particularly important in this regard.

These studies suggest potentially rewarding avenues that future research could pursue. The use of psychometric testing to monitor the response to treatment trials has already been touched upon. The relationship between brain and cognitive/psychiatric abnormalities could be further explored using other imaging techniques such as NMR Spectroscopy, which allows one to ascertain in vivo, quantitative measurements of biochemical and physiological processes. The significant correlations found between certain cognitive indices and T_1 relaxation times in macroscopically normal appearing white matter (*chapter 6)* illustrated the point that subtle brain abnormalities are present and exert a detrimental effect of cognition. Spectroscopy would be ideally suited to extend this line of research not only with regard to cognition, but also in the more elusive pursuit of psychiatric correlates.

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Table 1. Characteristics of patients and controls

	ON Subjects (n=42)	Control subjects (n=36) mean(sd)	*t-test/ chi-square*	*Sig.*
Sex M:F	20:22	19:17	$x^2=.05$	*NS*
Age	29.8 (6.8)	31.3 (11.1)	*t=-.69*	*NS*
Years of schooling	12.0 (1.5)	12.3 (1.6)	*t=-.74*	*NS*
Premorbid IQ (NART)	112.6 (8.6)	115.6 (6.8)	*t=-1.7*	*NS*

ON=optic neuritis
sd=standard deviation
Sig.=significance
NS=not significant

Table 2. Lesion area in optic neuritis patients

	mean	median	sd	range
pixels	128.6	23	261.52	0-1387
area (cm^2)	1.76	0.32	3.58	0-19

Table 3. T_1 and T_2 relaxation times in optic neuritis and controls.

	patients (n=30) mean (sd)	controls (n=30) mean (sd)
T_1 relaxation time (msecs)	419 (12.9)	421.1 (11.7)
T_2 relaxation time (msecs)	76.7 (2.3)	76.6 (3.3)

sd=standard deviation.

Table 4. ON subjects versus controls: psychometric results

	Group 1: Controls (n=36) mean(sd) or median(range)	Group 2: ON with normal MRI (n=19) mean(sd) or median (range)	Group 3: ON with Ab-normal MRI (n=23) mean(sd) or median (range)	*Oneway ANOVA/ Kruskal-Wallis*	*Sig.*	1 vs 2	1 vs 3	2 vs 3
Pegboard	41.8 (4.4)	37.3 (4.6)	37.7 (4.6)	***F=9.0***	***p<.0001***	*	*	.
Raven's Matrices	11.4(3.0)	10.5(2.5)	10.1(2.6)	***F=1.9***	***NS***	.	.	.
Stroop (C)	12.3 (2.3)	12.3 (2.3)	12.8 (2.6)	***F=.27***	***NS***	.	.	.
Stroop	22.4 (4.8)	22.1 (4.9)	25.1 (7.0)	***F=2.1***	***NS***	.	.	.
SDMT (mean)	11.8 (1.8)	12.0 (1.0)	12.9 (1.9)	***F=3.0***	***p<.06***	.	.	.
Letter Counting Speed	14.1 (3.8)	14.2 (2.4)	15.0 (2.8)	***F=.59***	***NS***	.	.	.
PASAT (4 secs)	2.0(0-8.0)	1.0(0-7.0)	3.0(0-14.0)	χ^2***=7.3***	***p<.03***	.	*	*
PASAT (2 secs)	7.9(3.7)	8.1(4.4)	11.2(5.4)	***F=4.3***	***p<.01***	.	*	.
PVSAT (4 secs)	0.5(0-6.0)	0(0-5.0)	1.0(0-15.0)	χ^2***=.14***	***NS***	.	.	.
PVSAT (2 secs)	4.8 (3.4)	5.9 (4.6)	7.8 (4.6)	***F=3.7***	***p<.03***	.	*	.
Alphabet Task	1.0(0-5.0)	1.0 (0-5.0)	1.0 (0-7.0)	χ^2***=2.2***	***NS***	.	.	.

Table 4 (continued)

ON=optic neuritis
sd=standard deviation
SDMT=Symbol-Digit Substitution Test
PVSAT=Paced Visual Serial Addition Task
PASAT=Paced Auditory Serial Addition Task
Time scores for the Stroop, SDMT and Letter Counting are in seconds.
Scores for the PVSAT, PASAT and Alphabet tests are number of errors made.
NS = not significant
1 vs 2 = post hoc comparisons between controls and ON group with normal MRI.
1 vs 3 = post hoc comparisons between controls and ON group with abnormal MRI.
2 vs 3 = post hoc comparisons between ON groups with normal and abnormal MRI.
"*" = significant differences ($p<0.05$) between 2 groups (post-hoc Tukey-Kramer analysis).
"." = not statistically significant.

Table 5. ON subjects vs. controls: reaction time results

	Controls (n=36) mean(sd)	ON with normal MRI (n=19) mean(sd)	ON with abnormal MRI (n=23) mean(sd)
SRT (0 secs)	0.35(.05)	0.37(.06)	0.35(0.1)
SRT (0.2 secs)	0.26(.04)	0.28(.05)	0.28(.09)
SRT (0.8 secs)	0.24(.04)	0.25(.05)	0.27(.09)
SRT (1.6 secs)	0.24(.05)	0.24(.04)	0.25(.09)
WCRT (0 secs)	0.44(.05)	0.46(.07)	0.46(.09)
WCRT (0.2 secs)	0.35(.05)	0.36(.05)	0.38(.08)
WCRT (0.8 secs)	0.32(.06)	0.34(.06)	0.32(.05)
WCRT (1.6 secs)	0.32(.06)	0.32(.05)	0.33(.06)
CCRT (0 secs)	0.43(.05)	0.43(.06)	0.44(.07)
CCRT (0.2 secs)	0.31(.05)	0.32(.06)	0.32(.08)
CCRT (0.8 secs)	0.28(.06)	0.30(.10)	0.28(.07)
CCRT (1.6 secs)	0.26(.05)	0.26(.05)	0.27(.06)

ON=optic neuritis
SRT=simple reaction time
WCRT=warned choice reaction time
CCRT=cued choice reaction time

Table 6. ON subjects versus controls: psychiatric results

	Group 1: controls (n=36) mean (sd) median (range)	Group 2: ON with normal MRI (n=19) mean (sd) or median (range)	Group 3: ON with Ab-normal MRI (n=23) mean (sd) or median (range)	*Oneway ANOVA/ Kruskal-Wallis*	*Sig.*	1 v s 2	1 v s 3	2 v s 3
HAD Anxiety	5.9 (3.9)	6.6 (2.2)	5.1 (3.4)	*F=.9*	*NS*	.	.	.
HAD Depression	2.0 (0.-10.0)	3.0 (0-9.0)	2.0 (0-9.0)	x^2*=1.5*	*NS*	.	.	.
SSSI	3.9(1.6)	4.1(1.6)	4.0(1.9)	*F=.06*	*NS*	.	.	.

ON=optic neuritis
sd=standard deviation
Sig.=significance
HAD=Hospital Anxiety and Depression Scale
SSSI=Social Stress and Support Interview
"."=not statistically significant

Table 7. Correlations between brain total lesion area and psychometric /psychiatric results.

	MRI brain total lesion area (cm^2)
pegboard	r=0.06
Raven' Matrices	r=-0.20
Stroop (secs)	r=0.30
SDMT (secs)	r=0.45*
Letter Counting Speed	r=0.22
PASAT (4 secs)	r=0.48**
PASAT (2 secs)	r=0.31
PVSAT (4 secs)	r=0.13
PVSAT (2 secs)	r=0.25
Alphabet Task	r=0.19
Mean SRT (secs)	r=0.10
Mean Warned CRT	r=0.11
Mean Cued CRT	r=0.11
HAD Anxiety	r=-0.26
HAD Depression	r=-0.12
SSSI	r=0.05

* = $p<0.01$
** = $p<0.001$
SDMT=Symbol-Digit Substitution Test
PASAT=Paced Auditory Serial Addition Task
PVSAT=Paced Visual Serial Addition Task
SRT=Simple Reaction Time Test
CRT=Choice Reaction Time Test
HAD=Hospital Anxiety and Depression Scale
SSSI=Social Stress and Support Interview

Table 8. Changes in psychometric performance over time

	N	Initial Assessment mean (sd) or median (range)	Follow-up Assessment mean (sd) or median (range)	*t-test/ Wilcoxon Matched Pairs*	*Sig.*
IQ deficit	33	0.0(-11.0-14.0)	0.0(-16.0-17.0)	*Z=-1.1*	*p=0.28*
GNT	34	22.1(4.5)	22.4(5.7)	*t=-0.49*	*p=0.63*
Verbal memory	35	13.0(6.0-15.0)	13.0(6.0-14.0)	*Z=-0.09*	*p=0.92*
Visual memory	34	11.0(2.9)	9.1(3.9)	*t=3.62*	*p=0.001*
WCST	33	4.0(0-17.0)	4.0(0-22.0)	*Z=-0.43*	*p=0.66*
Alphabet task	32*	2.0(0-6.0)	1.0(0-10.0)	*Z=-0.39*	*p=0.69*
Letter Counting Speed (secs)	14*	15.6(3.9)	16.2(3.5)	*t=-1.1*	*p=0.29*

N=no of subjects.
Sig.=statistical significance
GNT=Graded Naming Test; WCST=Modified Wisconsin Card Sort Test
* in the original study, only 32 and 14 patients out of the present 35 had given the alphabet and letter counting test respectively.

Table 9. Demographic and disease characteristics of patients at follow-up

	Group 1: CIL mean(sd) or median (range) n=16	Group 2: RR mean(sd) or median (range) n=12	Group 3: CP mean(sd) or median (range) n=7	*Oneway ANOVA/ Kruskal-Wallis*	*Sig.*	1 v s 2	1 v s 3	2 v s 3
Age (years)	41.3(10.6)	39.8(11.8)	40.4(13.8)	*F=0.06*	*p=0.94*	.	.	.
Sex (M:F)	6:10	3:9	4:3					
Education[1]	12.3(1.4)	11.6(1.4)	11.9(1.5)	*F=0.79*	*p=0.46*	.	.	.
Age of symptom onset	34.8(10.9)	34.1(10.9)	32.9(13.1)	*F=0.07*	*p=0.93*	.	.	.
Duration of symptoms[2]	76.3(39.9)	71.8(38.1)	90.9(25.8)	*F=0.60*	*p=0.55*	.	.	.
duration of follow-up[2]	55.5(6.7)	51.6(7.7)	55.1(6.3)	*F=1.11*	*p=0.34*	.	.	.
EDSS	1.35(0-4.5)	2.3(0-6.0)	4.5(1-8.0)	x^2*=8.8*	*p=0.01*	.	*	.
Total MRI lesion score	2.0(0-24)	18.5(4.0-36)	23.5(14-47)	x^2*=19.1*	*p=.001*	*	*	.
T_1 relaxation time (msecs)	425.9(15.4)	431.3(15.9)	440.9(28.6)	*F=1.3*	*p=0.28*	.	.	.

T_2 relaxation time (msecs)	78.0(3.1)	78.5(2.7)	80.6(6.6)	*F=0.91*	*p=0.41*	.	.	.

CIL=clinically isolated lesion group
RR=relapsing-remitting MS group
CP=chronic-progressive MS group

sd=standard deviation
Sig.=statistically significant
EDSS=Expanded Disability Status Scale
[1]=years
[2]=months
sd=standard deviation
"*"=statistically significant post-hoc Tukey analysis at a 5% significance level
1vs2=CIL compared with RR patients
1vs3=CIL compared with CP patients
2vs3=RR compared with CP patients

Table 10. Psychometric and psychiatric performance of the isolated lesion, relapsing-remitting and chronic-progressive groups

	Group 1: CIL mean(sd) or median(range) n=16	Group 2: RR mean(sd) or median(range) n=12	Group 3: CP mean(sd) or median(range) n=7	*Oneway ANOVA/ Kruskal-Wallis*	*Sig.*	1 v s 2	1 v s 3	2 v s 3
NART	112.1(7.5)	112.4(5.0)	106.1(8.2)	*F=2.2*	*0.12*	.	.	.
Full IQ	113.1(12.4)	113.0(8.6)	102.8(11.2)	*F=1.9*	*0.17*	.	.	.
IQ deficit	-0.93(8.1)	-0.67(6.6)	3.8(7.7)	*F=0.81*	*0.46*	.	.	.
GNT	23.5(4.8)	21.8(6.8)	21.0(6.4)	*F=0.53*	*0.59*	.	.	.
Verbal memory	13.0(8-14)	13.0(6-14)	11.0(8-14)	x^2*=2.0*	*0.36*	.	.	.
Visual memory	10.6(4.0)	7.6(3.2)	8.0(4.0)	*F=2.6*	*0.09*	.	.	.
Story Recall (i)	4.4(1.5)	4.5(1.2)	2.7(1.3)	*F=4.3*	*0.02*	.	*	*
Story Recall (d)	4.6(1.5)	4.5(1.2)	2.9(1.3)	*F=4.4*	*0.02*	.	*	*
PALT (semantic)	25.8(4.0)	26.5(3.5)	23.5(3.4)	*F=1.3*	*0.29*	.	.	.
PALT (noun-verb)	25.4(3.2)	24.1(4.7)	18.3(4.2)	*F=7.2*	*0.003*	.	*	*
WCST	5.2(5.1)	5.0(5.6)	5.2(4.3)	*F=0.01*	*0.99*	.	.	.
Alphabet Task	1.0(0-6)	0.5(0-3)	3.5(0-10)	x^2*=6.0*	*0.05*	.	*	*
Letter Counting speed	15.7(2.8)	15.6(3.5)	19.5(4.5)	*F=2.8*	*0.08*	.	.	.

CIS	8.4(7.6)	10.7(9.1)	16.0(9.3)	*F=1.9*	*0.16*	.	.	.
HAD Anxiety	5.3(3.8)	6.5(4.1)	6.0(3.8)	*F=0.32*	*0.72*	.	.	.
HAD Depression	3.7(3.1)	3.5(3.3)	9.3(4.9)	*F=6.5*	*0.003*	.	*	*
SSSI	5.0(1-6)	3.0(0-6)	2.5(0-6)	x^2=6.5	*0.04*	.	*	.

CIL=clinically isolated lesion group
RR=relapsing-remitting group
CP=chronic-progressive group

NART=National Adult Reading Test; GNT=Graded Naming Test; Story Recall (i) and (d)=*immediate* and *delayed* respectively; PALT=Paired Associate Learning Test; WCST=Modified Wisconsin Card Sort Test; CIS=Clinical Interview Schedule; HAD=Hospital Anxiety and Depression Scale; SSSI=Social Stress and Support Interview.

"*" denotes statistically significant differences between CIL, RR and CP groups following post-hoc Tukey analysis.

Table 11. Analysis of Co-variance results

	PALT.NV	RECALL (i)	RECALL (d)	ALPHABET TASK	HAD DEPRESSION
	t value Sig.	*t Sig.*	*t Sig.*	*t Sig.*	*t Sig.*
CIS	-2.90; 0.008	-1.14; 0.26	-1.42; 0.17	1.35; 0.19	
SSSI	-0.26; 0.70	0.41; 0.68	0.37; 0.71	-0.77; 0.45	-2.50; 0.02
EDSS	-3.60; 0.001	0.63; 0.53	0.19; 0.85	1.51; 0.14	0.60; 0.56
GENDER					0.52; 0.61
GROUP F value*	*2.59; 0.09*	*3.09; 0.06*	*2.67; 0.09*	*3.57; 0.04*	*1.95; 0.16*

CIS=Clinical Interview schedule; SSSI=Social Stress and Support Interview
EDSS=Expanded Disability Status Scale; PALT.NV=Paired Associate Learning Test (Noun-Verb)
RECALL (i)=Immediate Story Recall; RECALL (d)=Delayed Story Recall
HAD=Hospital Anxiety and Depression Scale
t=t value of the co-variate
*GROUP F value=differences between clinically isolated lesion, relapsing-remitting and chronic-progressive MS patients once the effects of the co-variates have been controlled for.

Table 12. Demographic comparisons between patients and controls

Values for matched control subjects in brackets.

	Age	Sex	Premorbid IQ (NART	Years of education	Raven's Matrices	EDSS 1	EDSS 2	Duration of symptoms (years)
Group A:								
patient 1	28(31)	M	114(121)	11(12)	100(100)	3.5	6.0	3
patient 2	29(31)	F	115(120)	13(13)	100(140)	3.5	5.0	3
patient 3	29(25)	F	114(119)	12(13)	70(110)	4.0	4.0	8
patient 4	29(32)	F	114(115)	13(12)	120(120)	1.0	1.0	5
patient 5	34(33)	F	102(108)	11(12)	80(140)	3.5	3.5	2
Group B:								
patient 6	44(45)	M	114(112)	13(12)	110(130)	2.0	2.0	23
patient 7	43(46)	F	124(120)	14(14)	140(130)	3.0	3.0	14
patient 8	58(57)	M	120(119)	10(11)	120(130)	2.5	2.5	22
patient 9	41(42)	F	119(123)	13(12)	140(130)	3.5	3.0	34
patient 10	43(41)	F	123(118)	13(12)	110(130)	3.0	6.0	19

EDSS1 and EDSS2=Expanded Disability Status Scale at entry and end of study.

Table 13. Patient and control groups: Psychometric and psychiatric results

controls scores in brackets.

	Group	mean	sd	median	range
Pegboard	A B	32.8(46.3) 26.5(42.8)	5.0(4.3) 3.9(4.2)	31.9(48.6) 27.5(41.5)	26.6-39.9(41.6-50.3) 20.3-30.1(39.3-50.1)
Stroop (secs)	A B	20.7(17.7) 27.9(21.8)	5.0(5.7) 10.0(3.0)	23.6(15.6) 24.6(22.6)	15.1-25.2(13.7-27.8) 18.1-43.8(16.8-24.4)
SDMT (secs)	A B	12.5(11.4) 17.2(11.8)	1.7(1.9) 4.9(1.5)	12.4(10.9) 16.3(12.2)	10.4-15.1(9.1-14.4) 12.9-24.7(10.3-14.0)
PASAT (4 secs)	A B	2.0(0.69) 2.7(0.78)	2.6(0.48) 3.9(0.75)	1.3(0.64) 1.1(0.63)	0.07-6.5(0.07-1.4) 0.40-9.6(0.13-2.0)
PASAT (2 secs)	A B	7.5(3.3) 8.5(4.4)	5.3(1.6) 7.2(0.81)	6.3(4.1) 4.4(4.6)	2.6-15.8(0.5-4.3) 2.8-19.5(3.0-5.1)
PASAT (4 secs)	A B	1.9(0.73) 2.4(0.45)	1.6(0.84) 4.3(0.51)	1.6(0.5) 0.6(0.1)	0.14-4.4(0-2.1) 0.12-10.1(0-1.1)
PVSAT (2 secs)	A B	4.9(1.1) 5.3(1.9)	3.6(0.61) 6.3(1.0)	5.7(1.0) 2.9(1.5)	0.79-8.9(0.43-2.1) 1.5-16.6(0.87-3.5)
SRT (0 secs)	A B	0.44(0.40) 0.48(0.43)	0.08(0.07) 0.08(0.03)	0.45(0.42) 0.49(0.41)	0.34-0.52(0.28-0.48) 0.37-0.58(0.40-0.48)

SRT (0.2 secs)	A B	0.33(0.28) 0.33(0.28)	0.09(0.06) 0.07(0.03)	0.32(0.30) 0.34(0.27)	0.20-0.42(0.18-0.34) 0.23-0.40(0.26-0.32)
SRT (0.8 secs)	A B	0.34(0.28) 0.31(0.27)	0.10(0.06) 0.05(0.02)	0.35(0.31) 0.32(0.27)	0.20-0.46(0.18-0.34) 0.23-0.35(0.25-0.30)
SRT (1.6 secs)	A B	0.31(0.27) 0.29(0.25)	0.08(0.06) 0.05(0.02)	0.31(0.28) 0.29(0.26)	0.18-0.38(0.18-0.32) 0.21-0.35(0.23-0.27)
WCRT (0 secs)	A B	0.49(0.43) 0.54(0.48)	0.09(0.07) 0.09(0.08)	0.49(0.42) 0.55(0.45)	0.38-0.59(0.32-0.52) 0.42-0.64(0.44-0.59)
WCRT (0.2 secs)	A B	0.43(0.37) 0.47(0.41)	0.09(0.6) 0.09(0.06)	0.42(0.36) 0.49(0.38)	0.31-0.53(0.27-.44) 0.37-0.59(0.36-0.52)
WCRT (0.8 secs)	A B	0.38(0.33) 0.40(0.34)	0.07(0.06) 0.07(0.05)	0.38(0.32) 0.42(0.34)	0.27-0.45(0.23-0.38) 0.29-0.48(0.29-0.42)
WCRT (1.6 secs)	A B	0.38(0.33) 0.39(0.35)	0.07(0.06) 0.05(0.05)	0.38(0.34) 0.41(0.34)	0.27-0.45(0.23-0.38) 0.31-0.44(0.30-0.44)
CCRT (0 secs)	A B	0.48(0.42) 0.52(0.46)	0.08(0.06) 0.08(0.05)	0.49(0.41) 0.52(0.44)	0.35-0.56(0.32-0.49) 0.42-0.61(0.42-0.55)
CCRT (0.2 secs)	A B	0.43(0.36) 0.45(0.40)	0.09(0.06) 0.07(0.05)	0.42(0.36) 0.48(0.37)	0.30-0.52(0.28-0.44) 0.37-0.53(0.36-0.49)
CCRT (0.8 secs)	A B	0.34(0.28) 0.32(0.29)	0.08(0.07) 0.05(0.02)	0.35(0.27) 0.31(0.29)	0.21-0.42(0.19-0.36) 0.26-0.38(0.26-0.31)
CCRT (1.6 secs)	A B	0.35(0.29) 0.34(0.31)	0.07(0.06) 0.05(0.03)	0.36(0.30) 0.35(0.30)	0.25-0.44(0.20-0.35) 0.26-0.40(0.27-0.34)

HAD Depression	A B	4.9(0.7) 3.0(2.0)	5.5(0.6) 1.6(1.5)	2.0(0.7) 3.3(1.3)	0-12.2(0.08-1.5) 0.3-4.7(1.0-4.5)
HAD Anxiety	A B	5.4(4.1) 4.2(3.8)	4.5(3.1) 1.9(2.1)	3.1(2.4) 4.2(2.8)	1.6-12.7(1.0-8.0) 1.3-6.7(1.8-6.8)
SSSI	A B	4.0(2.6) 4.0(5.4)	1.4(3.0) 0.70(0.89)	5.0(3.0) 4.0(6.0)	2.0-5.0(-2.0-6.0) 3.0-5.0(4.0-6.0)
Raven Matrices	A B	94.0(122.0) 124.0(130.0)	19.5(17.9) 15.2(4.8)	100.0(120.0) 120.0(130.0)	70.0-120.0(100-140) 110.0-140.0(120-130)

Group A=early, "active" MS; Group B=benign MS
SDMT=Symbol-Digit Modalities Test (mean time)
PASAT=Paired Auditory Serial Addition Task
PVSAT=Paired Visual Serial Addition Task
SRT=Simple Reaction Time
WCRT=Warned Choice Reaction Time
CCRT=Cued Choice Reaction Time
HAD=Hospital Anxiety and Depression Scale
SSSI=Social Stress and Support Interview

Table 14. Demographic characteristics of MS patients with and without psychosis

	Psychotic group mean(sd) (n=10)	Control group mean(sd) (n=10)
Age (years)	39.6(10.8)	37.9(8.9)
Sex (M:F)	5:5	5:5
Duration of MS (years)	10.0(7.1)	10.6(4.2)
EDSS	4.9(2.3)	4.6(2.1)
Disease course (RR:CP)	5:5	4:6

sd=standard deviation
EDSS=Expanded Disability Status Scale
RR=Relapsing-remitting MS
CP=Chronic-progressive MS

Table 15. Commonest symptoms and signs (PSE) in the psychotic group (n=10)

	%
lack of insight	100
persecutory delusions	70
non-specific evidence of psychosis	60
irritability	60
agitation	50
anxiety	40
sexual delusions	30
passivity phenomena	30
delusions of reference	20
grandiose delusions	20
second person auditory hallucinations	20
visual hallucinations	20
thought disorder	20
third person auditory hallucinations	10
thought broadcast	10

Table 16. MRI lesion scores in psychotic and control patients

	psychotic group mean(sd) or median(range) n=10	control group mean(sd) or median(range) n=10	t-test/ Mann-Whitney U test	Sig.
total lesion score	32.6(13.6)	27.4(13.8)	t=0.85	p=0.41
periventricular regions				
total score	19.3(8.1)	14.0(6.6)	t=1.60	p=0.13
temporal horn:R	2.0(0-3)	1.0(0-2)	Z=-1.91	p=0.06
temporal horn:L	2.0(0-3)	1.0(0-2)	Z=-1.82	p=0.07
trigone:R	3.0(0-3)	2.0(0-3)	Z=1.61	p=0.11
trigone:L	3.0(1-3)	1.5(0-3)	Z=1.83	p=0.07
temporal horn+trigone:R	5.0(0-6)	3.0(0-50	Z=-1.81	p=0.07
temporal horn+trigone:L	4.5(1-6)	2.5(0-5)	Z=-2.04	p=0.04
III ventricle	1.0(0-1)	0.0(0-1)	Z=1.74	p=0.08
temporal lobe:R	0.0(0-2)	0.0(0-3)	Z=-1.39	p=0.16
temporal lobe:L	0.0(0-2)	0.0(0-3)	Z=-1.22	p=0.22

R=right; L=left

There were no statistically significant differences between patients and controls for MRI scores in the frontal lobes/horns, occipital lobes/horns, parietal lobes, internal capsule, basal ganglia, IV ventricle and cerebellum.

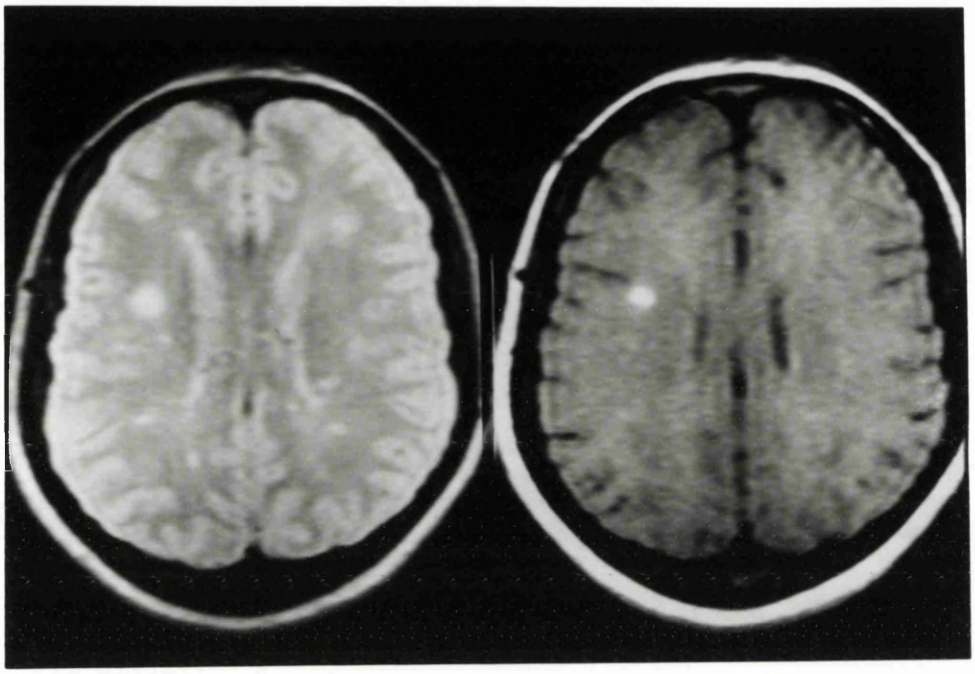


Fig. 1. MRI of the brain with and without contrast enhancement

Left image = without Gadolinium-DTPA
Right image = with Gadolinium-DTPA

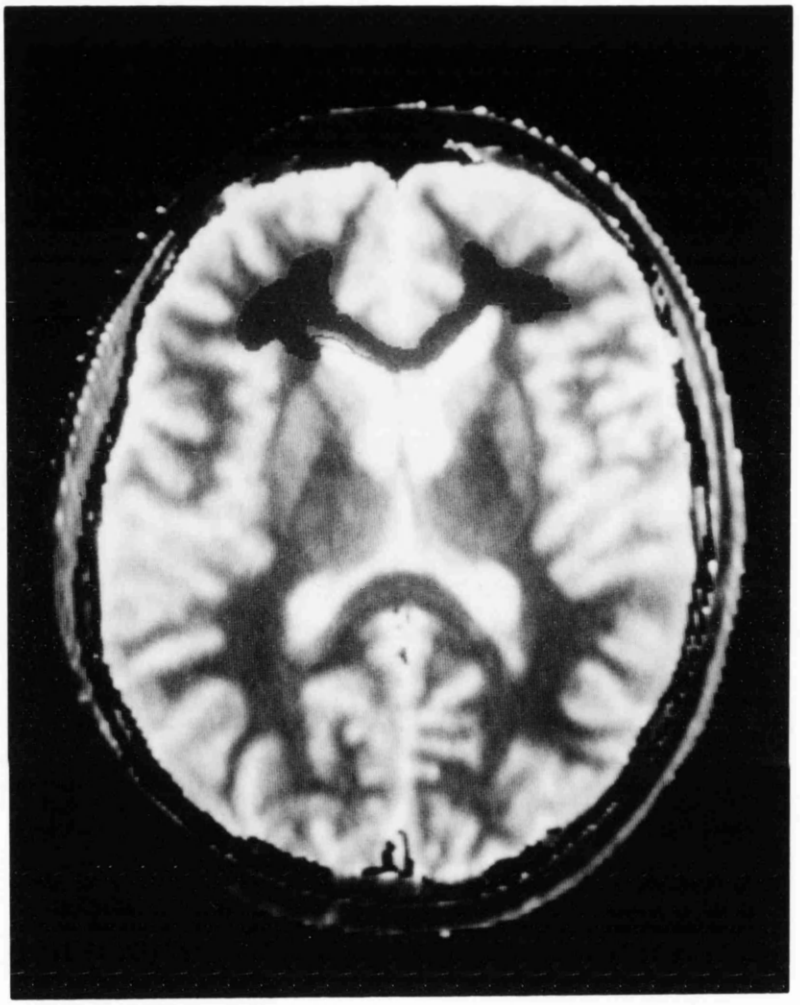


Fig. 2. Procedure for demarcating normal appearing white matter in the frontal lobes

Figure 3. Symbol-Digit Modality Test: Optic neuritis and control groups performances.

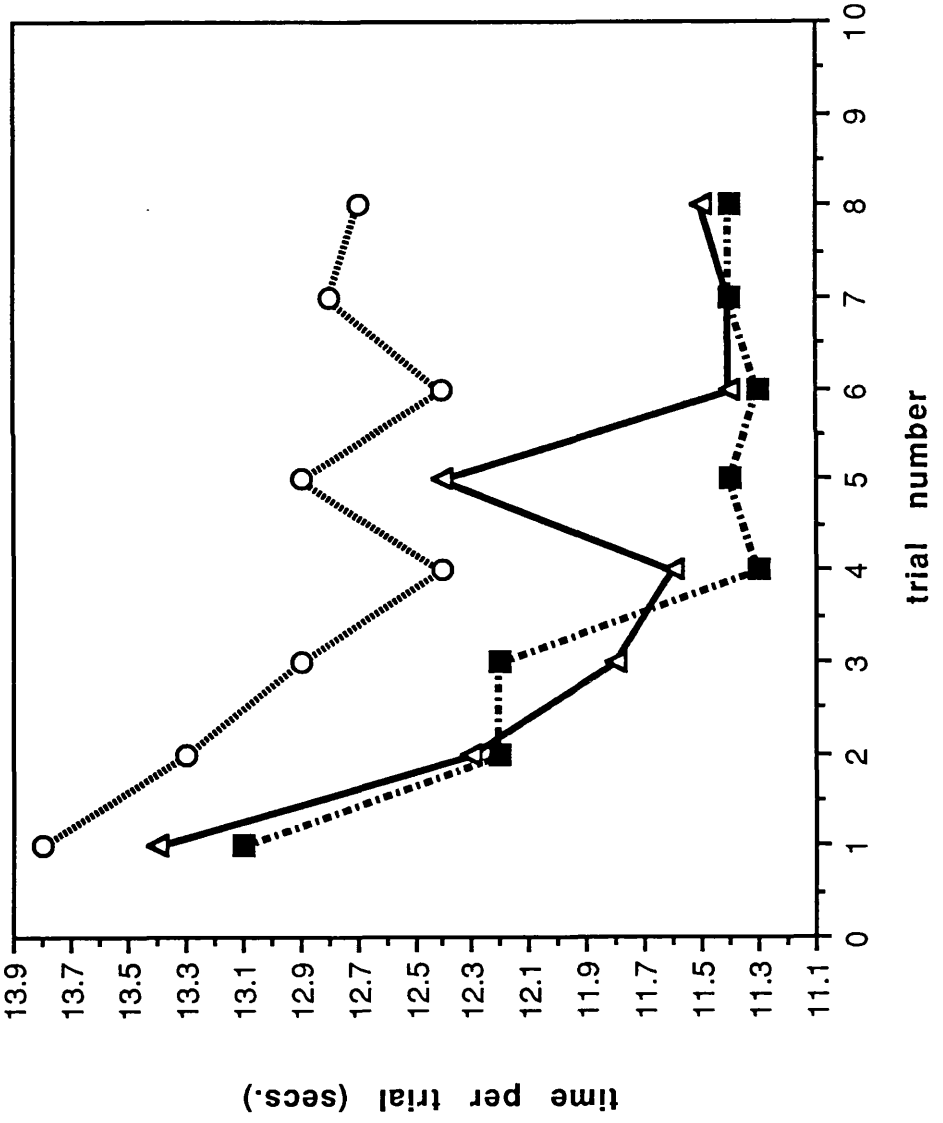


Fig. 4. Breakdown of follow-up sample

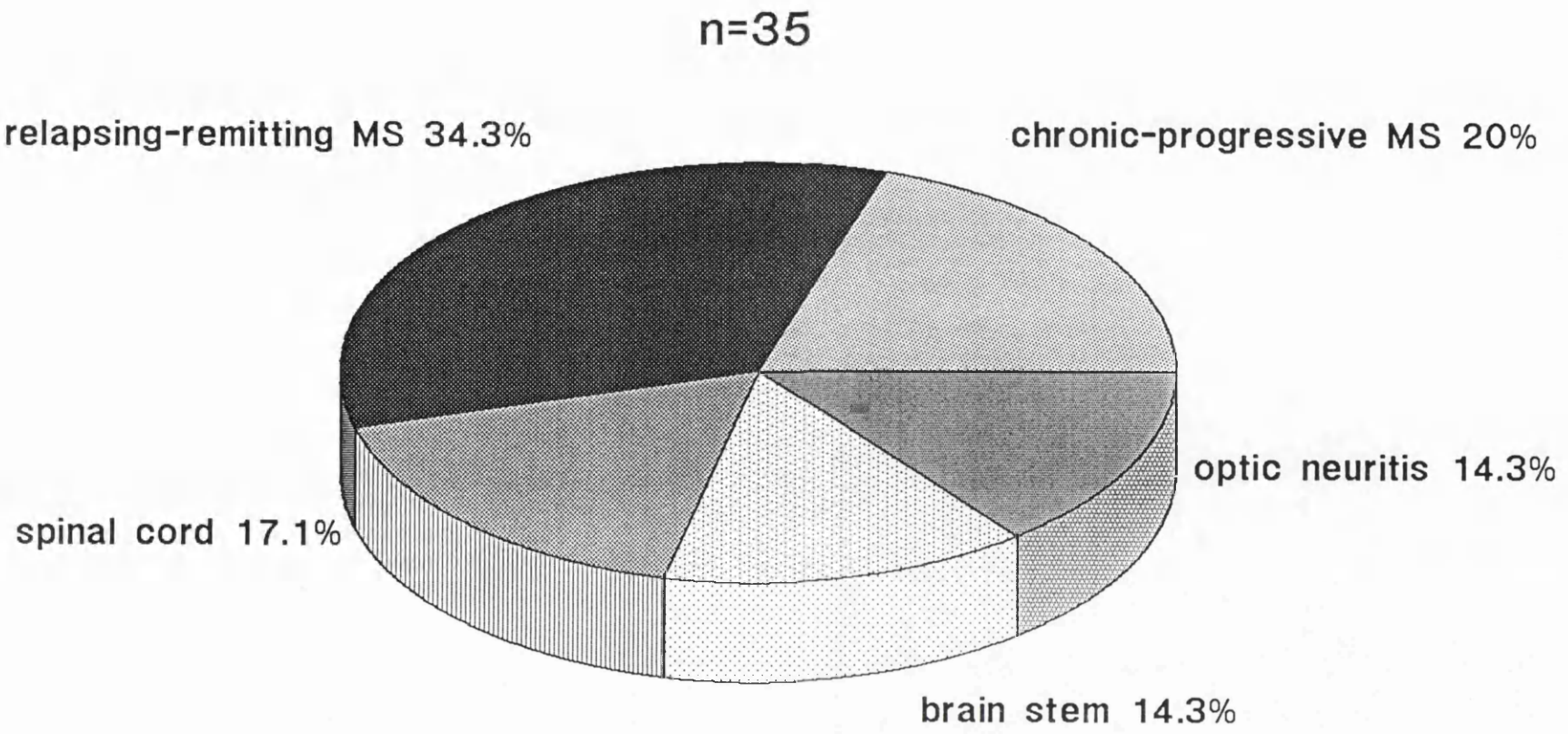


Figure 5a. MRI lesion scores.

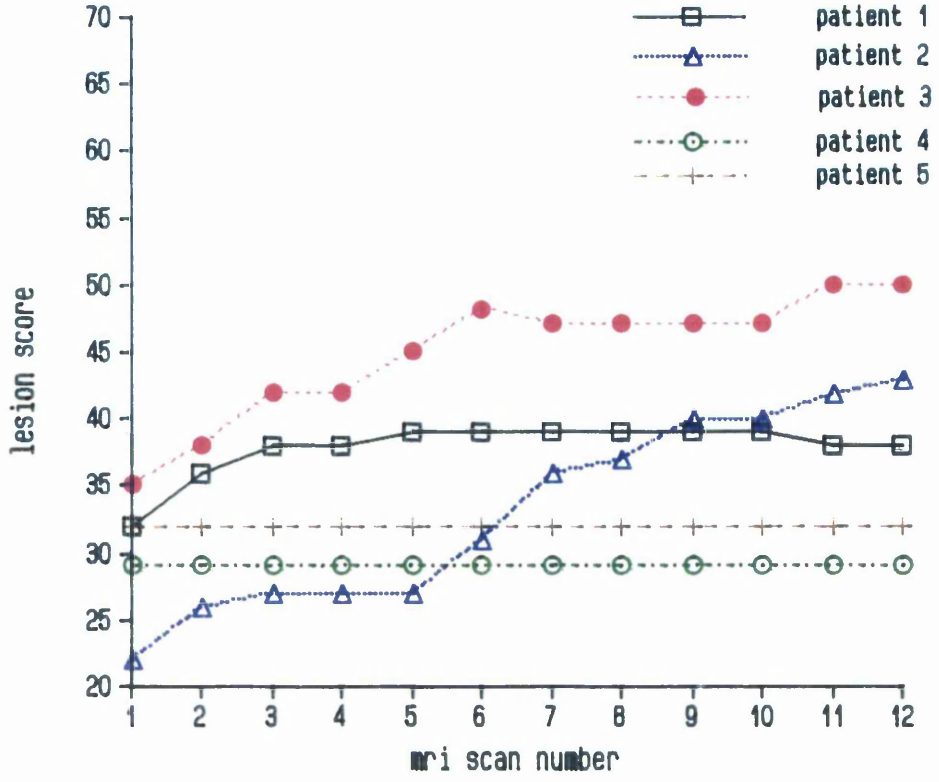


Figure 5b. Gadolinium enhancement scores

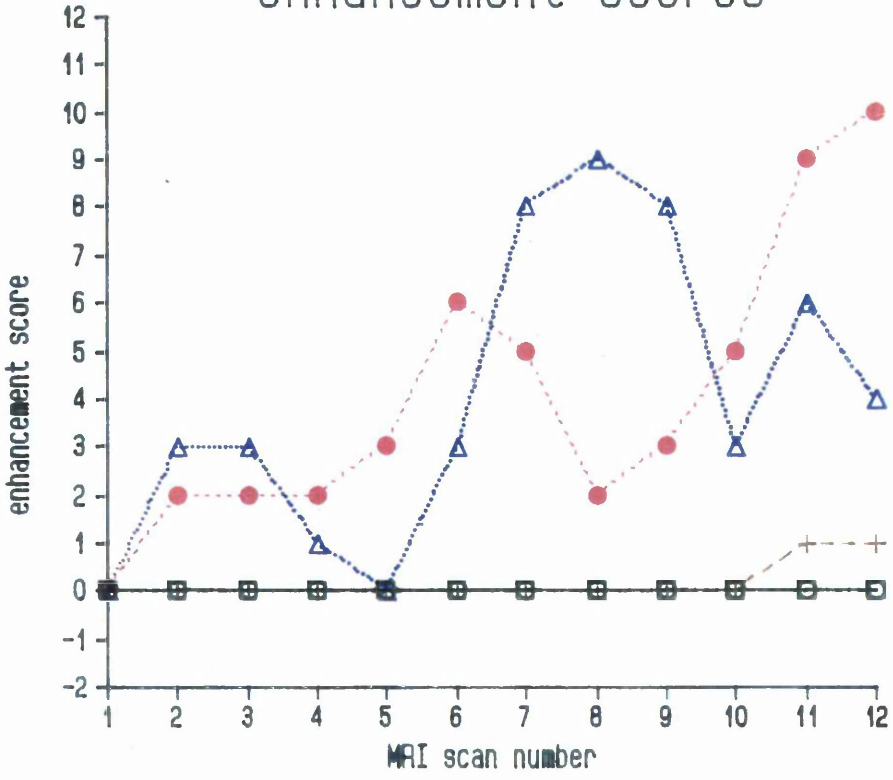


Figure 6a. MRI lesion scores.

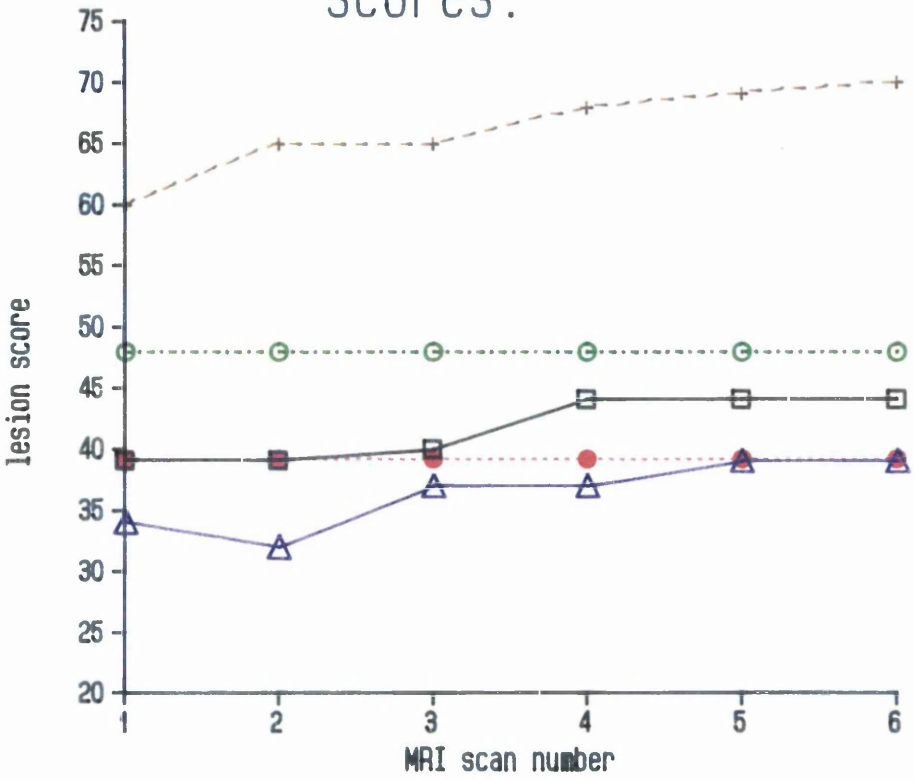


Figure 6b. Gadolinium enhancement scores

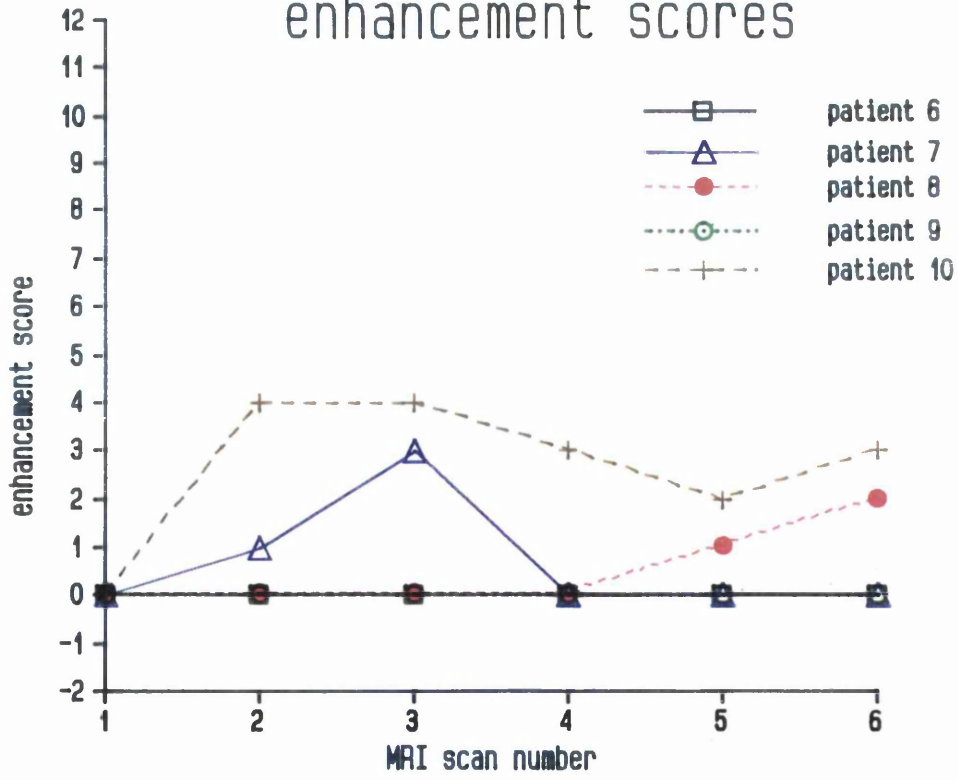
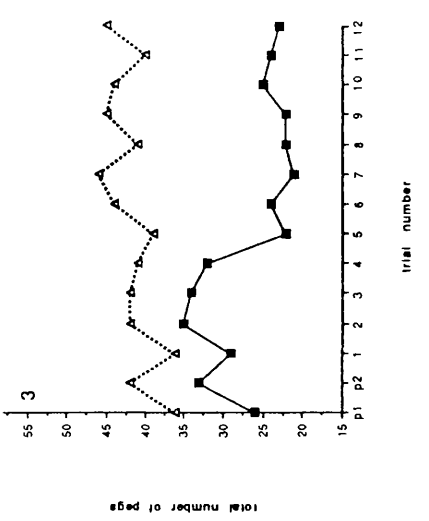
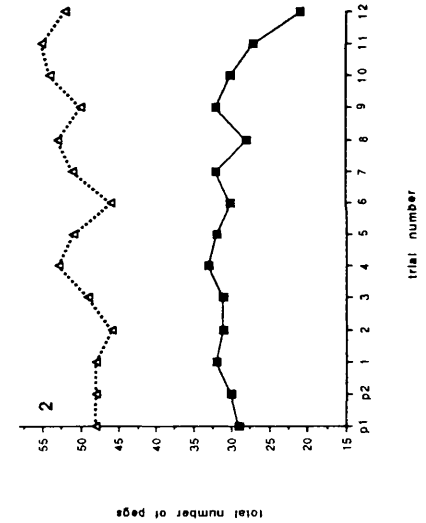
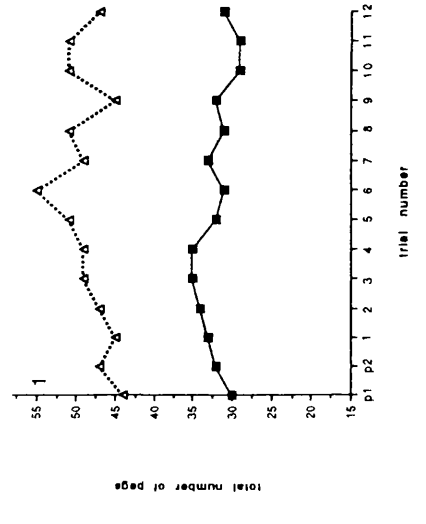


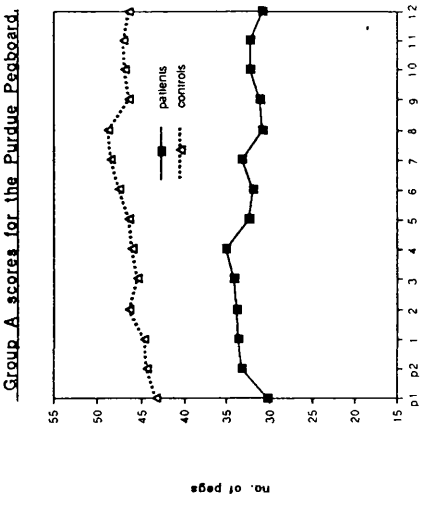
Fig. 7a. Individual and group performances on the Pegboard Test

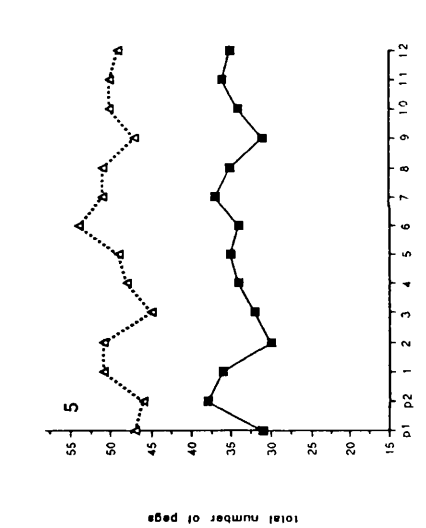






Group A scores for the Purdue Pegboard.





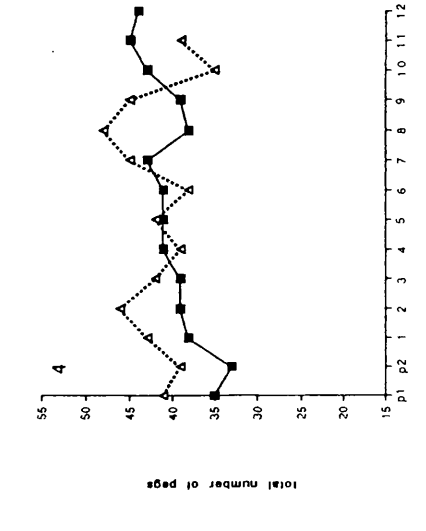


Fig. 7b. Individual and group performances on the Pegboard Test

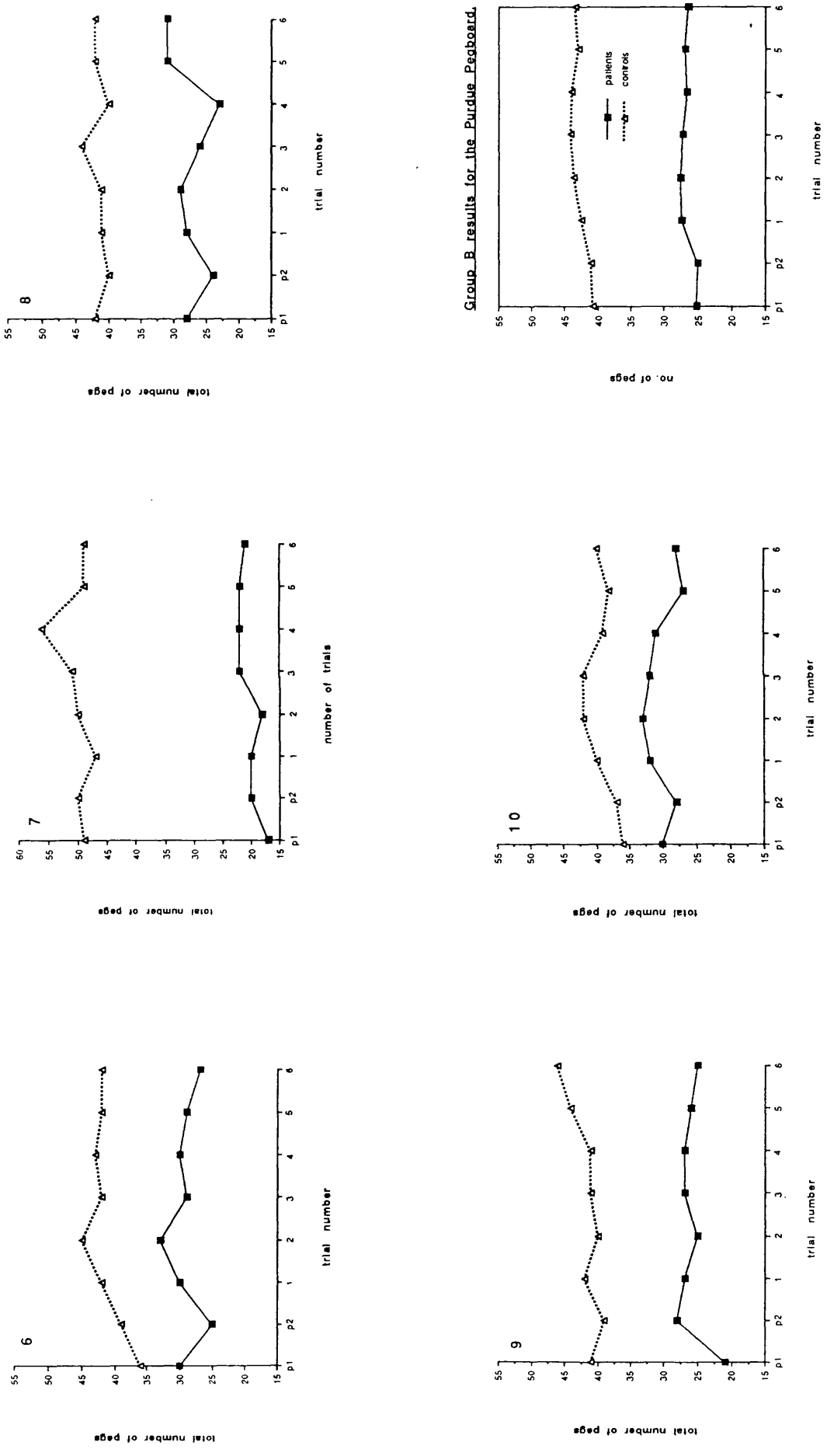


Fig. 8a. Individual and group performances on the Stroop Test

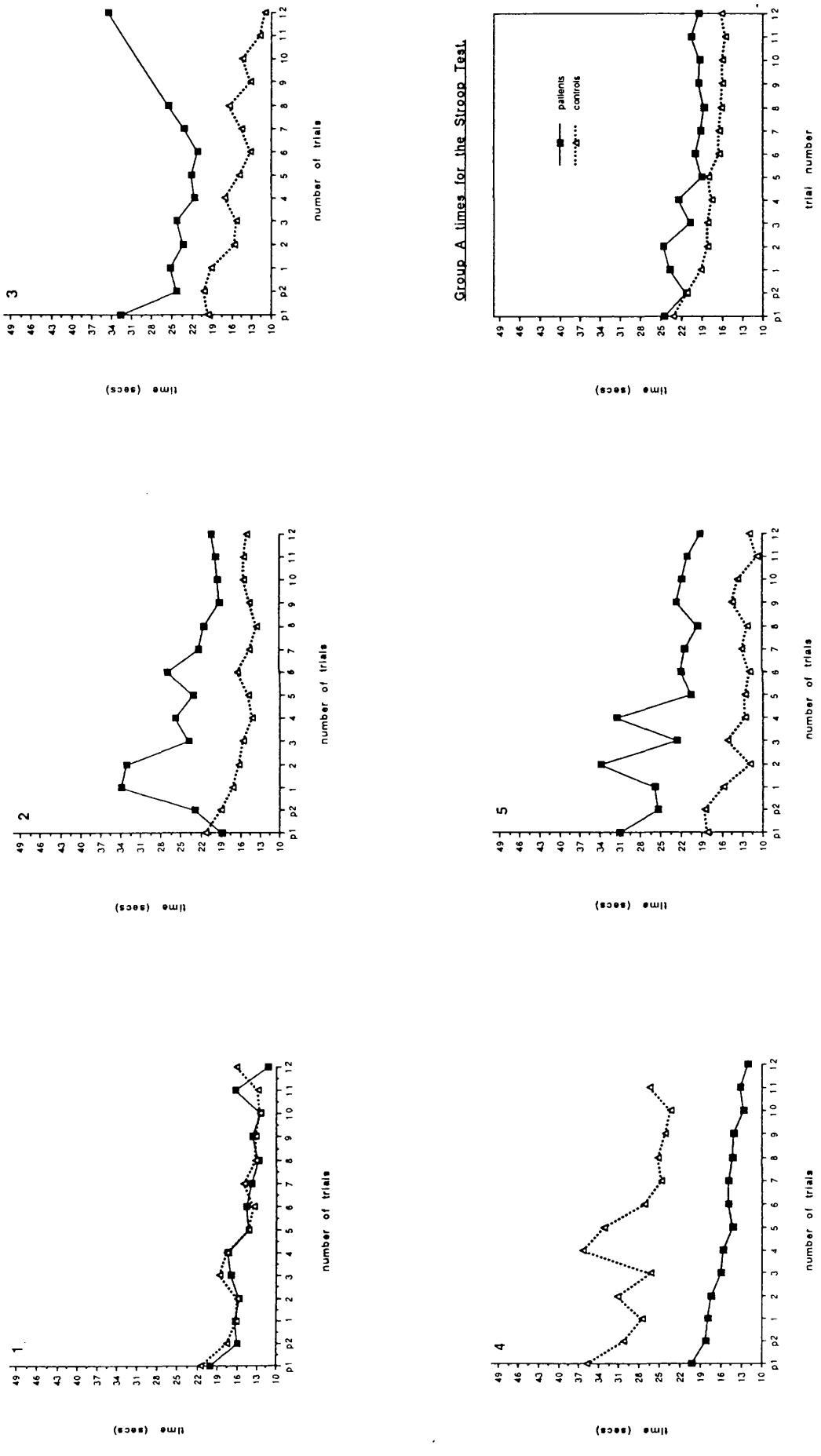


Fig. 8b. Individual and group performances on the Stroop Test

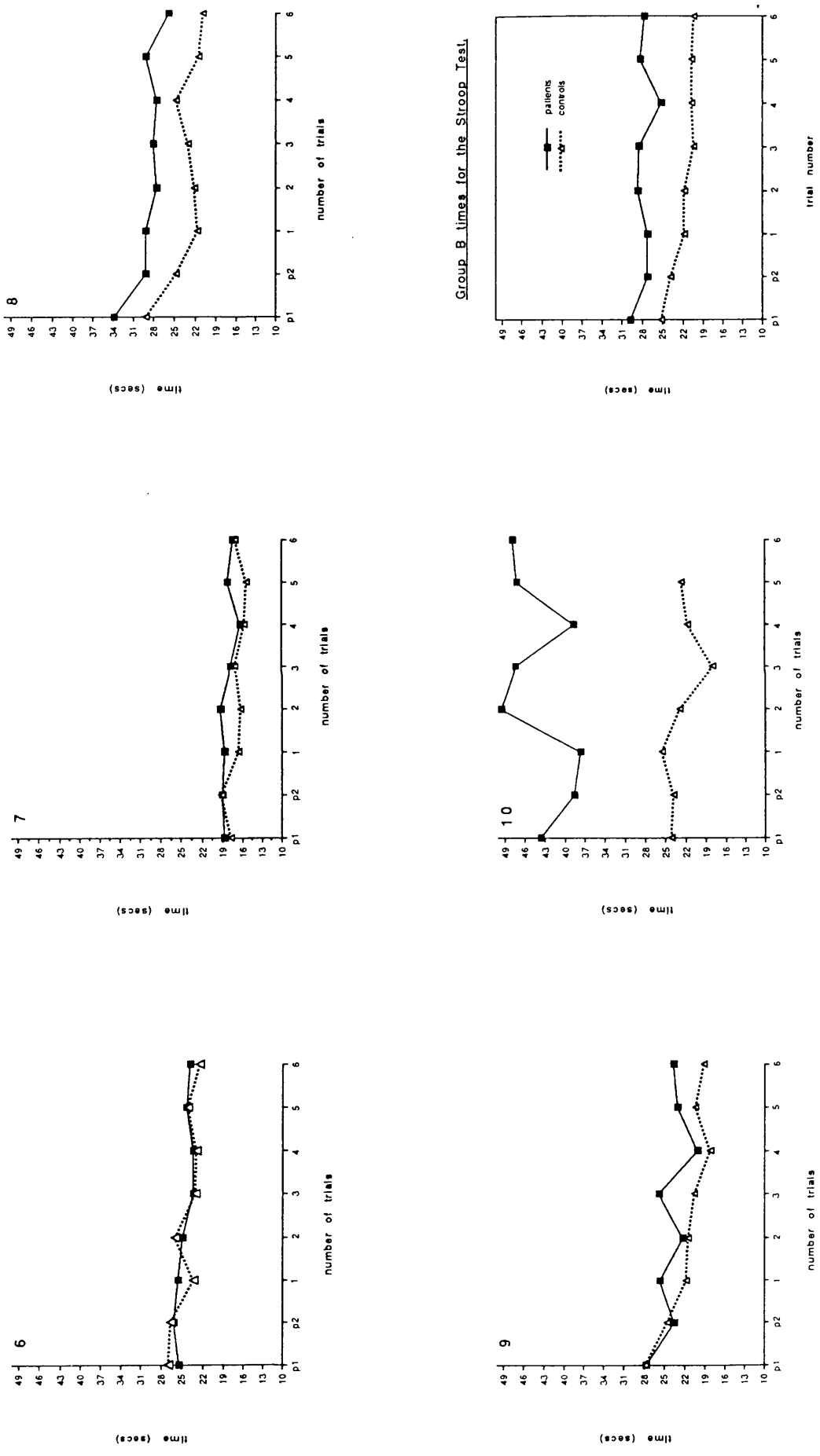
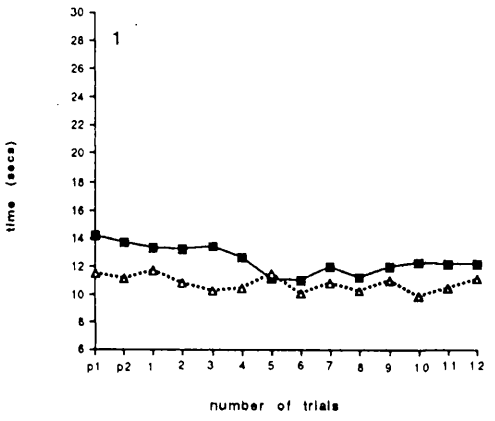
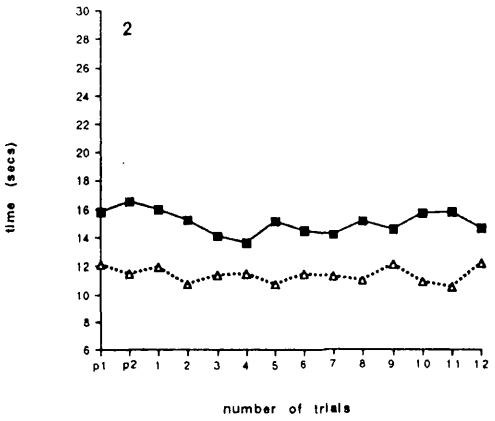
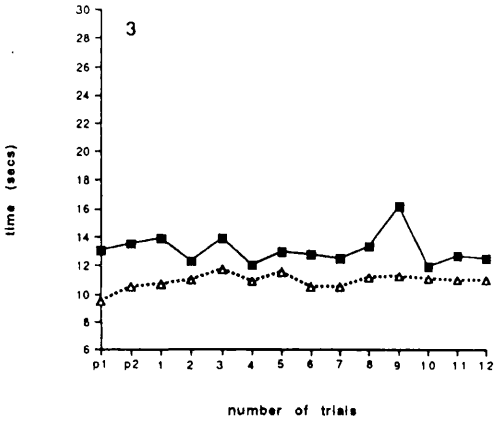
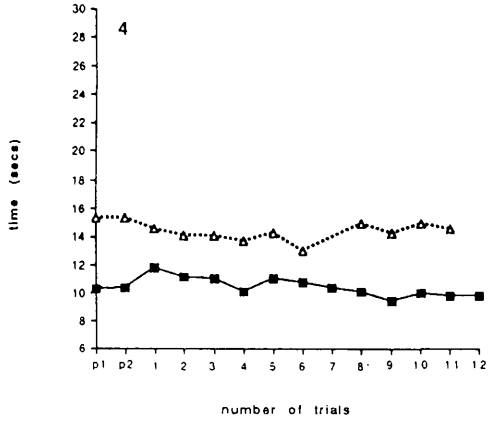


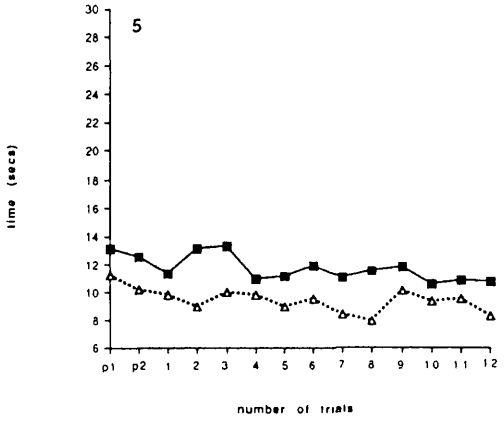
Fig. 9a. Individual and group performances on the Symbol-Digit Modalities Test











Group A scores for the Symbol Digit Substitution Test (mean time).

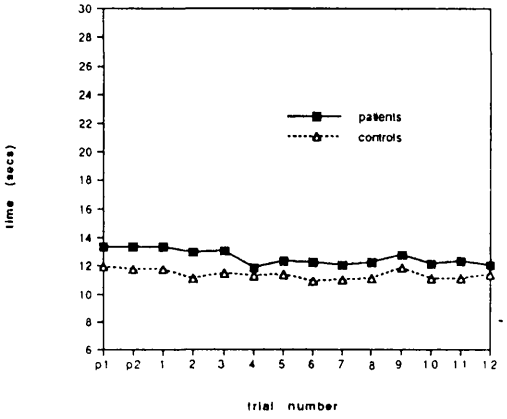
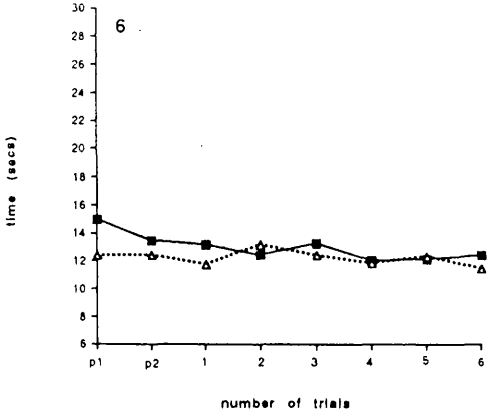
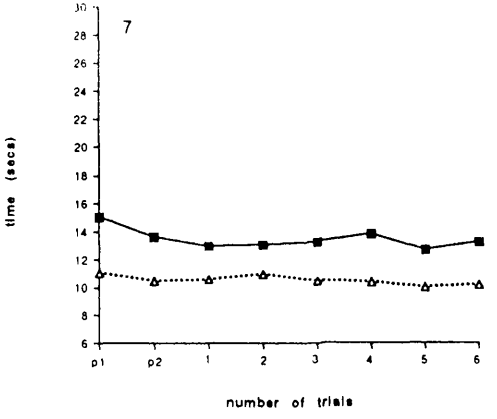
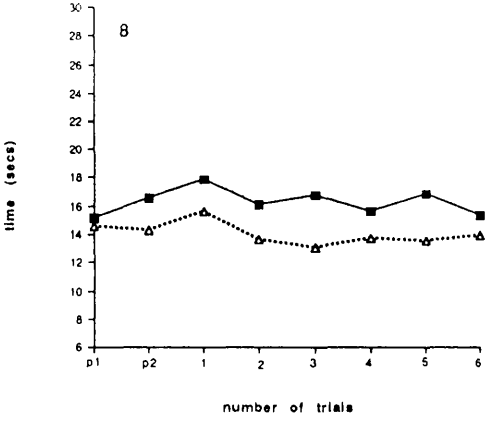
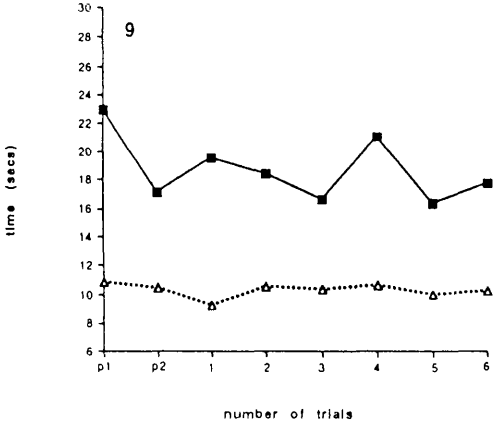


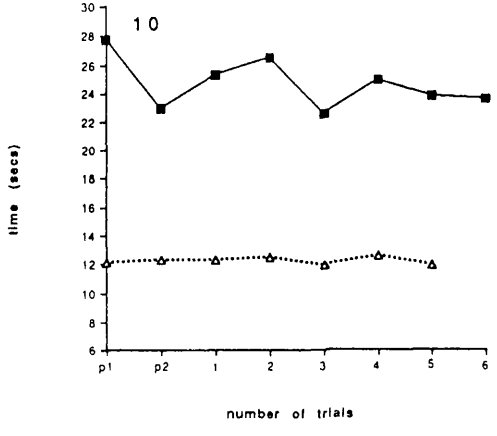
Fig. 9b. Individual and group performances on the Symbol-Digit Modalities Test











Group B scores for the Symbol Digit Substitution Test (mean time).

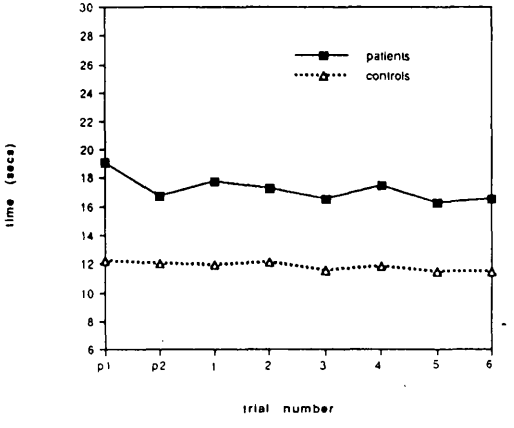
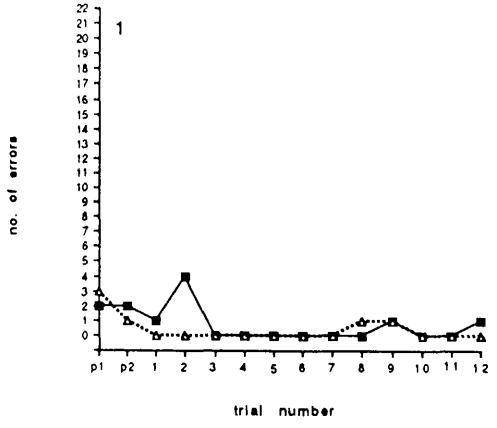
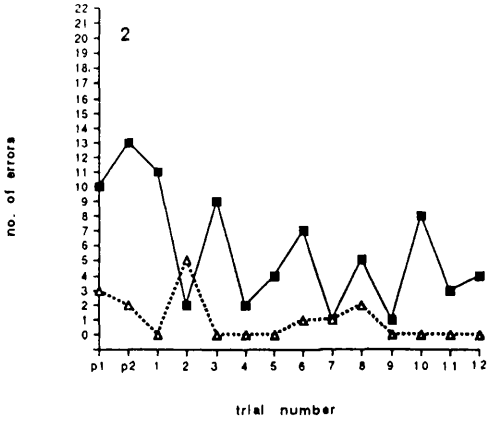
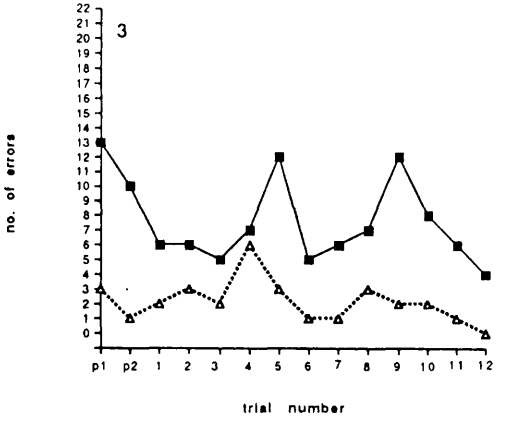
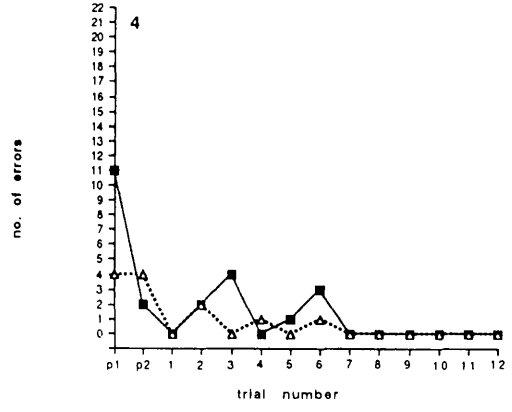


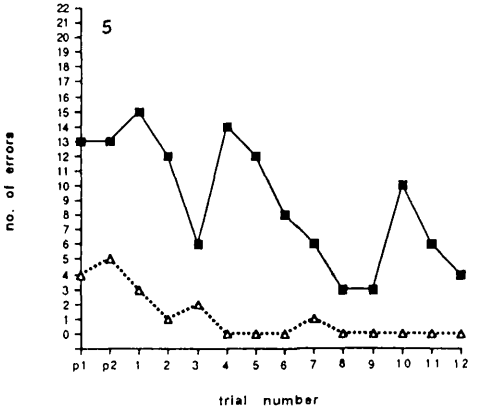
Fig. 10a. Individual and group performances on the Paced Visual Serial Addition Test











Group A errors on the PVSAT (2 seconds stimulus)

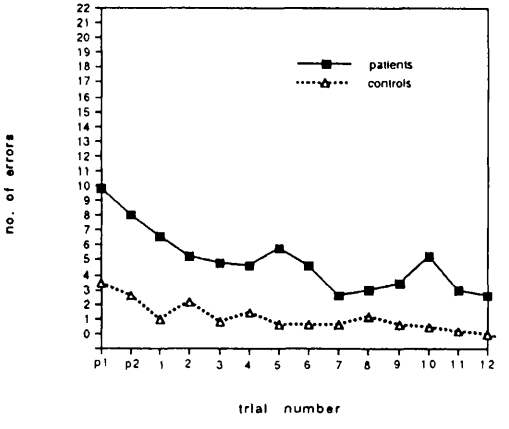
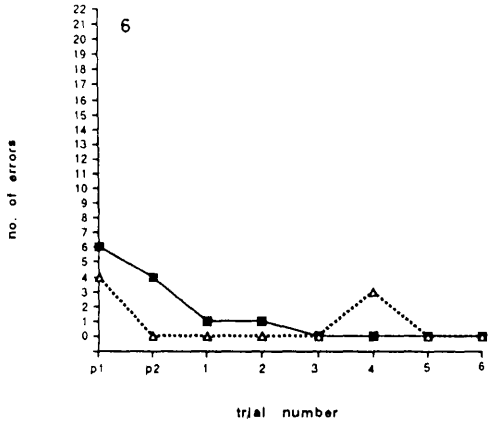
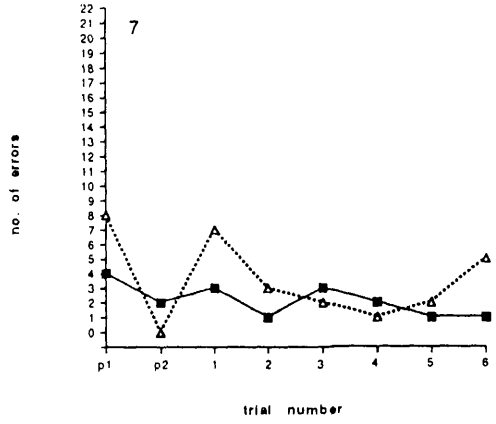
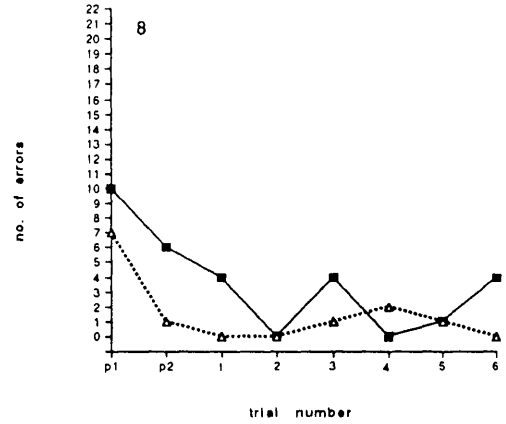
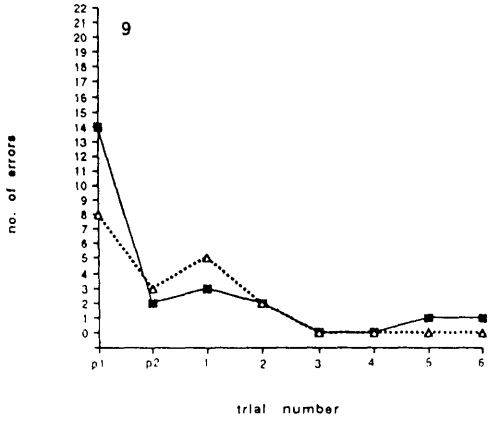


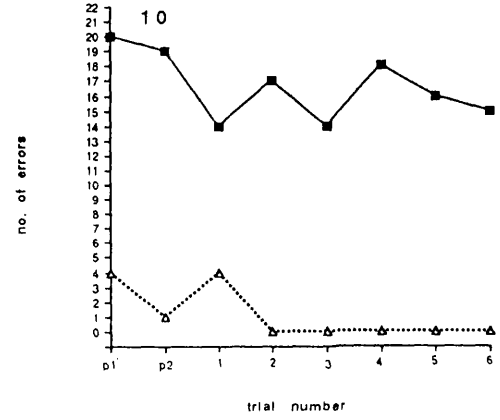
Fig. 10b. Individual and group performances on the Paced Visual Serial Addition Test











Group B errors on the PVSAT (2 second stimulus)

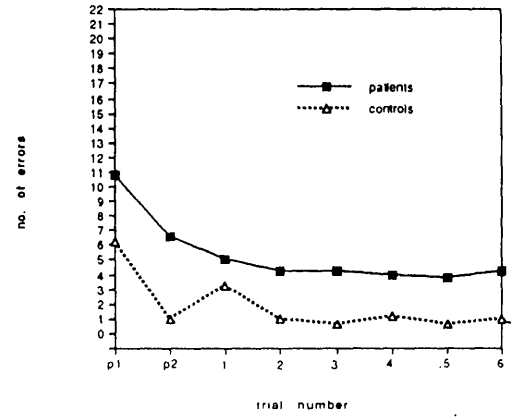
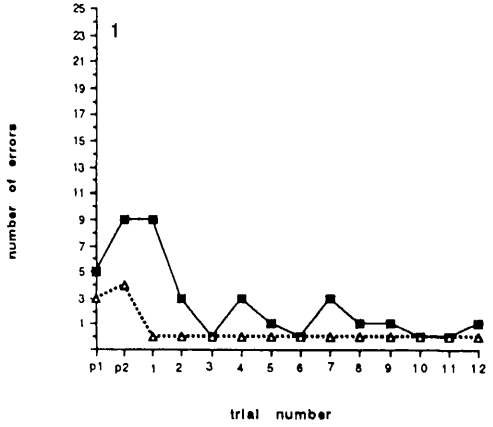
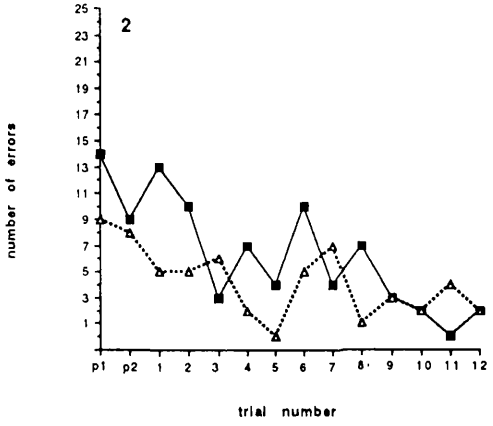
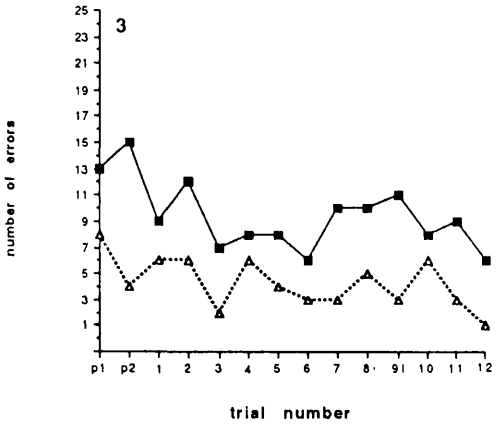
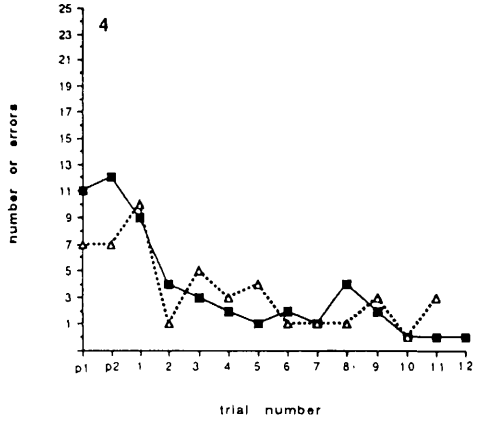


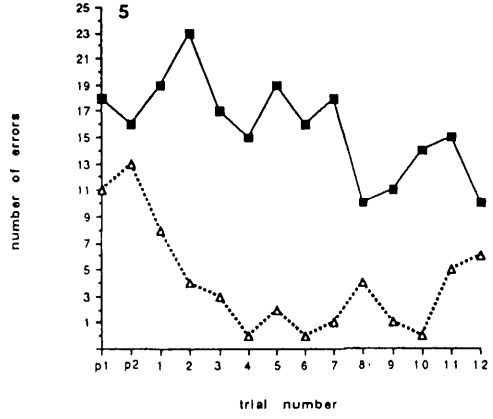
Fig. 11a. Individual and group performances on the Paced Auditory Serial Addition Test











Group A errors on the PASAT (2 second stimulus)

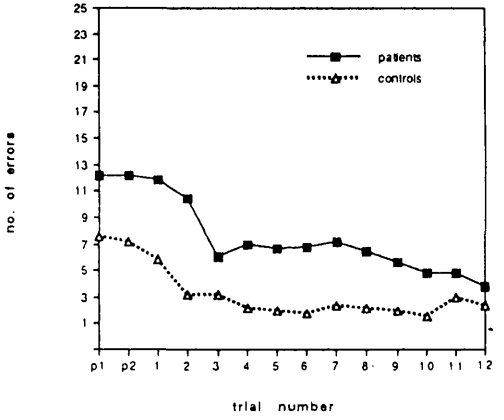
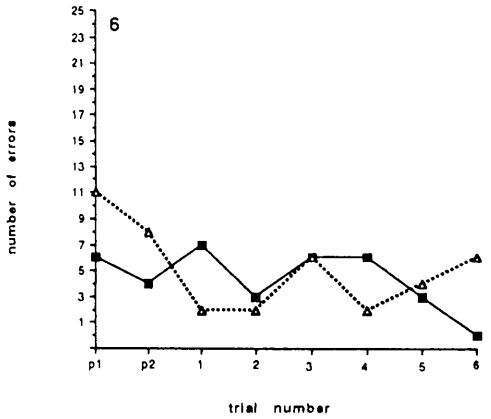
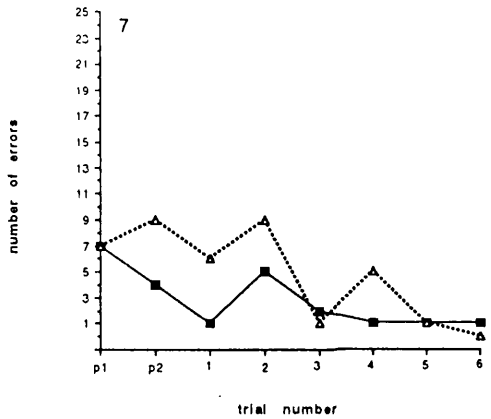
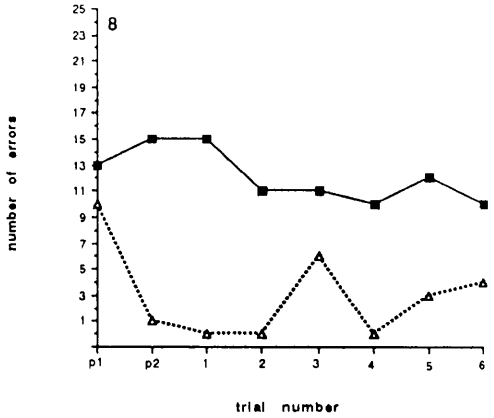
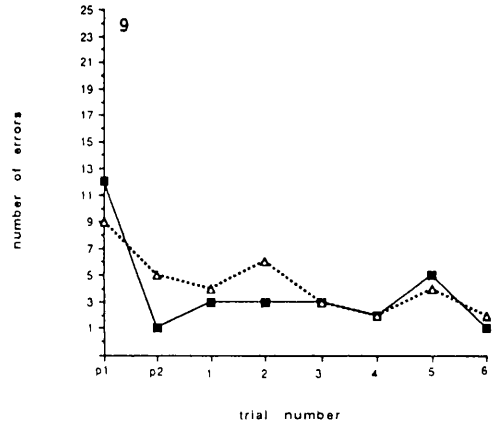


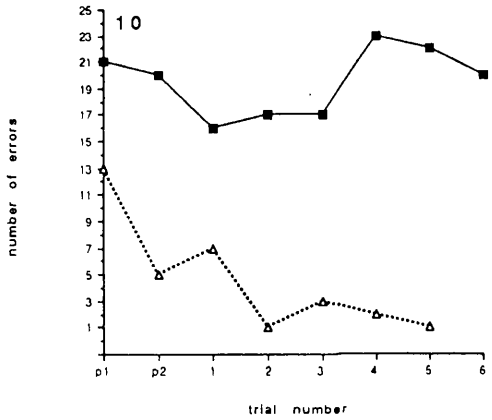
Fig. 11b. Individual and group performances on the Paced Auditory Serial Addition Test











Group B errors on the PASAT (2 second stimulus)

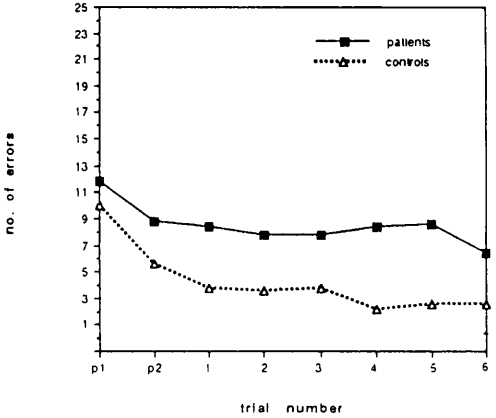
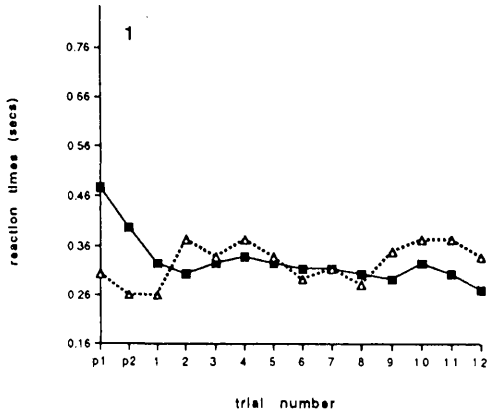
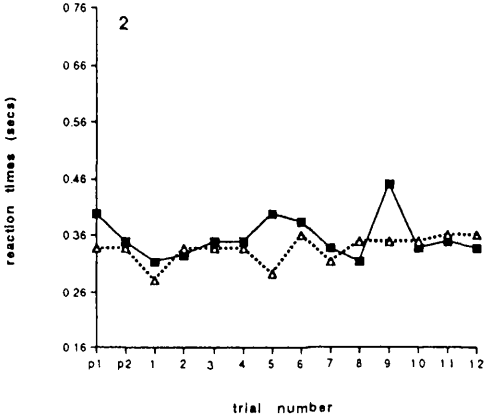
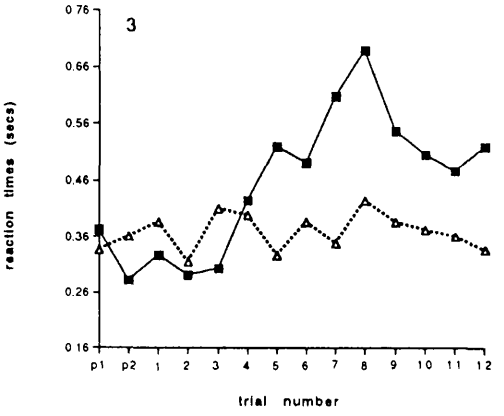
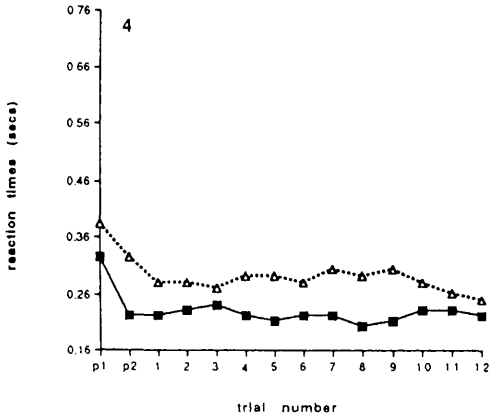


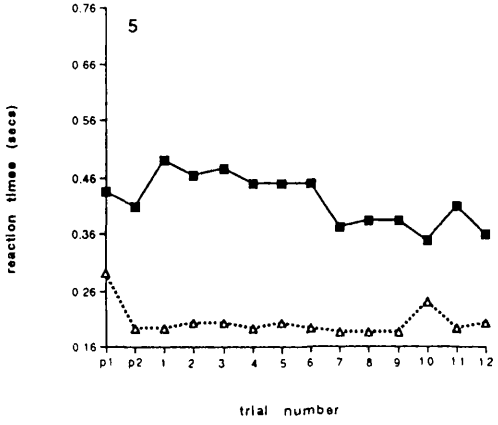
Fig. 12a. Individual and group performances on the Simple Reaction Time Test











Group A mean scores for the Simple Reaction Time Test.

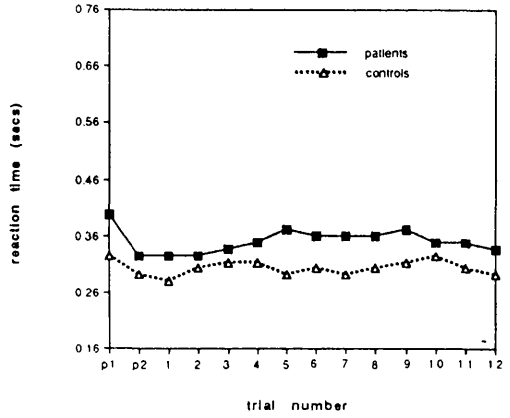
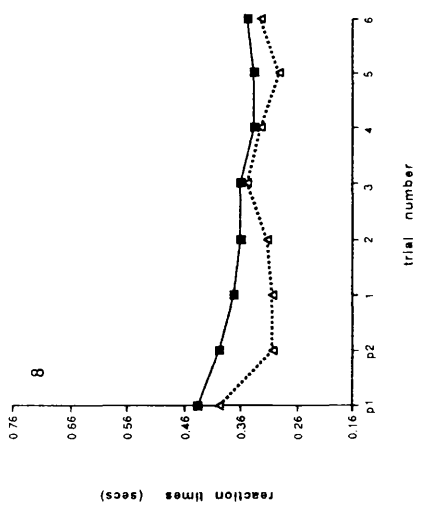
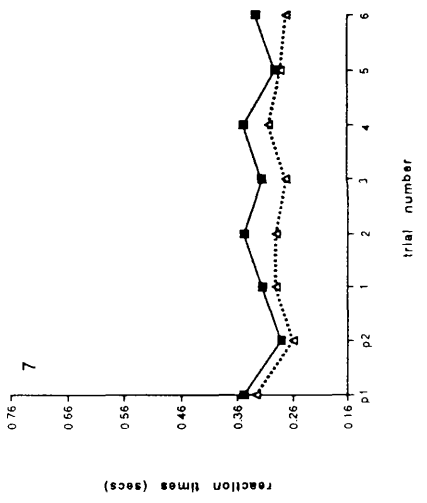
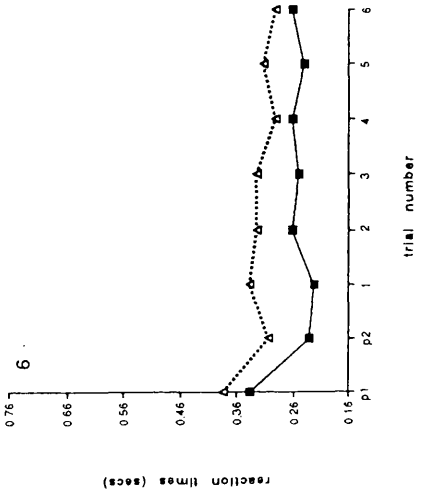


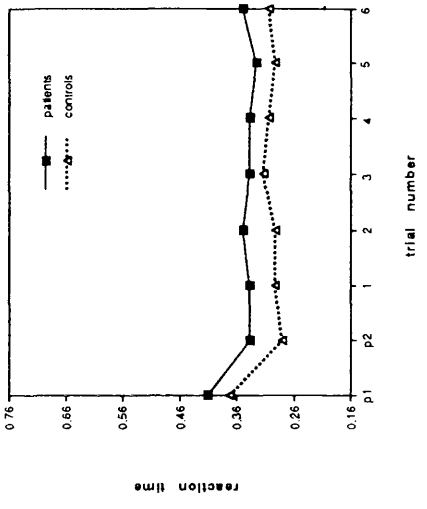
Fig. 12b. Individual and group performances on the Simple Reaction Time Test

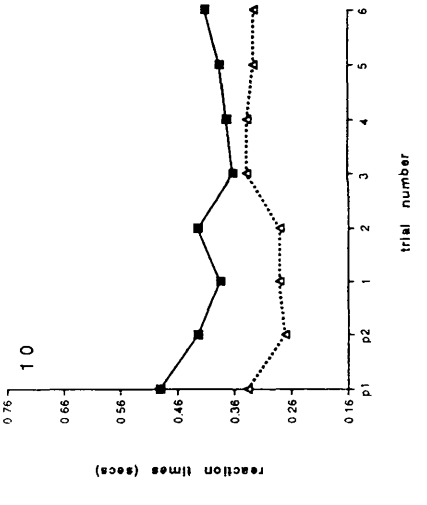






Group B mean scores for the Simple Reaction Time Test.





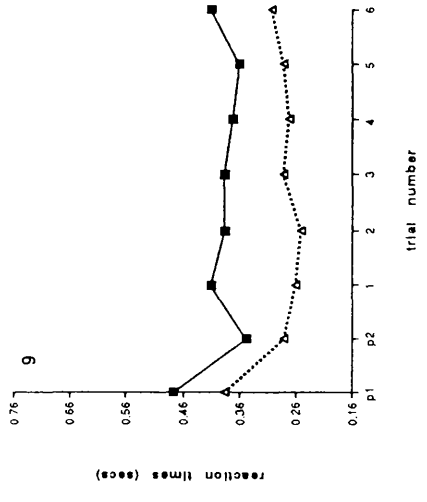
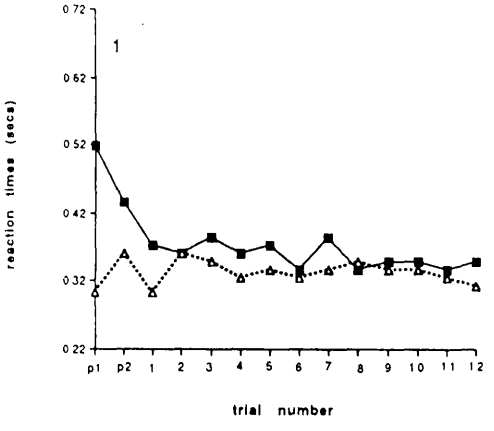
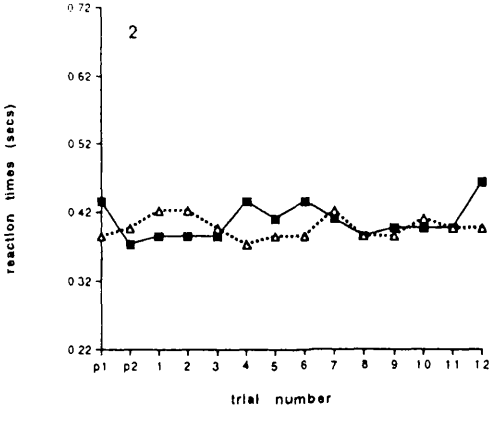
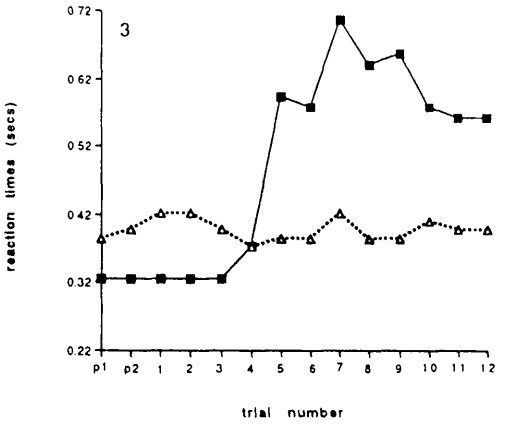
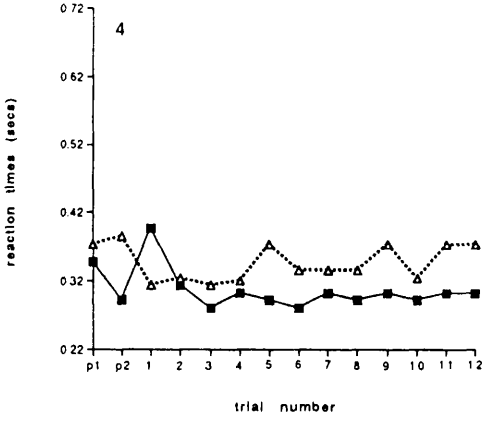


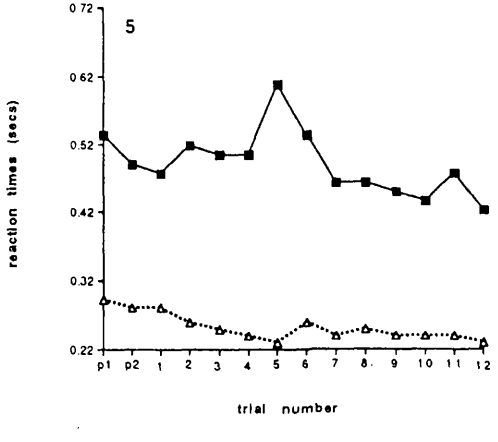
Fig. 13a. Individual and group performances on the Warned Choice Reaction Time Test











Group A mean scores for the Warned Choice Reaction Time Test.

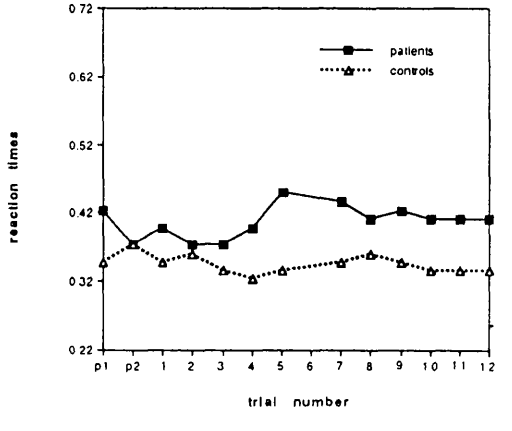
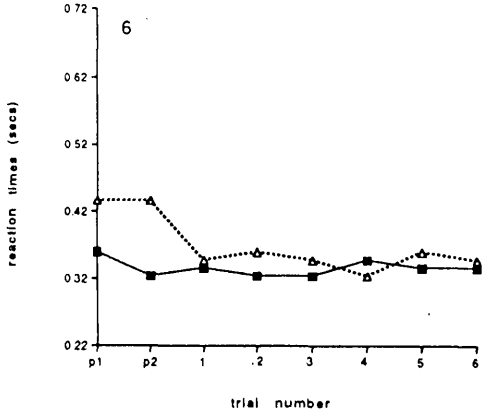
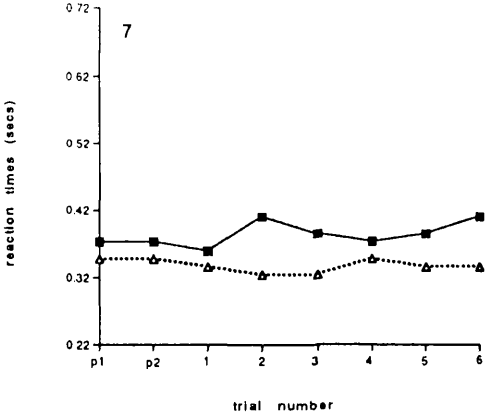
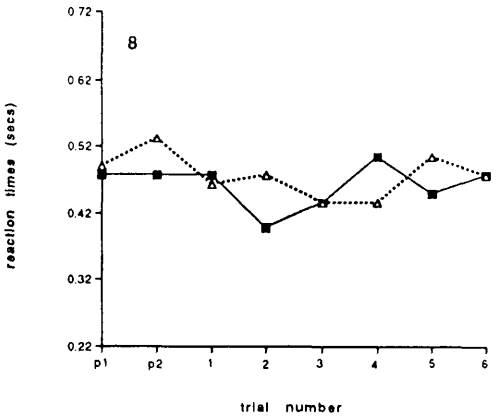
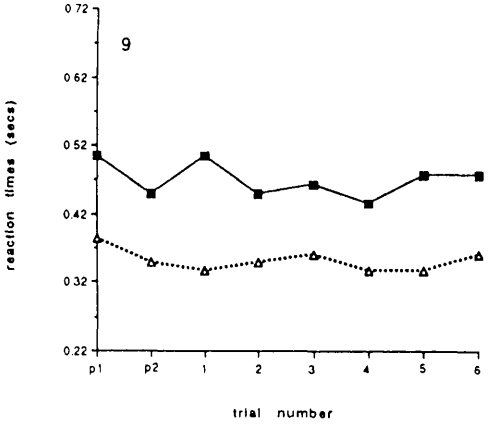


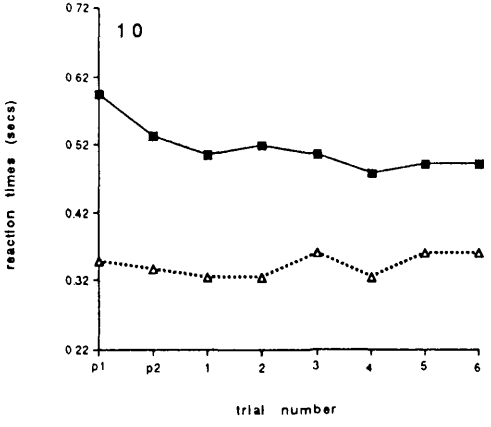
Fig. 13b. Individual and group performances on the Warned Choice Reaction Time Test











Group B mean scores for the Warned Choice Reaction Time Test.

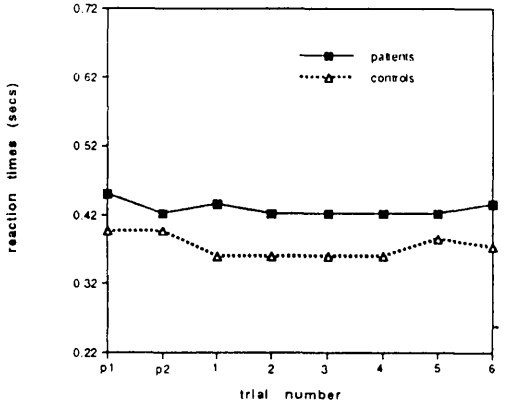
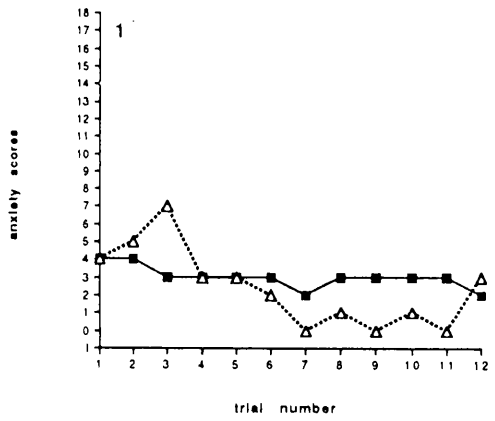
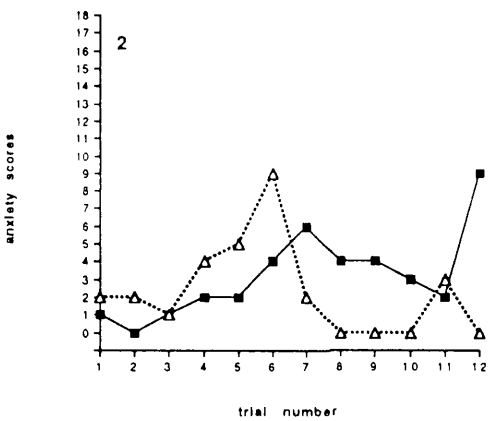
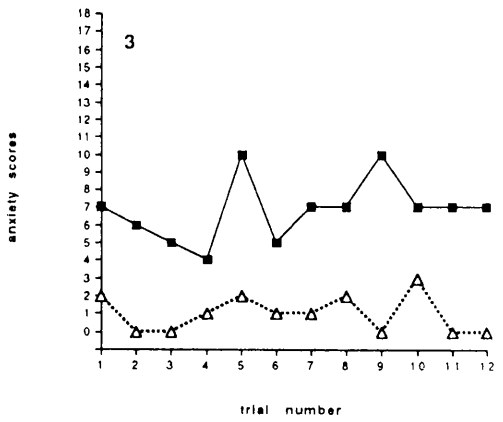
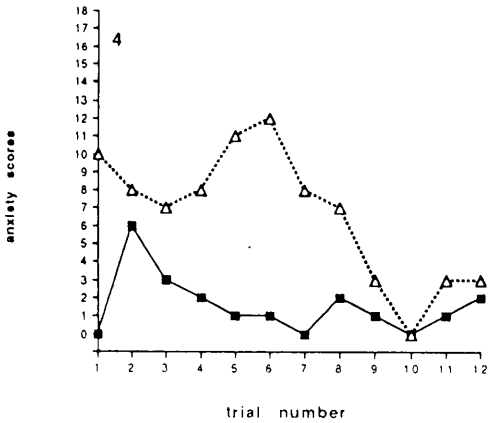


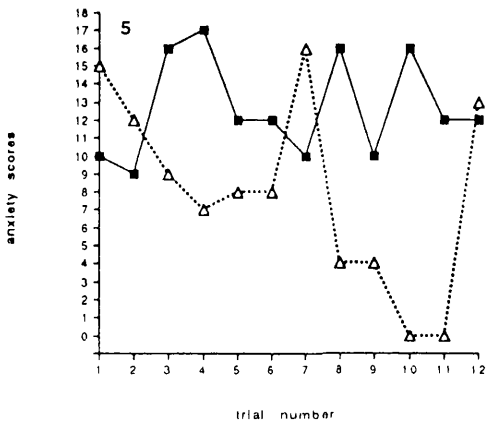
Fig. 14a. Individual and group performances for Anxiety on the Hospital Anxiety and Depression Scale











Group A scores for Anxiety on the HAD Scale.

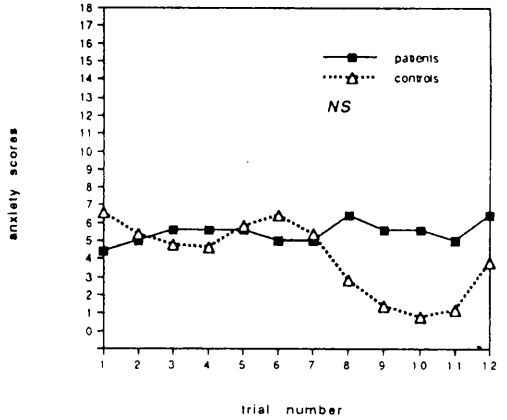
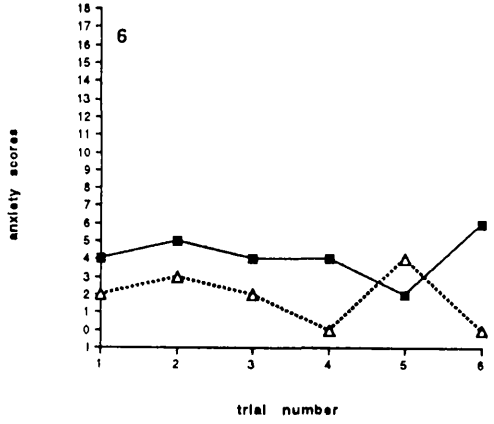
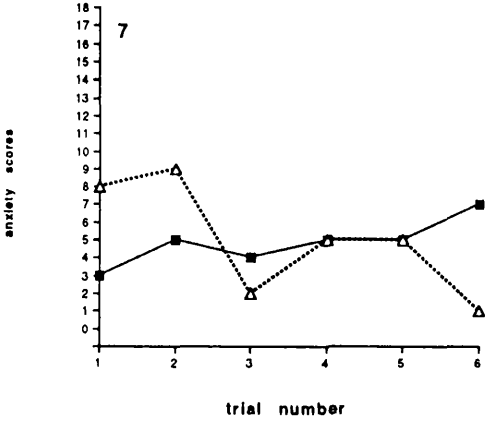
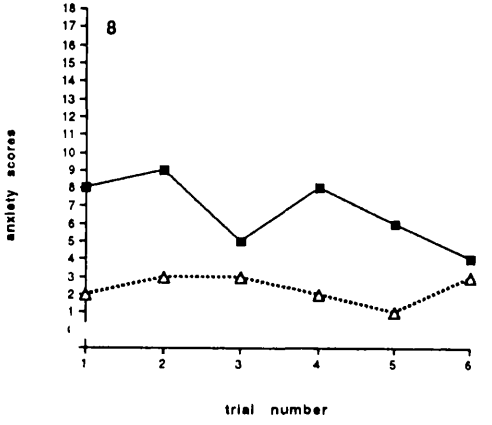
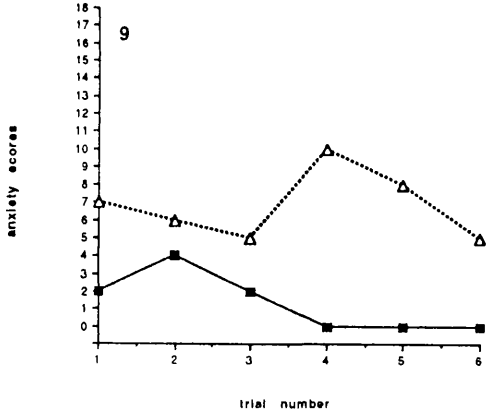


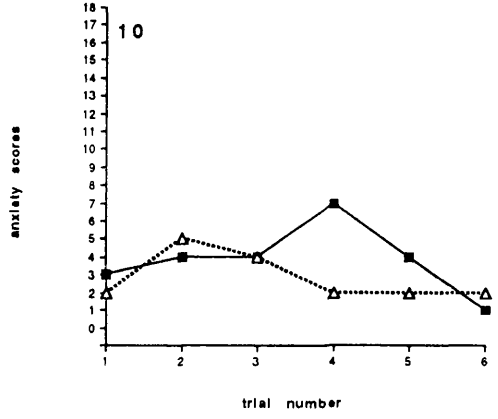
Fig. 14b. Individual and group performances for Anxiety on the Hospital Anxiety and Depression Scale











Group B scores for Anxiety on the HAD Scale.

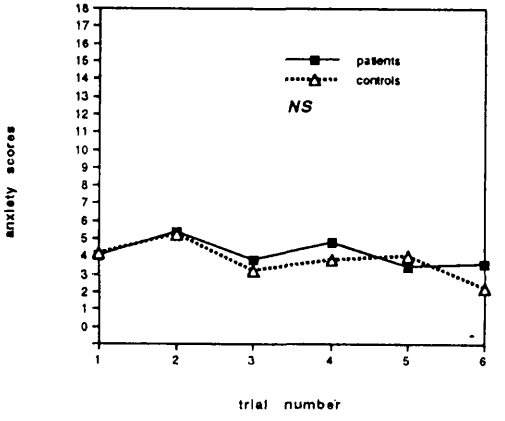
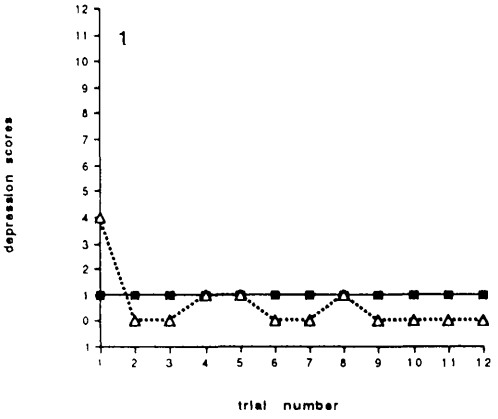
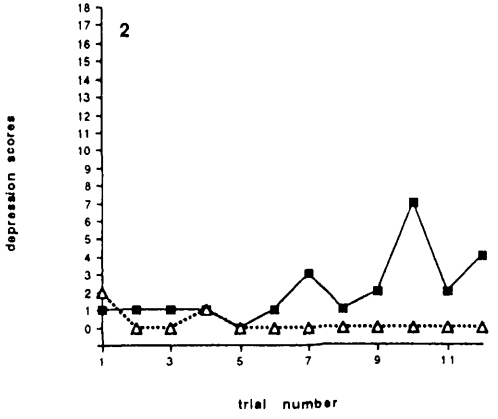
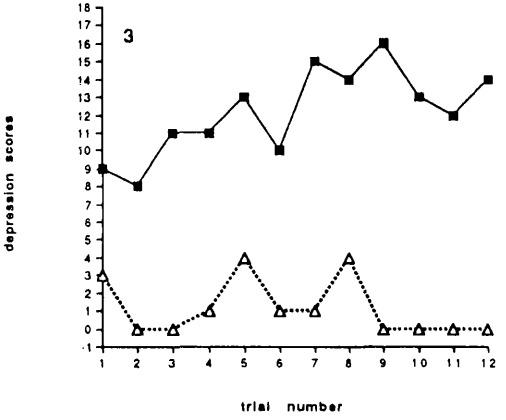
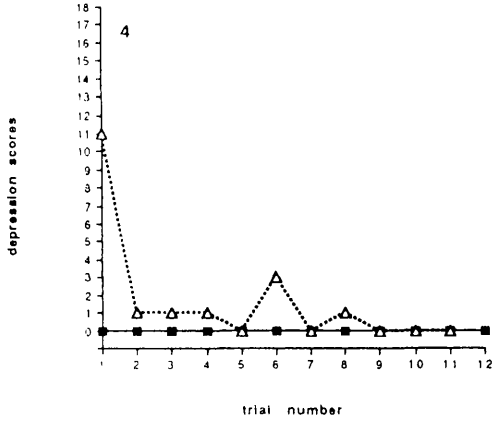


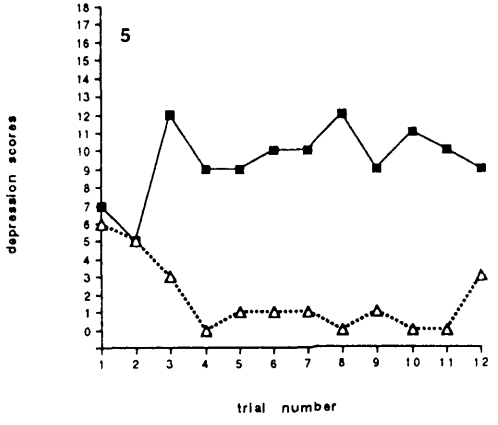
Fig. 15a. Individual and group performances for Depression on the Hospital Anxiety and Depression Scale











Group A scores for Depression on the HAD Scale.

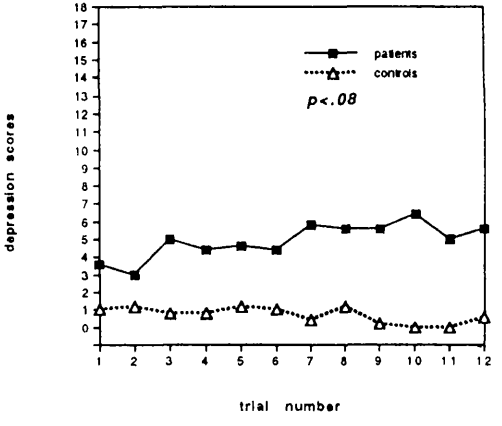
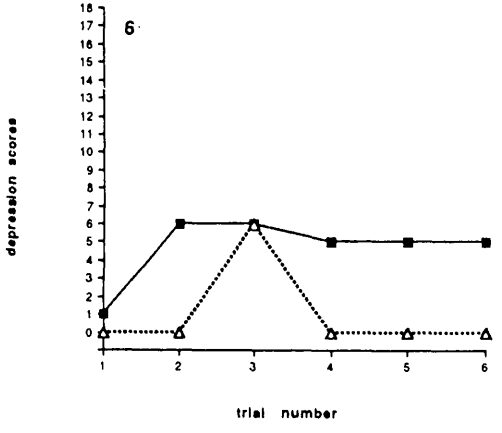
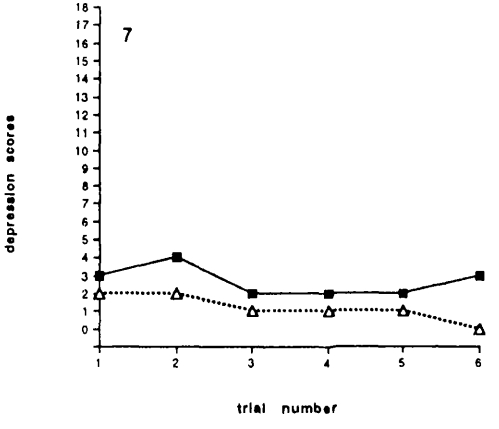
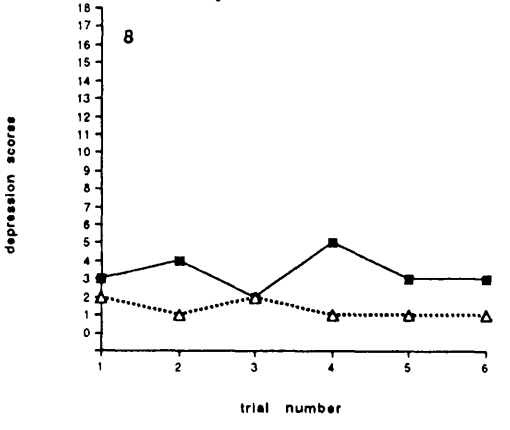
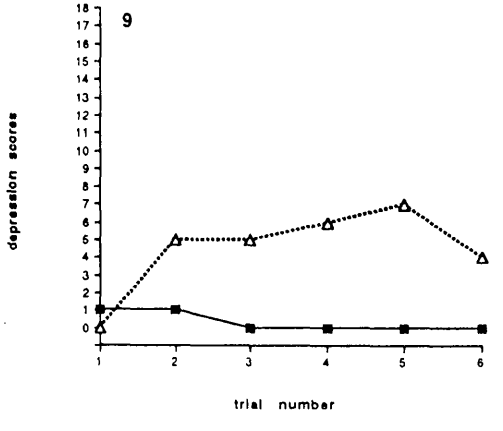


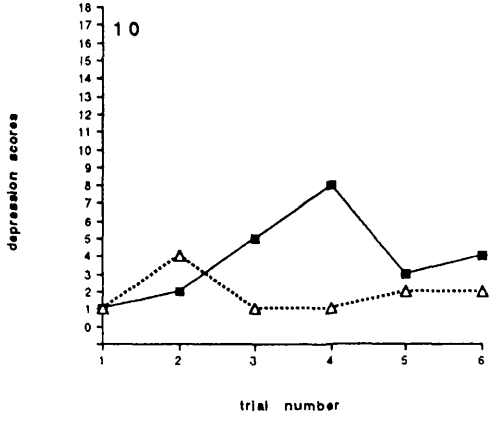
Fig. 15b. Individual and group performances for Depression on the Hospital Anxiety and Depression Scale



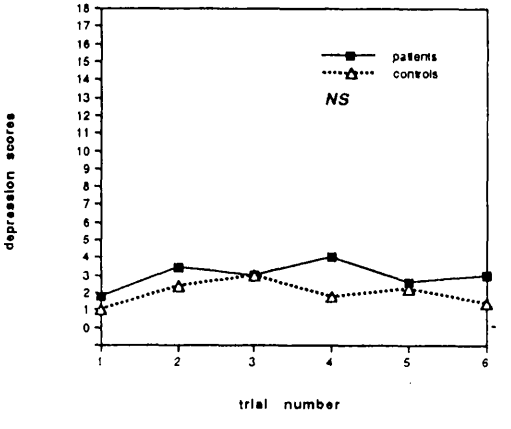








Group B scores for Depression on the HAD Scale.



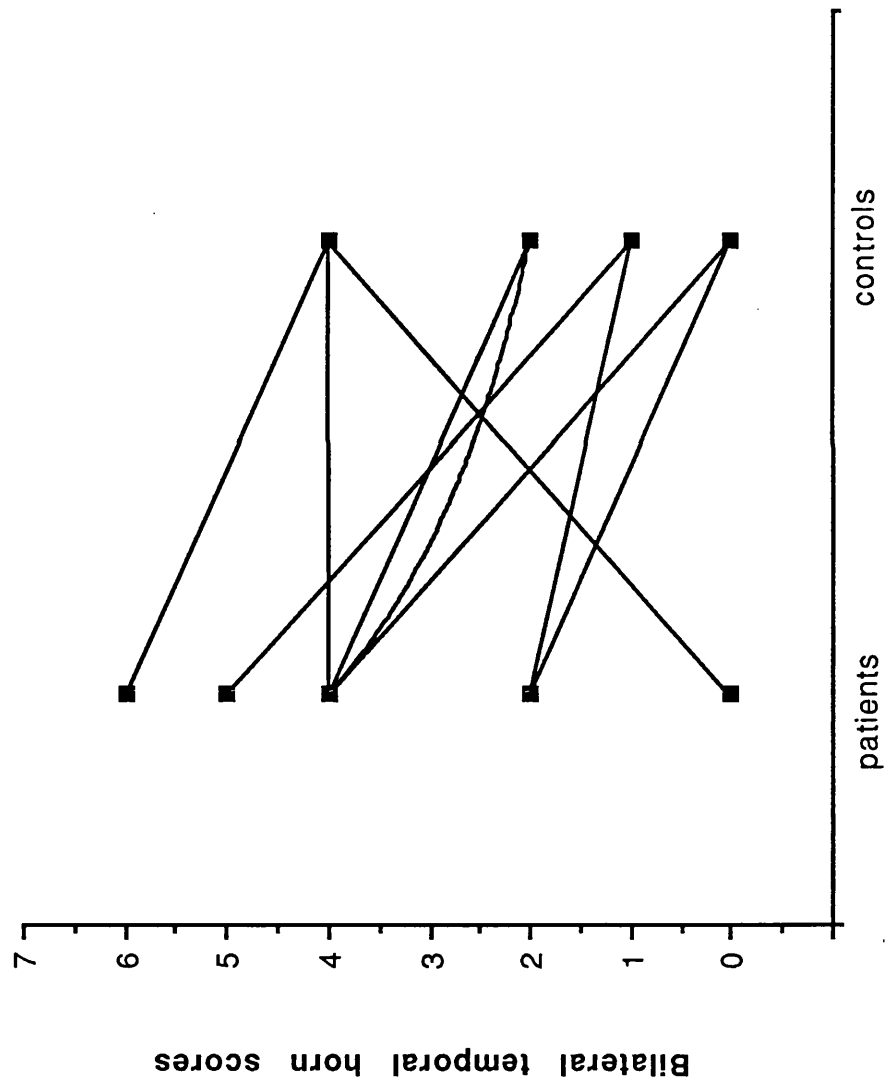


Figure 16. Temporal horn scores (bilateral) for psychotic and non-psychotic subjects

Fig. 17. Percentage lesion score distribution

periventricular areas