COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS: CLINICAL AND NUCLEAR MAGNETIC RESONANCE IMAGING CORRELATES

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ABSTRACT

Fifty-eight patients with Clinically Definite Multiple Sclerosis (MS) and forty-eight patients with clinically isolated lesions (CIL) of the kind frequently observed in MS, were psychometrically examined with a range of neuropsychological tests. The results were examined in conjunction with Magnetic Resonance Imaging (MRI), neurological, psychiatric and physical ability evidence and compared to a matched group of forty-six controls.

A method is described for calculating the overall cognitive efficiency of each individual and this measure is examined in relation to MRI, neurological, psychiatric and motor ability evidence. Measures of the cognitive speed of memory and object-naming are examined and the relationship between accuracy and speed on these functions is explored.

The MS group present with intact accuracy on Verbal Recognition Memory and Object-naming while demonstrating slowed cognitive processing in both functions. The CIL group also present with intact accuracy on these functions and, in addition, Abstracting Ability and accuracy of

Visual Recognition Memory are intact: however, CIL patients demonstrate slowed cognitive processing on Visual Recognition Memory, as do the MS group.

Dissociation between speed and accuracy was observed for MS and CIL patients and this is discussed with regard to the concept of 'subcortical' dementia. The interaction of speed with accuracy is different between the three groups with the CIL group occupying the intermediate level.

Impairment of function within the MS group is demonstrated to be related to lesions observed on MRI. Cognitive impairment within the CIL group, however, was not established as a correlate of MRI lesions but would seem to relate to disease status.

The results of the present study present evidence of impairment of cognitive efficiency and cognitive speed in patients with MS and in CIL patients. The level of impairment of the CIL group is intermediate when compared to that of the MS group and the controls.

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CHAPTER I

INTRODUCTION

Definite Multiple Sclerosis

Multiple Sclerosis (MS) was described much in terms as it is today over one hundred and twenty years ago (Charcot, 1868) and has since become recognised as one of the commonest diseases affecting the central nervous system in this country. It is characterised by episodes of neurological disturbance lasting weeks or months which tend to remit in the early stages of the disease. The clinical presentation of these neurological disturbances take the form of two kinds of symptoms: positive (for example, tingling) and negative (for example, weakness). The patients usually first present with symptoms in the third or fourth decade of life: it is extremely rare for cases to present before the age of 10 or after age 60. About 40% of patients present with weakness in the limbs or disturbance of gait, and about two thirds present with sensory symptoms (one-third with visual loss and one-third with tingling or numbness) (McDonald, 1982). The course of the illness is variable, from several relapses a year and fatality within five years to an interval of 20 or 30 years between the first and second episode. In 10 to 20% of cases the illness is steadily progressive from the onset. Factors influencing the course of MS are poorly

understood (McAlpine et al, 1972), and the cause is unknown though environmental and genetic factors appear to be important (Acheson, 1977). There is no effective treatment.

The essential pathological features of MS are plaques of demyelination and their multiplicity throughout the central nervous system which have certain sites of predilection: the optic nerves, brain stem, cervical spinal cord and periventricular regions (Ikuta and Zimmerman, 1976). In addition, there is evidence at autopsy that such lesions occur in patients in whom no neurological disease had been suspected in life; so giving rise to the concept of 'benign' or 'unsuspected' MS (Gilbert and Sadler, 1983). This finding illustrates the range of clinical severity that is encountered within the population of patients that are considered to have multiple demyelinating plaques (Herndon and Rudick, 1983).

Diagnosis, in the absence of a specific test for MS, remains clinical: "unequivocal evidence of abnormalities in at least two separate sites in the central white matter in a patient with a history of at least two episodes of neurological disturbance. Support for the diagnosis comes from finding an oligoclonal pattern in the gamma globulins at cerebrospinal fluid (CSF) electrophoresis" (p.16, McDonald, 1982).

Several laboratory and clinical diagnostic procedures have been advanced for the clinical classification of MS (Schumacher et al, 1965; Brown et al, 1979) and these feature different terminology. Poser and his colleagues (1983) published guidelines for research protocols and a more exact criteria for diagnosis than existed earlier in order to validate comparisons of epidemiological surveys and to enable therapeutic trials in multicentre programs to be conducted. These diagnostic criteria are employed in the present study.

Clinically Isolated Lesions (CIL)

(i) Optic Neuritis

A common manifestation of demyelinating disease is Optic Neuritis (ON), which is the presenting feature in approximately 20% of cases of MS, and occurs during the course of the illness in about 75% of MS cases (Shibasaki et al, 1981). Evoked Potential responses are helpful in the diagnosis, but in typical cases the diagnosis remains clinical (Ebers, 1985): presentation may be visual blurring or diplopia. Studies have been conducted into the risk factors of ON patients going on to develop MS (McDonald, 1983), with estimates varying widely and some identification of the predictive indicators. Factors proposed to be related to an increase in the risk are age, sex, winter onset and presence of oligoclonal bands in CSF (Moulin et al, 1983). In the United Kingdom the risk

estimate is placed at about 75%, that is, about three-quarters of ON cases could be expected to go on to develop MS (Hutchinson, 1976).

(ii) Brain Stem Disorder

The other diagnostic group that may similarly be at risk to go on to develop MS, though it has not been studied as systematically as ON, is Brain Stem disorder (BS). Acute brain stem disturbance is the presenting feature in about 15% of MS cases, and occurs during the course of the illness in the majority of patients (Shibasaki et al, 1981).

(iii) Spinal Cord Syndrome

The third disorder considered to be a possible precursor of MS is spinal cord syndrome (SC): this has not been studied with the same attention as ON regarding it's possible conversion to MS. It is the presenting feature in approximately one-third of patients with MS (Shibasaki et al, 1981).

In a recent related study (Ormerod et al, 1987) it was reported that over 50% of the patients presenting with symptoms attributable to isolated lesions (ON, BS and SC) had additional lesions demonstrated on Magnetic Resonance Imaging (MRI) at presentation. Repeat scans on 25 ON and 10 BS patients demonstrated new lesions in 20%. This 20%

of the group fulfilled the criteria for Poser et al's (1983) diagnosis of probable MS.

The aforementioned CIL groups offer a unique opportunity to study early manifestations of demyelinating disease and investigate:

(1) whether cognitive abnormalities are detectable at this stage, that is, at the presentation of what may be the initial symptom(s) of MS;

(2) whether cognitive abnormalities found correlate with brain lesions detected on MRI; and

(3) the pattern of deficit and how it compares to that found in patients with MS.

Magnetic Resonance Imaging (MRI)

MRI has been demonstrated as a very sensitive technique in detecting lesions in MS patients (Young et al, 1981). This observation has been widely confirmed and there would seem no doubt at the present time that MRI is superior to other imaging techniques in this field (Young et al, 1981; Lukes et al, 1983; Runge et al, 1984; Ormerod et al, 1986). The distribution of lesions demonstrated on MRI corresponds with that recognised pathologically (Lumsden 1970; Allen 1984). Stewart et al (1984) demonstrated that reasonable images can be obtained from postmortem material: a recent study examined the brains from 4 patients dying with clinically definite MS (Ormerod et al,

1987). The results demonstrated a good correspondence between the areas of abnormality in the MRI and the histological lesions, although the outlines were not exactly the same. Ormerod and his colleagues (1987) concluded that MRI abnormalities originated from chronic plaques of MS.

It is suggested that MRI of the brain is a more sensitive technique than Computerized Tomography (CT) in detection of brain lesions (Ormerod et al, 1984) and further suggested that it correlates more closely with cognitive abnormalities than does CT. Groswasser and his colleagues (1986) conducted a study on patients during the late post-traumatic period (following head injury): eleven patients had CT scans of the brain performed 4 to 24 months post-trauma that were considered as normal. The patients were reported to be still hospitalised at that stage because of a variety of cognitive and behavioural disturbances, though their motor deficits were minimal. These patients were further evaluated by MRI in order to assess the anatomical substrate of their disability. MRI studies in all of these patients revealed abnormalities: the main pathology was confined to the frontal and temporal lobes. This study suggests that MRI is superior to CT scanning in these areas of the brain as bone does not cause artifact abnormalities on the former in the way it can with the latter: indicating that MRI may enable a

better understanding of patients' clinical and neurobehavioural disturbances (Groswasser et al, 1986).

Motor Functions in MS

It has long been observed and reported that a percentage of patients with MS become physically disabled in one respect or another. There is some debate in the Rehabilitation literature as to the means that one should use to assess disability, and how useful or valid these measures are (Haworth and Hollings, 1979; Lawson et al, 1985).

The present study does not attempt to measure pure function with regard to the assessment of motor ability: the aim was to observe the motor movement of patients and grade it according to independence level or the degree of assistance required. This was undertaken in an attempt to provide the information considered most relevant to the execution of the cognitive tests administered.

A modified version of the Northwick Park Activities of Daily Living Assessment was used but with a grading system that was the responsibility of the author (being slightly different to that believed to be currently in use). Again, this grading system was devised to yield measures considered most relevant to the information needed. This four-point grading system ranged from 0 for independent

completion of the task to 3 for a patient who was unable to complete the task. The two intervening grades referred to assisted completion of the task with an aid or human assistance (Grade 1) or completion of the task requiring both levels of assistance (Grade 2). For the purposes of the present study this was considered to yield information as to the level of motor ability possible for the subject at the time of testing and does not purport to indicate a pure measure of function or disability.

Two of the cognitive tasks in the present investigation are motor oriented and it is necessary to know whether the movement can be executed and to what level independent tests indicate. Controls were matched with the MS subjects with regard to whether they needed mobility aids or not (e.g. wheelchair or walking stick).

Psychiatric Morbidity in MS

Mental illness in patients with MS was also reported in Charcot's early study (1877) and has received considerable attention in the literature since. Depression, euphoria and disturbances of emotional expression were the first and most commonly described symptoms (Cottrell and Wilson, 1926). Psychotic features are less often reported though cases with schizophrenia have been described (Davison and Bagley, 1969).

The psychiatric assessment in the present study was conducted in close liaison with the psychological and physical assessments and will constitute a separate thesis for the psychiatric assessor. The results of this psychiatric assessment with regard to the CIL group have been published in a separate paper (Logsdail et al, 1988). Data with regard to a number of psychiatric assessment results on the groups of patients in the present study have been kindly provided so that information with regard to depression, anxiety and other measures may be examined in conjunction with cognitive performance.

CHAPTER II

RESEARCH ON COGNITIVE ABNORMALITIES

Early descriptions of MS included recognition of the presence of cognitive impairment (Charcot 1868; Wechsler 1922) though it is only in the last three decades that attempts have been made to identify, in any standardised way, deterioration of discrete functions.

The collating of results from a number of different studies has inherent problems: the range of psychometric tests used; the spectrum of severity with regard to the neurological status of the MS patients and, following on from this last point, the standardization of the classification of the disease itself. These confounding variables apply to many areas of neuropsychological investigation, and the study of MS is no exception. When considering comparisons between studies, or when making general conclusions from a number of studies, one needs to bear in mind these potentially confounding factors.

A) Intellectual Functions in MS

'Deterioration of intellectual functions' has been used to describe impairment of a range of cognitive functions such as memory and problem-solving abilities. Such a description, in some previous reports, is not used to

infer changes in intellectual quotients. In the present study, however, 'intellectual deficit' refers to a drop in IQ level as measured by standardised tests such as the Wechsler-Bellevue or the later Wechsler Adult Intelligence Scale (WAIS).

In the 1950s neuropsychological correlates of MS remained unclear. Assessment of Full Scale IQ, involving Performance subtests that are timed and heavily reliant on motor ability, is complicated in MS sufferers by the motor deficits present in the majority of such patients. The results of investigations in the 1950s, and indeed since, reflect this. Diers and Brown (1950) found a normal distribution of IQ in their sample of 24 patients with MS, though when the pattern of IQ subtest results was compared with the expected mean, it was found that they performed poorly on three timed motor tests and one verbal subtest, Digit Span. They omitted, however, to provide details of the patients' motor functioning.

The Digit Span component of the IQ assessment has been excluded from some studies because it is thought to be sensitive to the presence of anxiety (Peyser et al, 1980). This additional factor, given that information about anxiety levels was not reported, could be another confounding variable in Diers and Brown's findings. However, this subtest has also been used as a measure of

immediate memory-span (Jambor 1969) and such a function is commonly reported to be intact in groups of MS patients as will be discussed below. Lowered Digit Span was reported in Hirschenfang and Benton's study in 1966 in their sample of 23 MS patients. They also reported lowered scores on another WAIS verbal subtest, Similarities.

It has been suggested that, because poor performance on the Similarities subtest has been found to be associated with poor abstracting ability (Peyser et al, 1980), this subtest may require a greater degree of abstraction. Deficits in abstracting ability have been consistently reported in groups of MS patients, and will be discussed below. It may be that deficits in discrete functions have the effect of lowering tested IQ levels, so that abstracting ability and poor immediate memory may have the same effect on tested Verbal IQ as motor dysfunction has on tested Performance IQ. In 1957 Parsons and his colleagues found that only those MS patients who were impaired on a nonverbal abstracting task had significantly lower Verbal IQ. This study, however, used very small samples (N=17 for control group and for MS group) and did not include an estimation of premorbid IQ.

A recent study on the WAIS as a lateralising and localising diagnostic instrument suggests that "it seems likely that the analysis of the subcomponents of the

complex skills assessed by the WAIS will provide better diagnostic tests of selective deficits associated with a focal lesion" (Warrington et al, 1986 [p.9 of original Ms.]). It would seem, therefore, that one has to examine the pattern of subtest results when looking at IQ deficit, especially in the absence of a standardised estimate of premorbid IQ level; and take into account other recorded deficits, including the visual deficits that are often inherently present in the disease of MS. Reitan and his colleagues (1971), whose sample of MS patients had a significantly lower score on Verbal IQ, stated that their patient group performed poorly on all cognitive measures. However, they did not include disability ratings on their subjects and did not have a measure of premorbid IQ. Furthermore, the unmatched Control group had consistently superior Verbal, Performance and Full Scale IQs while the MS patients scored in the average range for these assessments.

These factors must also be borne in mind when one considers the study by Canter in 1951. This study was carried out on World War 11 veterans who had undertaken the Army General Classification Test (AGCT) and later happened to go on to develop MS. Canter retested these veterans and compared their results with the AGCT taken before the onset of illness. He reported a significant fall in their performance, with the greatest drop in those

classified as 'severe' from the neurological standpoint. A second part of this study was a test-retest of IQ with a six month interval on 47 MS sufferers and 37 controls. The finding here was that while the controls improved their performance at retest, which was expected given a practice effect factor, the MS patients' IQ level declined.

This drop in IQ may well have been a function of a number of possible factors: deterioration in motor ability (there were no clinical ratings of MS patients' motor functioning in this investigation) or increased anxiety, for example, may have been operating rather than a drop in general intellectual level per se. Furthermore, one might not expect the MS subjects to benefit from an expected 'practice effect' given Vowels' (1979) and other studies' reports of impaired learning in such groups (to be fully discussed below).

A later study which attempted to estimate premorbid levels but based on education and occupation, reported no drop in Verbal IQ (Peyser et al, 1980). Peyser and his colleagues excluded motor tests and those thought to be sensitive to anxiety, though they did include the subtest Similarities and accordingly reported that a decline in performance on this was associated with poor abstracting ability. This finding confirmed an earlier one where the Verbal IQ of 78

MS patients and 79 controls was compared and no significant differences were found between the two groups (Jambor 1969). Again, Jambor used a shortened version of the WAIS Verbal IQ test but did not specify which subtests. Jambor did conclude, however, that there was a deterioration in general intellectual efficiency based on the discrepancy between a vocabulary score and a score combining knowledge of current events and memory functions. A later study (Ivnik 1978) reported a significant drop in the vocabulary subtest so suggesting that this is not a reliable measure of premorbid levels in this group of patients. Furthermore, the MS patients in this study were all under 40 years of age and fairly intact, so the results cannot be generalised to a more representative MS population.

Goldstein and Shelley (1974) replicated Reitan et al's study mentioned above and another similar study. They demonstrated that, while the IQs were different across three groups of MS patients, the pattern of results were similar: deficits tended to be associated with motor dysfunction and verbal skills were intact. However, no objective scoring of disability status was used and no clinical ratings of motor functioning were provided. The varying levels of IQ across different MS groups reported in this study highlight the necessity to obtain a reliable way of estimating premorbid IQ level, and using this

measurement as a baseline to establish the presence or absence of deterioration.

An alternative research design would be to repeatedly measure function over a long period of time, necessarily years - given the variability and individuality of the disease process. Ivnik (1978), in a longitudinal study over one year, reported little or no significant deterioration in IQ levels, though a significant drop in the Information and Vocabulary subtest scores was demonstrated. This is contrary to what one would expect, given that these subtests are thought to be most resistant to effects of brain damage (in the absence of aphasia). However, this result is of heuristic value in that it focuses attention on the need to use measures other than vocabulary alone when estimating premorbid levels of verbal ability.

Marsh (1980) concluded from her study of 48 MS patients that severity of disability, as measured on the Kurtzke Disability Status Examination, was not significantly correlated with WAIS IQ levels, though Performance subtests with a large motor component had lower mean scores than Verbal subtests. No information was provided with regard to premorbid levels of functioning, so the relationship between IQ deterioration and disability remains unclear.

It seems clear that lowered Full Scale IQ in patients with MS may be related to motor dysfunction due to the involvement of timed motor tests in this assessment. When these motor oriented tests are excluded some researchers have demonstrated that deterioration occurs in Verbal IQ levels and this would seem to be associated with an increase in neurological impairment (Harrower and Kraus, 1951; Fink and Houser, 1966).

Premorbid IQ

The evidence in the literature on Intellectual deterioration in MS patients is contradictory and remains controversial due to potentially confounding variables, one of which is the absence of reliable measurements of premorbid levels of functioning.

Up until fairly recently estimations of premorbid intellectual functioning relied on, at worst, idiosyncratic measures of the researcher and, at best, a component of an established test that was considered most resistant to effects of brain damage. The latter usually took the form of the Vocabulary subtest of the WAIS; a good choice if it was known that aphasia was not part of the patient's presenting problem. However, as the results in a number of studies cited above illustrate, for some groups of MS patients in some studies Vocabulary seems as vulnerable to the effects of widespread brain dysfunction

as other tests (Ivnik, 1978). When the test did prove resistant to brain damage effects, one had to then find a way to measure the discrepancy between this 'premorbid' level and the present tested level of other, sometimes unrelated, tests in order that an interpretation could be made about estimated deterioration.

Clearly this was open to rather subjective and individual measurements rather than subject to a standardised assessment of deficit. Consequently inferences were made about deterioration in intellectual level by a number of different procedures; so confounding valid comparisons across studies. However, research evidence relating to the 'holding' power of the Vocabulary subtest would seem to have proved heuristically valuable in the development of a more reliable indicator of estimated premorbid intellectual functioning.

In 1982 careful research on two reading tests resulted in the publication of a standardised measurement of estimated premorbid Full Scale IQ, Verbal IQ and Performance IQ (Nelson, 1982). This measurement consisted of the Schonell Graded Word Reading Test (GWRT) and the National Adult Reading Test (NART). The NART was developed to include words of an unusual and irregular pronunciation which flouts the conventions of phonetic spelling: the theory being that if the word is not in one's vocabulary

then one cannot read it correctly. The GWRT was included because it was a more reliable indicator, when combined with the NART, for IQ levels in the lower ranges. These tests are now widely used and accepted as a standardised measurement of Estimated Premorbid IQ levels.

Present Assessment of Intellectual Functioning

The present study uses the shortened form of the WAIS to prorate Full Scale, Verbal and Performance IQs which are examined in conjunction with a standardised measurement of premorbid IQ (GWRT and NART scores combined).

B) Memory Functions in MS

Charcot, in one of the first descriptive accounts of patients with MS (1877), noted 'enfeeblement of memory' and this observation has been confirmed in many reports since. Jambor (1969), who reported that her MS group had intact memory span (tested with the WAIS subtest, Digit Span), concluded that MS patients showed impaired sentence and word definition learning and impaired delayed recall of pictures.

Investigations have compared the performance of MS patients on learning and recall tasks with that of normal controls (e.g. Grant et al, 1984), non-brain-damaged control patients with disabling conditions (e.g. Elpern et al, 1984) and psychiatric patients (e.g. Jambor 1969).

The majority of such comparative studies have found greater impairment in the MS groups.

As with the case of IQ Deficit, it has been suggested that memory impairment is related to degree of motor disability. Baldwin, as early as 1952, reported that MS patients with more severe neurological deficit performed poorly on learning and recall tasks given their age and vocabulary score. Beatty and Gange (1977) demonstrated impaired verbal learning in their group of 26 MS patients on a free recall memory test; correlations between motor and memory performance were consistently higher in those subjects with MS. They suggested that this was indicative of one of two possible conclusions: that memory impairment is secondary to the primary motor deficit; or, that memory functions, like motor functions, are especially vulnerable to the demyelination process. In 1979, a study by Vowels concluded that MS patients did indeed present with impaired learning and delayed recall of verbal and visual-spatial material, while having intact memory span, and that this deficit was found to be related to degree of disability. However, reporting on the disability level of most of the experimental groups in these studies was sparse: degree of motor deficit was descriptive, sometimes via performance on tests involving a motor component.

A study by Rao and his colleagues (1984), using the Kurtzke Disability Scale, reported that the severity of upper extremity motor disturbance is correlated with the degree of memory impairment. However, the researchers note that results on verbal memory measures cannot be accounted for by motor deficit, and conclude that the findings may be indicative of the fact that both memory and motor signs are produced from a similar distribution of plaques within the CNS. This would support the notion mentioned earlier that memory and motor functions are equally vulnerable to the demyelination process.

Studies have been published in which verbal memory is reported as intact in MS patients (Staples and Lincoln, 1979). The inconsistencies in the literature would seem to be subject to the type of memory test used in the assessment and, therefore, the type of memory under investigation. On Williams Delayed Recall test of immediate and delayed verbal and visual-spatial memory, MS patients were reported to perform significantly worse than controls while on the Wechsler Memory Scale's Logical Memory Test (a verbal assessment) the MS subjects had similar results to the controls (Staples and Lincoln, 1979). It would seem, also, that on tests of recognition memory the performance of the MS group does not differ significantly from that of a matched (age, sex and education) control group (Carroll et al, 1984).

Carroll's study, using a picture recognition task and a verbal recognition task devised by the researchers and employing rather modest group numbers (N=21 for each group), concluded, in addition, that verbal recognition memory was impaired only for those MS patients using a semantic encoding strategy. The words presented in the Verbal recognition task were organised into nine categories of five related words each and one category of nine unrelated words. After the testing procedure subjects were asked whether they had used a strategy to remember the words: the responses for those who declared that they did use a strategy (N=12) were examined and a semantic encoding strategy was deduced by studying the response-words within the categories presented. MS patients who used this strategy performed less well than the controls.

While in this study recognition memory was reported, on the whole, to be intact in the MS group, other studies report either a smaller difference between MS and controls on recognition tasks than on free recall (Rao et al, 1984), or that impairment of recognition memory is demonstrated only in patients with chronic progressive MS as opposed to recently diagnosed patients (Elpern et al, 1984).

It may be that MS patients, especially in the early stages of the disease, seem unable to employ search-strategies successfully to retrieve previously presented information but can recognise the same if no strategy for remembering is employed.

Stimulus modality differences have been reported (Rao et al, 1984) and the MS patients' failure to retrieve material appears to occur on tasks using both verbal and/or visual stimuli. This observation is compatible with the diffuse, bilateral lesions observed on scans of MS patients as opposed to lateralized brain disorder.

The performance of the MS group on memory measures has been demonstrated to be unrelated to psychotropic medication use (e.g. Heaton et al, 1985), but group differences were observed in studies involving patients with a relatively brief illness duration (e.g. Grant et al, 1984) so suggesting that impairment of memory function is not confined to long-term chronic MS patients. However, Grant et al's study, using the Brown-Petersen Test, reports that the rapid rate of forgetting with interference did appear to be related to illness duration and to exacerbation status at the time of testing. The MS group's performance in the 'no delay' and 'no interference' condition was normal, but significantly poorer than controls when asked to recall material

(consonant trigrams) following an interference condition (counting backwards serial threes). The rate of forgetting would seem to increase, therefore, with number of episodes of neurological disturbance (duration of illness being defined as the number of 12-month periods containing a new relapse) and current neurological status. This suggests that some degree of cumulative brain damage is operating.

As briefly mentioned above, the WAIS Digit Span subtest has been used to indicate capacity of short-term memory in some investigations of MS patients. The general finding is that it is comparable to controls, though the exception to this is Hirschenfang and Benton's study (1966) which reports observing lowered Digit span in their group of 23 MS patients. The Grant et al findings suggest that immediate memory is similar to that of controls but that there is a rapid rate of forgetting with controlled interference conditions and this would seem to be related to neurological history and severity at the time of testing.

Present Assessment of Memory Ability

In the present study two memory tests are employed: both test recognition memory using visual modality and involving an enforced semantic encoding process, one of verbal (that is, written words) and the other of visual

(that is, photographs of male faces) material. Previous reports suggest that any deficit in recognition memory seems to be related to length of illness and it was considered of interest to examine this particular type of memory in conjunction with the range of demyelinating process, exacerbation status and also duration of illness.

The aim is to investigate whether this memory process is affected by cumulative brain damage, as it would appear other conditions of memory recall are; and to examine how deficient either verbal or visual recognition is in the very early stages of the demyelination process. The recognition memory tests used in the present study constitute two of the few tests with good standardised sensitivity to atrophic conditions and lesions in all section of the cortex. Furthermore, the tests employed require no motor involvement in the test or response procedure.

In addition to the above, the recognition memory tests used in the present study are the only ones available that have been validated as being resistant to the effects of anxiety factors (Coughlan and Hollows, 1984). This was considered to be of some importance with the present subject group given previous reports in the literature on the presence of anxiety in the MS population. Information with regard to anxiety and depression levels is provided

by an extensive psychiatric assessment on the groups in the present study.

With the exception of the Vowels study, it would seem that the weight of previous research suggests that recognition memory, especially verbal, might be expected to be intact in the majority of MS patients. If this proves to be the case in the present study it allows the opportunity to examine whether speed of cognitive processing is maintained with recognition accuracy. Response latency and accuracy were recorded for picture recognition memory in a study on 22 MS patients (Carroll et al, 1984) but the results of the latency recordings were not presented or discussed, only the accuracy measures and the encoding strategies. Carroll and her colleagues (1984) also administered a Perceptual Memory Task (presenting pictures on a slide) which required the subjects to name the object on the screen as quickly as possible. Response latency was again recorded (with a chronoscope connected to a voice operated relay attached to the slide presentation mechanism) and the researchers conclude that latency to naming objects was significantly slower for MS subjects ($p < 0.01$). Carroll et al suggests that "this is presumably due to the motor slowing which often accompanies MS" (p. 299). The physical impairment of this MS group in this study was described as varying widely but no motor or physical assessments were reported.

The plan of the present assessment procedures includes an investigation into the time taken to recognise previously presented stimuli, both verbal and visual. This examination of the speed of cognition is presented in more detail below. A further aim of the present study is to look at, in greater detail, any MS patients presenting with recognition memory deficit. This is in order to examine whether they represent a distinct subgroup: to look at whether they are different to the rest of the group on any other measures or factors.

C) Abstracting Ability in MS

As long ago as 1877, Charcot referred to difficulties with conceptual judgement and the planning and organisation of behaviour in patients with MS. Since then, clinical reports continue to describe such problems and this cognitive deficit is measured in a number of studies by employing tasks that involve abstract reasoning and conceptual learning. It was not until relatively recently that specific tests designed to measure this function were administered to the MS population.

Abstracting ability is frequently reported to be impaired in patients with MS via the analysis of results on a variety of tests. Knehr (1962) concluded that there was no impairment of abstract reasoning in his group of MS subjects (N=11) when compared to normal controls (N=11)

and neurological controls (N=11). However, this study did not use a test designed to assess abstracting ability, and used only ambulatory MS subjects which may therefore have had minimal impairment. Reitan et al (1971) administered the Halstead Battery and concluded that their MS subjects (N=30) showed mild impairment on tasks requiring abstract reasoning. An earlier study by Ross and Reitan (1955) concluded that MS patients were not impaired on abstract reasoning tasks when compared to normal controls or non-brain-damaged controls. However, a number of studies using normal or non-brain-damaged controls have reported that the MS group performed significantly worse with regard to this function.

Parsons et al (1957) administered the Grass Block Substitution Test and concluded that the MS group (N=17) had difficulty with nonverbal abstraction. The sample used in this study was small, however, given the range of MS severity status. Nonverbal abstracting difficulty was also reported in Jambor's (1969) study while she concluded that verbal conceptualisation was intact.

Consistent results emerge from more recent studies suggesting that the MS population are impaired on tasks requiring abstract reasoning (Elpern et al, 1984; Heaton et al, 1985; Peyser et al, 1980; and Rao et al, 1984) when compared to normal controls. Studies comparing the MS

population to mixed brain-damaged controls (Goldstein and Shelley, 1974; Ivnik 1978; Matthews et al, 1970 and Ross and Reitan, 1955) suggest that the performance of MS patients is nearer that of the brain-damaged population with regard to abstracting ability.

Rao (1986) has pointed out that the underlying cognitive deficit that can occur on conceptual reasoning tasks may result from defective attention or memory, or be as a result of low motivation, distractibility or impulsiveness. No studies are known at the present that have measured attention in this group, or analysed results of abstraction tasks in conjunction with performance on this ability. The majority of studies have used the Category Test (Halstead 1947) which does not allow for an analysis of patient error patterns.

A study by Rao and Hammeke (1984) assessed concept formation strategies in MS patients using a two-choice visual discrimination test developed by Levine (1966). Their conclusion is that MS patients tended to perseverate with an incorrect strategy despite negative feedback, while controls tended to make errors that appeared to be more random. Similar perseverative tendencies have been observed on this task in patients with unilateral frontal tumours (Cicerone et al, 1983).

Tests of frontal lobe functioning have been administered to MS patients (Vowels and Gates, 1981) and it is suggested that there is major involvement of the frontal lobes in their observed and tested difficulties. Vowels and Gates implicate frontal lobe dysfunction in the euphoric states frequently described in MS patients.

Frontal lobe dysfunction is also implicated in the MS groups' performance on tests on abstraction. The major criticism of the Vowels and Gates' study is that no anatomical data is provided on the subject samples (MS N=100 with an unspecified control group). In her study in 1981, Lincoln also implicated the frontal lobes in her finding that MS patients presented with abstracting ability deficits (MS N=25, physically disabled controls N=25). Again, Lincoln's study provided no anatomical data for the subject groups.

Present Assessment of Abstracting Ability

It has been suggested in one study in the neuropsychological literature that the Picture Arrangement subtest of the WAIS may be a measure of frontal lobe dysfunction (McFie and Thompson, 1972), so it would seem clear that performance on a number of tasks or tests may be considered to be an indicator of abstracting ability. However, bearing in mind Rao's (1986) comment on the importance of analysing patient error patterns, the

present study employs the Modified version of the Wisconsin Card Sorting Test (Nelson, 1976). This test is capable of yielding a number of measures that distinguish between different types of errors (Heaton 1981). Most of the studies that have used this task with MS patients have used only a single summary index.

The present study looks at total number of errors made by subjects; also total number of perseverative errors and number of categories correctly sorted. While these three error indices will be examined, only one will be used in the final analyses. The aim is to measure nonverbal abstracting ability with a task that requires minimum motor involvement. It is hypothesised that the MS group will perform poorly on this task when compared to the controls.

D) <u>Attention Functions in MS</u>

Deficits in attention were not known to have been systematically studied in patients with MS at the commencement of the present investigation, although sustained attention has been implicated in frontal lobe dysfunction (Wilkins et al, 1987); an area that has been repeatedly investigated in patients with MS. Fatigue is a common subjective complaint of MS sufferers and although this is usually understood in the physical sense, it may be that this results in inattention and distractibility.

A recently published study (Rao et al, 1989a) examined patients with definite or probable MS with a range of cognitive assessments including three tasks designed to measure attention and concentration. The researchers conclude that a large percentage of their MS group were cognitively impaired, but do not discuss the results of the attention assessment in detail.

Present Assessment of Attention Functions

The present study aims to measure speed of visual attention and accuracy of auditory attention to observe whether MS patients' performance is deficient when compared to controls. Visual acuity and fatigue factors will also be measured so that their effect on attention may be observed.

Measurement of attention ability allows performance on other tests and tasks to be observed taking into account the possible effect of distractibility on their results. The hypothesis is that MS patients will perform significantly worse than controls on these tasks, and that attention ability will not be solely dependent on level of fatigue.

E) Naming Ability in MS

In 1977 Olmos-Lau et al reported a case of 'motor aphasia' in a 17-year-old woman with clinically definite MS: she was described as having reduced spontaneous speech, paraphasias in naming and repetition and marked orofacial apraxia with relatively intact written language and auditory comprehension. Plaques in the grey matter of Broca's area were implicated. These researchers found 14 other published case reports of aphasia in MS: 12 of which were published prior to 1953 and only 4 of which had pathological confirmation of MS. This raises questions regarding the validity of the diagnosis of MS used in these early studies, and all were criticized for their brief and poorly documented clinical descriptions. Such reports of focal lesions producing language dysfunction in MS are rare.

Systematic neuropsychological investigations of language functions have not been reported for patients with MS. Studies exist where limited language testing was administered as part of larger test batteries (Heaton et al, 1985; Jambor 1969). Jambor administered tests of naming, reading, spelling and comprehension to MS patients, normal controls, psychiatric controls and muscular dystrophy patients. She reported that the MS group performed at a poorer level when compared to the controls on naming and reading, but concluded that speech

functions did not appear to be impaired in patients with MS. No information was provided as to which subtests were used for prorating IQ measures, and the sample was restricted to persons under 40 years of age.

Heaton and colleagues (1985) administered the Aphasia Screening Test and the Thurstone Word Fluency Test and found that chronic progressive MS patients made significantly more errors on the Aphasia Test than did relapsing remitting MS patients and Normal controls; while both MS groups performed more poorly than did the controls on the Thurstone Test.

While these two studies suggest that language disturbance can occur in patients with MS, Rao (1986) points out that their data does not provide "adequate qualitative information to determine whether a characteristic pattern of language breakdown occurs" (p.523) in such patients.

Goldstein and Shelley (1974) administered the Reitan-Heimburger Aphasia Test to their subject group of MS patients and concluded that they had well preserved language. Their subjects were all male; the sample size was small with a wide range of MS status, and no objective scoring of disability status was used. Rao et al (1984) administered Sentence Production Subtest of Minnesota Aphasia Battery to his sample of MS patients and does not

suggest impairment of language function in his conclusions.

Present Assessment of Naming Ability

The MS literature includes a limited number of published studies of investigations of language function and though the results are somewhat contradictory and inconclusive, there is some suggestion that this ability may be impaired in patients with MS.

The present investigation does not set out to attempt to fill this gap in the literature; this would require a thorough and systematic study of the range of language function in a large number of subjects with a wide range of MS status. This study concentrates on one aspect of language ability, that of Object Naming, using a test which comprises pictorial presentation of objects of graded difficulty. This test does not constitute part of any Battery but is a test with it's own norms and validity studies. The added dimension of timing each subject's response to each picture presentation was included in order to examine the speed of cognitive processing (this aspect of the test is dealt with in greater detail below).

F) Speed of Cognition in MS

The relationship between speed and accuracy is not well understood in normal subjects. Does dissociation between speed and accuracy occur? Studies of patients with dementia suggest that the subcortical dementias can be clearly distinguished clinically from cortical dementias (other than frontal dementias) with regard to disturbances of timing and activation (Albert et al, 1974).

The issue of timing in the Cortical versus Subcortical debate is of particular interest in relation to MS, since this includes subcortical lesions on scan analysis (Ormerod et al, 1987). In Albert et al's reported case studies of subcortical dementia patients (1974) one subject was described as having "..slowness of thought processes: forgetfulness (not a true memory loss, except that it takes him longer than normal to find words and ideas).." (p.122). The present investigation included, therefore, recording the response latency of all subjects on both memory tests administered. This was undertaken in order examine whether recognition memory was slowed in this group of patients when compared to controls when accuracy was normal; and to investigate the difference in speed of recognition between the two types of memory and whether this was the same for the control group as for the experimental groups.

Timing a recognition memory test was considered less complicated than timing free recall as the former requires all subjects to respond to the same number of stimuli. In contrast, a free recall test may elicit 20 responses from an accurate subject and only 4 from an impaired subject so creating a differential in timing that would be more complicated to measure accurately; and so producing more difficulties when attempting to look at the relationship between speed and accuracy in a memory task.

Reaction time has been studied in MS patients (Elsass and Zeeberg, 1983) in order to investigate whether cognitive processing is slowed: it is suggested here that such an investigation using a motor oriented task may produce results that are due to a 'fatigue' factor rather than slowed cognition. Such investigations using motor components could be further confounded by the physically disabling nature of MS.

In 1963 Rochford and his colleagues extended their previous work on normal subjects to examine the manner in which language functions recover after they have been impaired by cerebral lesions. Their main findings were that greater learning was seen on the 'easy' than on the 'hard' items, and 'easiness' is related to general frequency of usage.

The naming test used in the present study consists of a list of objects in ascending order of difficulty, the names of which are all of low frequency of usage. This precludes the examination of the relationship between speed of naming and word-frequency in this investigation, the focus of the present study is on the relationship between speed and accuracy.

Oldfield and Wingfield (1964; 1965) showed that the time taken for normal adult subjects to name pictures of objects was linearly related to the logarithm of the frequency of the object-names in print. This study was extended by Newcombe, Oldfield and Wingfield in 1964 and this result was also reported for patients with localized cerebral lesions; suggesting that the aphasic group differed only in degree from that of the normal group. As far as errors in naming were concerned, there was only a significant difference between the brain damaged and control subjects for names with a low frequency (that is, a frequency of less than ten per million as measured by the Thorndike Lorge (1944) word count). Barker and Lawson (1968) conducted similar experiments, using a population of senile dements. They were able to confirm that for this group of neurological patients also, when compared with the normal elderly population, significant differences in respect of latency and naming errors were a function of word frequency.

Speed versus accuracy in object naming has not been studied in the population of patients with MS. In the one study found where response latency of object naming in MS patients was examined (Carroll et al, 1984) it was conducted as part of the procedure of a Perceptual Memory Test. This research concluded that those patients with MS had significantly longer latencies than the controls. The results in Carroll et al's study, however, were not analysed to examine frequency in relation to speed. Furthermore, the subjects in this study were told to respond as quickly as possible, so making them aware of, and alert to, the timing process. Subjects were asked to respond with the "most readily available name" (p. 299) and speed in relation to accuracy was not systematically analysed.

Present Assessment of Speed of Cognition

The present investigation attempts to examine this phenomenon in MS patients; and furthermore will be investigating whether language function (naming ability) is intact and if so, how it compares to the normal group with regard to latency of responses. It has been suggested in one study (Goldstein 1948) that naming an object involves some degree of abstraction: the ability to abstract has been shown to be deficient in MS patients yet there is little or no research examining object-naming in this group. The present study attempts to examine MS

subjects:

1) to see whether object naming when comparable to controls' performance produces a response latency that conforms to what is hypothesised theoretically as 'normal' or 'expected' in terms of it's nature and direction and

2) to analyse whether their response latencies, whether deviant from the expected or not, are significantly slower than the controls'.

The hypothesis of the present study, given the presence of subcortical lesions in the disease of MS, is that the experimental group would be expected to produce response latencies significantly slower than those of the controls.

In the absence of any knowledge with regard to the relationship between speed and accuracy for subjects with a disease process such as MS; and given the evidence to suggest that such a relationship remains similar to normals in groups with localized cerebral lesions, it is hypothesised that the difference between the experimental and the control groups in the present study in this regard will be a matter only of degree.

With regard to timing recognition memory the aim of the present study is to examine, in addition to the aims mentioned above, whether extent of lesions in the brain

are related to speed of cognition: given the acknowledged presence of subcortical lesions in the brains of MS patients it is hypothesised that there will be a relationship between the two. The timing of such cognitive functions seemed a promising area of investigation.

G) Cognitive Abnormalities in CIL

The cognitive performance of patients with clinically isolated lesions (CIL) has only been studied in a handful of cases (Lyon-Caen et al 1986) which included only Optic Neuritis patients and mild abnormalities were found. Lyon-Caen et al examined 21 patients with Definite MS and Probable MS (N=11 and N=10 respectively), 9 patients with Optic Neuritis and 29 controls: these groups were described as showing no clinical or social evidence of cognitive impairment. These subjects were examined with three subtests of the WAIS: Block Design, Similarities and Vocabulary; the Wisconsin Card Sorting Test; and the Wechsler Memory Scale. The authors conclude that calculation, verbal fluency, naming and construction were normal but that Memory (visual and verbal), verbal and nonverbal efficiency were abnormal. Four of the 11 Definite MS patients were considered to have impairment of intellectual functions; eight of the 10 Probable MS patients were described as having 'cognitive impairment' and six of the 9 ON patients were also described as being

'cognitively impaired'. These figures represent 36% of the Definite MS group as impaired, 80% of the Probable MS group as impaired and 67% of the ON group as impaired (almost twice as much as in the Definite MS group). No correlation was reported to have been found between degree of handicap, or disease activity, and cognitive impairment.

On closer examination of the results presented in this paper, it was observed three of the ON group, possibly four, appear to present with some abnormality while the remainder seem to perform near or around the norm expected. The subjects in Lyon-Caen's study were compared with a heterogeneous group of patients, some of whom were likely to have been brain damaged.

In the present study patients with ON are examined with a range of psychometric tests as are two other groups with Clinically Single Lesions: Brain Stem disorder and Spinal Cord syndrome. The possibility that subtle psychometric abnormalities may be one of the earliest counterparts of brain pathology in the demyelination process remains to be explored. Some of the present study's results with regard to the CIL group have been recently published by the author (Callanan et al, 1989) and apart from this report there is no other study known at the time of writing that investigates in any detail the cognitive performance of CIL patients and its correlation with scan data.

CHAPTER III

METHODOLOGY

1. STATISTICS

The present data were examined statistically via two stages of analysis:

1) by investigating the differences between group means and the associations within a group on various measures; and

2) via performance grades assigned to the psychometric scores and via quartile grades assigned to an MRI measure (the Total Scan Score) and to Cognitive Speed results. This was in order to assess the performance of each group in terms of numbers or percentage of individuals obtaining scores within a particular attainment range.

a) Stage 1

Statistical comparisons were computed with the Mann-Whitney U-test on two groups and the Kruskal-Wallis 1-way ANOVA on more than two groups: statistical examination of correlations between scores was explored using the Kendall tau test.

A number of psychometric test results (e.g. IQ and Memory tests) fulfil the conditions for parametric statistical analysis. However, in order to be able to compare the results of one statistical analysis with another, nonparametric statistics were used throughout. The only exception to this is the use of the MANOVA statistical procedure on data that fulfils the criteria for parametric analysis: this was to enable comparisons of group performance on IQ measures while taking into account group performance on a disability measure. When a nonparametric procedure such as the Kendall tau is used, on data to which the Pearson r is properly applicable, the tau is said to have efficiency of 91 per cent. That is, tau is approximately as sensitive a test of the existence of association between two variables in a bivariate normal population with a sample of 100 cases as is the Pearson r with 91 cases (Siegel, 1956).

b) Stage 2

(i) PERFORMANCE GRADES

A grading system (0 to 3) was devised, based on the performance of the Control group, for each psychological function measured:

GRADE 0 This was assigned to scores at or above the 50^{th} percentile of the Control Group.

GRADE 1 This was assigned to scores falling with the range of the 25^{th} and 50^{th} percentiles of the Control Group.

GRADE 2 Assigned to scores falling within the range of the 5^{th} and 25^{th} percentiles of the Control Group.

GRADE 3 This grade was assigned to scores equal to and worse than the 5^{th} percentile of the Control Group.

Grades were assigned as closely as possible to the above percentiles: it was not possible with one measure (Graded Naming Test) to be exactly within these percentiles as the clustering of the Controls' scores did not allow it.

The above grades were assigned to each function measure within the psychometric assessment; in the case of IQ it was applied to the 'IQ Deficit' measure only. In the case of the results of the Modified Wisconsin Card Sorting Test it was applied to the Total Error Score only.

It is pertinent to note that the control group's performance on each test was the same as the established norms. As there was one test without such norms (Auditory Attention) it was considered more reliable to compare the Experimental groups' performance on each test to that of the control group's rather than just to the norms

available.

The grades were labelled according to the level of ability they were considered to represent: Good (grade 0), Fair (grade 1), Poor (grade 2) and Deficient (grade 3).

This procedure yielded the following data for each subject:

1. IQ Deficit Grade
2. Verbal Memory Grade
3. Visual Memory Grade
4. Abstracting Ability Grade
5. Visual Attention Grade
6. Auditory Attention Grade
7. Naming Ability Grade

These individual grades were then summed across for each subject yielding a general measure of overall cognitive ability in what will be referred to as a 'Cognitive Efficiency Score': the possible maximum being 21, ranging from zero.

The Cognitive Efficiency Score was further graded according to the Control Group's percentiles as above; this produced for each subject:

8. Cognitive Efficiency Grade.

(ii) MRI QUARTILES GRADES

The Total Scan Score was examined via quartile grades within each experimental group:

GRADE 0 Those with Total Scan Scores in the first quartile (that is, those with the lowest scores and falling within 0 to 25^{th} percentile) were assigned this Grade;

GRADE 1 This grade was assigned to Total Scan Scores in the second quartile (25^{th} to 50^{th} percentile);

GRADE 2 Assigned to those within the third quartile (50^{th} to 75^{th} percentile);

GRADE 3 Assigned to the worst or highest scores which fell within the last quartile (75^{th} to 100^{th} percentile).

This allowed examination of psychometric performance in relation to four different levels of degree of brain lesions within each experimental group.

(iii) COGNITIVE SPEED QUARTILE GRADES

Quartile grades, based on the results of the Control Group, were assigned to the Cognitive Speed results of each subject using the same procedure as described above.

All statistical analysis of the Grades was done using nonparametric tests, namely, the Mann-Whitney U-test and

the Chi Square statistic. The latter will be discussed in further detail below. With the exception of some Chi Square analyses all statistical work was carried out using the Statistical Package for Social Sciences (SPSS/PC+) (Norusis, 1986) on a microcomputer.

(iv) THE CHI SQUARE STATISTIC

One of the basic assumptions of the Chi Square test is that, where there is more than one degree of freedom, the expected frequency of each cell should be at least five (Kirk, 1978). All other basic assumptions being fulfilled it was necessary to collapse the Accuracy and Speed Grades of three measures in order to fulfil the parameter regarding expected frequencies of five or more. Therefore, for the purpose of statistical analysis via the Chi Square test, Cognitive Speed Quartile Grades were collapsed into two categories, Fast (Grades 0 and 1) and Slow (Grades 2 and 3) for Verbal Memory, Visual Memory and Naming Ability. The Performance or Score Grades on each of these measures were also collapsed, but into three categories: Grade 0 and 1 remaining the same and Grade 2 and 3 combining to represent scores within the 0 to 25^{th} percentile range (i.e. the poorest score quartile). This produced a 3 x 2 contingency table on each measure for each group and the method for the analysis of frequency

data for multiple classification designs (Sutcliffe, 1957) was followed. The observed and expected frequencies used in the statistical analyses for this data are presented in Appendix 1. In this analysis the Score effect was not to be investigated therefore expected frequencies were calculated on the basis of this fixed variable, that is the Control Group's observed frequencies for Score Grade. The expected frequencies for the Speed Grade were based on the Null Hypothesis of 'No Effect', that is, 50% in each of the two categories of Fast and Slow within each Score Grade (Sutcliffe, 1957).

2. GENERAL METHOD

(1) AIM OF PRESENT STUDY

This study employs a 'Within-and-Between Subjects' design; with a matched Patient Control group (Control Group 2) to control for any extraneous variables; and a Normal Control group (Control Group 1) for comparative Magnetic Resonance Imaging (MRI) analysis.

Impaired cognitive functions have been found in a significant percentage of patients with a diagnosis of Definite Multiple Sclerosis (MS). Attempts have been made to relate the degree and type of cognitive dysfunction with pathological sites of cerebral involvement (Brooks et al, 1984; Rao et al, 1985) using measures of brain atrophy. The increased sensitivity of MRI enhances the possibility of clinicopathologic correlations, but the possibility that lesions may be widespread at the time of initial diagnosis may confound any attempt at correlation of dysfunction with specific site/s. For this reason it was considered of interest to examine a cross section of demyelinating disease, and investigate, with MRI and psychometric assessment, patients presenting with early manifestations of demyelination. Therefore, patients who presented with syndromes considered to have some risk of developing MS were examined alongside those with a definite diagnosis.

(2) GROUPS

(A) Experimental Groups

a) Source

With the exception of a small subgroup of patients, all patients examined were under the care of a Consultant Neurologist working at the National Hospitals for Nervous Diseases. These patients had undergone intensive investigations to help clarify the neurological diagnosis, including CSF examination and electrophysiological testing as considered appropriate.

Collaborative research with another neurological unit led to the referral for MRI a group of patients with lesions of the Spinal Cord. They had undergone similar intensive neurological investigations elsewhere. Advantage was taken of the presence of this group, who agreed to undergo psychiatric and psychometric assessments during their visit to the hospital.

b) Inclusion Criteria

Subjects for the Experimental Group were selected on the following basis:

1- They were referred for and scheduled to have an MRI scan.

2- Their diagnoses were established.

3- They were examined psychiatrically and psychometrically thereafter subject only to the

patients' consent and the time availability of the examiners.

c) Exclusion Criteria

Patients were excluded from the study if they came into any one of the following categories:

(1) The presence of a second, unrelated central nervous system disorder, or a systemic disease known to be associated with brain pathology. Thus, patients with hypertension, epilepsy or diabetes were excluded.

(2) In the course of the assessments further information with regard to medical and social history and general background of the subject was gathered. Subjects were excluded from the study if such information was indicative of possible underlying brain damage from a cause other than one of the diagnostic categories under investigation:

(a) A history of previous head injury associated with a loss of consciousness and a post-traumatic amnesia of 24 hours or more.

(b) A history of regular excessive alcohol intake, confirmed by the patient or the medical notes to be three pints of beer (or its equivalent) or more per day.

(c) A history of drug abuse.

(3) The cultural and educational bias in some of the tests employed in the psychometric assessment necessitated

excluding subjects who:

(a) Did not have English as their first language.

(b) Were not educated in England for the majority of their years in education (certainly the formative years of education MUST be in England).

(4) The nature of the psychometric tests necessitated excluding those subjects who were officially registered as blind, or whose visual acuity (obtained from their hospital notes) was poorer than 18/9.

d) Description

(i) Experimental Group 1 - Clinically Definite MS

The patients were part of a large cohort undergoing a study of MRI abnormalities at the National Hospitals for Nervous Diseases. The criteria used for diagnosis of Clinically Definite MS are those of Poser et al (1983):

Clinically Definite Multiple Sclerosis: two attacks and evidence of two separate lesions, or two attacks and evidence of one lesion and paraclinical evidence of another, separate lesion. The two attacks must involve different parts of the central nervous system, be separated by a period of at least one month, and must last a minimum of 24 hours. It is considered permissible to substitute certain historical information for evidence of one of the two lesions within the first set of criteria. Such information must be reliable, adequate to localize a lesion typical of MS and

have no other explanation. A remission is defined as a definite improvement in signs, symptoms or both that has been present for at least twenty-four hours.

A selected group of 58 patients (18 males and 40 females) with Clinically Definite MS were included in the study: ages ranged from 24 years to 67 years with a mean of 38.3 (standard deviation of 8.8). 10 of these patients used walking aids and a further 10 were wheelchair-bound; the remaining 38 were physically independent at the time of testing. 53 of this group were right-handed and 5 were left-handed. 2 were receiving steroids, 2 were taking antidepressants, 6 were on anxiolytic drugs and 5 were receiving antispasmodic drug treatment at the time of testing.

Years of active disease was calculated on the basis of the number of 12-month periods containing a new relapse (Grant et al, 1984): of this patient group 24 had between 1 and 8 years of active disease and 4 had between 9 and 14 years of active disease. Data on 30 patients with regard to this factor is not available. The mean years of active disease, therefore, is 5.75 (standard deviation of 3.4). At the time of testing 17 of this group were in relapse.

(ii) Experimental Group 2 - Clinically Isolated Lesion

The diagnosis of clinically isolated lesion of the type commonly found in MS was made after subjects had undergone appropriate neurological assessment to exclude other possible aetiologies. Patients presenting with an isolated clinical episode of neurological dysfunction comprised three clinically distinct diagnostic groups:

a) Optic Neuritis (ON)

b) Brain Stem disturbance (BS)

c) Spinal Cord syndrome (SC)

As a combined group these will be referred to as the **Clinically Isolated Lesion (CIL)** group.

The operational criteria used in the study are those of Poser et al (1983): Isolated Episode: signs of neurological dysfunction demonstrable by a neurological examination that can be explained by the presence of an anatomical lesion in either the Optic Nerve, Brain Stem or Spinal Cord. Such neurological signs are acceptable even if no longer present, provided that they were elicited and recorded in the past by a competent examiner.

a) OPTIC NEURITIS

14 patients presented with Optic Neuritis (ON); all of this group were physically independent using no mobility aids. There were 6 males and 8 females with a mean age of

34.2 (standard deviation of 10.8). All were right-handed.

7 of this group were in relapse at the time of testing and did not perform the visual attention tests for this reason. The remainder had corrected normal visual acuity. 3 were on steroids and 2 were receiving benzodiazepines.

b) BRAIN STEM DISORDER

16 patients presented with Brain Stem Disorder (BS): one subject was wheelchair-bound and the other 15 were physically independent using no mobility aids. There were 3 males and 13 females with a mean age of 33.1 (standard deviation of 7.8). All were right-handed.

7 patients were in relapse at the time of testing; one patient was on steroid medication; 7 were taking benzodiazepines and 2 were receiving anxiolytic drugs. Corrected visual acuity was normal in all.

c) SPINAL CORD SYNDROME

18 patients presented with Spinal Cord Syndrome (SC); 2 subjects were wheelchair-bound, two used walking sticks and the remaining 14 were physically independent. There were 8 males and 10 females with a mean age of 40.7 (standard deviation of 11.8). One patient was left-handed and the remaining 17 were right-handed.

3 patients were in relapse at the time of testing; 3 were on steroid medication, 3 were receiving benzodiazepines and 4 were taking antispasmodic drugs. Corrected visual acuity was normal in all.

CIL Group In Summary

Forty-eight patients (18 males and 30 females) with clinically isolated lesions were included in the study. Their ages ranged from 20 to 61 years with a mean of 36.3 (standard deviation of 10.7). Forty-three patients were physically independent requiring no mobility aids, while two used walking sticks and three were wheelchair-bound. Seven were receiving steroid medication and fourteen were receiving benzodiazepines (mainly as night sedation) at the time of the study. Seventeen patients were in relapse at the time of testing including seven with unilateral optic neuritis. With the exception of these seven all had corrected normal visual acuity.

(B) Control Groups

(i) Group 1

Individuals in this group were psychiatrically normal, apparently healthy and able-bodied, and were not inpatients or outpatients at any hospital. They were in the same age range as the Experimental Group in order that the effect of age on scan appearance could be examined. All members of this group were volunteers working in a

London-based office of the Salvation Army. Each subject was screened by means of an interview schedule in order to establish the absence of any factors listed under the exclusion criteria.

The Salvation Army (S.A.) was sent a written communication explaining the purpose of the study and requesting volunteers. This was met with prompt co-operation. The point of contact was the S.A.'s Head Office in London. Regular weekly appointment times were given to the Head of this office, and he then gave these appointed times to any volunteers. The initial written communication stressed the inclusion criteria, which was later checked by the assessors on meeting with the volunteers.

(ii) Group 2

Individuals in this group were randomly selected from hospital inpatients at the National Hospital for Nervous Diseases, and a small subgroup were randomly selected from in- and outpatients at the Royal Free Rheumatology Unit. These patients were suffering from disorders that were physically disabling, or potentially so, but with no known cerebral involvement.

Appropriate subjects were found by a regular perusal of the hospital's admission lists, and subsequently the patient's hospital notes.

The patients were then approached with an explanation outlining the purpose of the study and what would be required of them should they be willing to take part. If the patient gave permission to proceed, the assessments were set up and carried out as soon as possible.

Royal Free outpatients were all assessed at the National Hospital, and Royal Free inpatients were assessed on their ward with the co-operation of the nursing and medical staff.

(iii) Inclusion Criteria

A set procedure was followed to ensure that group 2, the physically disabled patients, matched as closely as possible the patients examined in the MS group: a record sheet was kept on the MS patients seen, detailing:-

a) the decade of their age:

b) what physical aids they used (None, Walking Aid or Wheelchair) and

c) their sex.

This sheet was used to calculate the percentage of males and females; percentage of those physically independent, using walking aids, and those wheelchair-bound; and the percentage in each age decade so that similar percentage figures could be fulfilled when obtaining subjects for control group 2. An attempt was made to match the

percentage figure in each category as closely as possible. As each percentage category was filled, control patients who came along who would fall into that category were not approached for participation in the study.

(iv) Exclusion Criteria

The same general exclusion criteria were applied to the Control groups as were applied to the Experimental Groups.

(v) Description

a) Control Group 1 - Able-bodied non-patients:

This group comprised 40 volunteers aged between 19 and 64 years, with a mean age of 39.9 years. There were 19 females and 21 males.

They each scored 3 or less on the thirty item General Health Questionnaire (Goldberg 1972) to ensure a low psychiatric morbidity.

b) Control Group 2 - Physically disabled patients:

This group of controls comprised 18 males and 28 females, 44 of whom were right-handed and 2 of whom were left-handed.

Their ages ranged from 20 years to 68 years, with a mean age of 39 (standard deviation of 12.6). All had normal visual acuity.

Of these, 27 were physically independent, using no physical aids; 9 required walking aids and 10 were wheelchair-bound. 31 of these were in relapse at the time of testing; 2 were taking steroid medication, 3 were receiving antidepressant drugs and 1 was receiving anxiolytic medication.

3. INVESTIGATIONS

All subjects in the MS group, the Clinically Isolated Lesion (CIL) group and the normal volunteer group (Control Group 1) underwent MRI along with a random selection of 18 of the physically disabled controls (Control Group 2). As Control Group 1 were normal controls for scan analysis this group of subjects did not undergo any of the other assessment procedures except for a screening interview which included the General Health Questionnaire. All subjects within the other three groups (MS, CIL and Control Group 2) were investigated psychometrically, psychiatrically and underwent the motor ability assessment. For these three groups also were collected details of previous medical history, present medication intake, present exacerbation status and information with regard to Years of Active Disease . Years of Active Disease is a concept formulated by Grant et al (1984). A year of active disease is defined as a twelve month period during which at least one new symptom compatible with further demyelination has occurred. It has the potential

of being a more accurate indicator of overall disease activity than years since onset of the first symptom of MS. An exacerbation is defined as the occurrence of a symptom or symptoms, with or without objective observation, and lasting more than twenty four hours (Poser et al, 1983). Hospital notes were consulted for details of present corrected visual acuity.

The MRI investigation lasted approximately thirty minutes; with a one-hour psychiatric examination; a ninety-minute psychometric investigation and a motor ability assessment lasting thirty minutes. In all but a few patients these assessments were performed on the same day: all assessments were carried out within a period of two weeks (if new neurological symptoms arose in the interim between tests then no further assessment was undertaken and the subject was excluded from the study). The order in which the investigations were carried out varied from one subject to the next within each group: in this way it was hoped to avoid the factor of the effect of undue stress or fatigue on any one assessment result.

4. RESULTS OF RELATED INVESTIGATIONS

A) MRI Investigation

(a) METHOD AND MATERIALS

The imager used in the study was 0.5 tesla Picker superconducting system used to form proton NMR images. This machine was used in a much larger study and details of the apparatus are reported elsewhere (Ormerod et al, 1987) as is the precise methodology of the scan analysis (Logsdail et al, 1988). In brief, the presence and size of lesions was examined in seven periventricular areas (body of the ventricles, frontal, temporal and occipital horns, trigone and third and fourth ventricles) and in the following areas of the brain parenchima: internal capsule, basal ganglia, frontal, Parietal, temporal and occipital lobes. Lesions in each of these areas were given a score from 0 to 3 depending on the size of their longest diameter (0= <2mm; 1= 2 to 5mm; 2= 5 to 10mm; 3= >10mm). A total scan score was obtained by adding the partial scores of the various areas examined. In addition a 'periventricular' score was obtained by adding the scores within the relevant areas.

(b) RESULTS OF THE MRI ANALYSIS

There were two measurements used in the scan analyses which were obtained by summing the lesion scores contained within the periventricular area; and by summing all the lesion scores obtained on the scan:

1. Periventricular Score

2. The Total Scan Score.

TABLE A presents the mean scores of each area measured on scan for each group and also displays the number of individuals in each group that had no lesions at all in the area concerned. Analyses concentrated on the above two scan measurements as these had by far the highest means and the largest group numbers.

(i) MS Group

The scores obtained on analysis of the MRI of this group are presented in TABLE A. The general scan appearance of subjects in this group was diffuse lesions mainly centred in the periventricular area. Only one patient had a normal scan and none of the group presented with focal isolated lesions.

(ii) CIL Group

Nine of this group obtained normal appearance on MRI: 3 of these were in the ON category; 4 in the BS and 2 in the SC category. The means for the group as a whole are presented in TABLE A. The commonest MRI abnormality observed in this group was a periventricular rim of increased signal often accompanied by discrete lesions in the brain parenchyma. The total lesion score of this group was significantly different from those of the 2 control groups (Total lesion scores 9.8, .71 and .52

respectively, p.<.001). There was no significant difference in the total lesion score between the clinical subgroups (ON, BS and SC) but in those with cord lesions the score was significantly correlated to the duration of neurological symptoms (Callanan et al, 1989).

(iii) Normal (Able-bodied) Controls

This group of 40 volunteers underwent MRI investigation only and 5 of this group were considered to have abnormalities present in their scans.

(iv) Physically Disabled Controls

A random selection of this control group were scanned. Abnormalities were detected in the scans of 2 of the 18 subjects who had MRI investigation. The proportion and type of abnormalities detected in these controls were similar to those found in the normal controls (Callanan et al, 1989). Of the eighteen controls who were scanned, two had abnormal scans: one obtained a Total Scan Score of 5, and the other a score of 7. Of a group on normal non-patient controls (Control Group 1) who had MRI investigations approximately 12% had abnormalities in the brain (Logsdail et al, 1988; Callanan et al, 1989) which is similar in proportion to the present finding in this group of patient controls (2/18 = 12%). The non-patient controls with abnormal scan appearance were all over 42 years of age: the two patient controls in Control Group 2

with abnormal scans were aged 51 (diagnosed prolapsed intervertebral disc) and 62 (diagnosed spinal neurofibroma). The latter had periventricular abnormalities, two small discrete lesions in the frontal lobes and another in the Parietal lobe (scoring 7 on Total Scan Score). The 51-year-old had minor abnormalities in the periventricular region and a total scan score of 5.

B) Psychiatric Investigation

(a) METHOD AND MATERIALS

The assessment of mental state was made after the collection of background data, using the Clinical Interview Schedule (CIS), which is a semistructured interview developed by Goldberg et al (1970) which concentrates on low level morbidity and thus is sensitive to relatively minor change, although serious upset of the mental state is also recorded. It has become well established in psychiatric research and is of known high validity and reliability. The CIS has been used in the assessment of psychiatric morbidity in a wide range of clinical conditions, including abnormal neurological states. Symptoms such as depression, anxiety, elation (euphoria) and fatigue are rated on a four point scale of 0 to 3 according to both subjective and objective observations. There are eleven symptoms rated giving a maximum CIS score of 33: those subjects who scored 14 or more were considered 'Psychiatric Cases', that is

suffering a high level of psychiatric morbidity.

A self rating depression questionnaire, the Beck Depression Inventory (BDI) was also filled out by each patient. The BDI is of known high validity (Beck et al, 1961) and is not weighted towards physical symptomatology, thus minimising a false elevation of score because of the symptoms of physical disease.

(b) RESULTS OF PSYCHIATRIC ANALYSIS

Four measures were taken from the psychiatric assessment and used in the present study:

1. Clinical Interview Schedule (CIS) Total Score
2. CIS rating of Depression
3. CIS rating of Anxiety (the psychiatrist's objective rating)
4. Total Beck Score for Depression

(i) <u>MS Group</u>

Of this group 25 scored high enough on the CIS to be termed 'Psychiatric Cases'; 17 scored for Depression and 16 scored for Anxiety. As can be seen on TABLE B this group's CIS scores differed significantly (see also TABLE 10) to those of the CIL group and the Control Group. On the Beck Total Score ten patients scored higher than 17 indicating that they are scoring high enough to be described as 'depressed cases': the Total Beck Score was

significantly higher in this group than in the CIL group or the Control Group (see TABLE 10).

(ii) CIL Group

Eight patients in this group scored as 'psychiatric cases' on the total CIS score though they did not differ significantly from the Control Group on this variable (see TABLE 10). Three of these 'cases' were in the BS category and five were in the SC category, making this variable significantly different between the three subgroups ($p < .03$). Ten of the CIL group scored on Depression; and thirteen on Anxiety. Three patients scored high enough on the Beck to be described as 'depressed cases': the Beck Total Score, in this group, did not differ significantly from that of the Control Group (see TABLE 10).

(iii) Control Group 2 - Physically Disabled Patients

Two of the Control group scored as 'psychiatric cases' on the CIS Total Score: five scored on the Depression rating and sixteen on the Anxiety rating. The group's scores on the Total CIS did not differ to those of the CIL patients but were significantly different to the MS group's results (see TABLE B and TABLE 10). None of the controls scored as 'depressed cases' on the Beck Depression Inventory.

C) Motor Ability Investigation

(a) METHOD AND MATERIALS

A measure of the ability to perform everyday tasks was undertaken for patients with MS, CIL and for the physically disabled controls (Control Group 2). Motor assessment was carried out by the author and a Research Occupational Therapist (Mrs. L. Jones) with the help and co-operation of the O.T. department of the National Hospital for Nervous Diseases.

Activities of Daily Living (ADL):

This test consisted of seven motor tasks related to everyday living: Dressing; Walking; Stair-climbing; Bathing; Transfer from floor to chair; Tea-making and Feeding. These ADL components were modified from the Northwick Park version of the test. Performance on each of the components was graded 0 to 3: 0 - task completed correctly and independently; 1 - completion of the task required some human or physical assistance (e.g. an aid); 2 - completion of the task required human and physical assistance and 3 - subject was unable to attempt or complete the task due to severe physical or motor difficulties. This assessment gave a further measure of actual motor ability level with a grading system developed by the author to highlight the degree of dependence on assistance required. This grading differs slightly from the one widely used with the ADL (Steinbrocker, 1949;

Haworth and Hollings, 1979).

(b) RESULTS OF MOTOR FUNCTION ASSESSMENT

A measure was taken of the level of motor ability in both experimental groups and the physically disabled controls. This measure was the Total Activities of Daily Living Score (ADL).

(i) MS Group

The mean for this group on the mobility measure may be seen in TABLE C: there is no significant difference between these patients and the controls on level of mobility (see TABLE 10).

(ii) CIL Group

This group's level of mobility (ADL) was found to be significantly better than that of the controls and that of the MS group (see TABLE 10).

(iii) Control Group - Physically Disabled Patients

The Control Group performed similarly to the MS patients and significantly poorer than the CIL Group on the ADL measure (see TABLE 10).

TABLE A

MRI RESULTS IN MS and CIL GROUPS

	DEF MS GROUP	No. of Subjects With No Lesions	CIL GROUP
MEASURE	MEAN(sd)		MEAN(sd)
Scan Total	23.8 (13.4)	1 / 9	9.9 (10.7)*
Periventricular	15.3 (8.0)	2 / 12	6.4 (6.3)*
Frontal Lobe Total	2.1 (1.7)	15 / 28	1.0 (1.5)*
Temporal Lobe Total	0.2 (0.9)	52 / 44	0.1 (0.4)
Occipital Lobe Total	0.3 (0.7)	45 / 41	0.2 (0.4)
Parietal Lobe Total	2.5 (2.0)	16 / 24	1.2 (1.5)*
Frontal Total	5.3 (3.3)	8 / 23	2.2 (3.0)*
Temporal Total	1.9 (2.4)	23 / 37	0.4 (1.1)*
Occipital Total	2.5 (2.0)	11 / 19	1.5 (1.5)*

* significantly different p<.002

TABLE B

PSYCHIATRIC RESULTS in ALL GROUPS

MEASURE	MS	CIL	CONTROLS
	Mean (sd)	Mean (sd)	Mean (sd)
CIS Total Score	12.5 (7.4)*	7.4 (8.3)**	5.2 (4.2)
Beck Total Score	10.5 (7.3)*	6.8 (8.7)**	4.7 (5.1)

* significantly different to Controls $p < .0000$

** significantly different to MS Group $p < .001$

TABLE C

MOTOR ABILITY RESULTS in ALL GROUPS

MEASURE	MS	CIL	CONTROLS
	Mean (sd)	Mean (sd)	Mean (sd)
ADL	3.0 (4.7)**	1.5 (4.0)	3.9 (6.1)*

* controls significantly worse than CIL group $p < .05$

** MS group significantly worse than CIL group $p < .005$

CHAPTER IV

PSYCHOMETRIC INVESTIGATION:

Procedures and Results

GENERAL PROCEDURE

All subjects in the MS Group, CIL Group and in the Physically Disabled Controls (Control Group 2) underwent the full psychometric assessment. The assessment lasted approximately one and a half hours; the tests, described in more detail later, were administered in the following order:

1. Graded Naming Test (McKenna and Warrington, 1983) with response latency yielding a measure of Object Naming Ability (Cognitive Speed).
2. Schonell Graded Word Reading Test and the National Adult Reading Test (Nelson, 1982) yielding a measure of Estimated Premorbid IQ, also referred to as NART Reading IQ.
3. Recognition Memory Tests (Warrington, 1984) [Memory for Faces was administered before Memory for Words] with their response latencies yielding measures of verbal and visual memory ability and Cognitive Speed.
4. Shortened version of Wechsler Adult Intelligence Scale (Wechsler 1955) yielding measures of

Full-scale, Verbal and Performance IQ.

5. Modified Wisconsin Card Sorting Test (Nelson 1976) yielding a measure of Nonverbal Abstracting Ability.
6. Speed of Letter Counting Test (Willison et al, 1980) yielding a measure of Visual Attention Ability.
7. Auditory Attention Test yielding a measure of Auditory Attention Ability.

These assessments also yielded three measures of Cognitive Speed:

1) Recognition Verbal Memory Speed
2) Recognition Visual Memory Speed
3) Object Naming Speed

A further measure that is examined is the Cognitive Efficiency Score which is obtained by summing the performance grades attained on each function: this provides a measure of the general overall cognitive ability of each subject.

The three subgroups of the CIL group (ON, BS and SC) did not differ to any significant degree on any of the psychometric measures (Table 1): they are treated from here on as one group in the analyses presented.

The two experimental groups (MS Group and CIL Group) were similar in age ($z = 1.66$, $p = .10$); as were the Control and MS Group ($z = .0393$, $p=.97$) and the Controls and the CIL Group ($z = .9347$, $p = .35$).

1. INTELLECTUAL FUNCTIONS

A) Method

(1) Shortened version of Wechsler's Adult Intelligence Scale (WAIS):

In this version the following subtests were administered: Arithmetic, Similarities, Digit Span, Vocabulary (Verbal tests), Picture Completion, Picture Arrangement and Block Design (Performance tests). These subtests were administered according to the standard procedure (Wechsler 1955). The results were prorated to yield a measure of Verbal, Performance and Full Scale IQ.

Two of the subtests administered in the assessment of Performance IQ require motor involvement and are timed (Block Design and Picture Arrangement). It was observed that subjects who failed on either one of these tasks, due to lack of time, failed because of slowed or dysfunctional thinking processes and not, it seemed, because they were hampered with slow motor movements: when they were allowed as much time as they wanted they still failed to complete the task correctly. Therefore, with regard to motor

ability, it was the level of this function rather than it's speed that was considered more closely related to performance on the motor oriented psychometric tasks.

(2) National Adult Reading Test (NART) and Schonell Graded Word Reading Test (GWRT)

The NART and a shortened version of the GWRT were administered according to a standard procedure (Nelson 1982) to provide an estimate of the subject's premorbid optimal level of intellectual functioning. The combined reading scores of these tests were transformed to IQ equivalents.

The discrepancy between a subject's reading IQ equivalent and his current overall WAIS IQ (i.e. Reading IQ minus Full Scale WAIS IQ) provides an index of deterioration, hereafter referred to as the IQ Deficit.

B) Results

(1) GROUP COMPARISONS

The Estimated Premorbid IQ (NART IQ Equivalent) measure was similar across the three groups with no significant difference observed between the group means (TABLE 2 and TABLE 3).

(a) CIL v. CONTROLS

The MANOVA procedure was employed on comparisons for Full Scale IQ (FSIQ) and Performance IQ (PIQ) to take into account level of motor ability (TABLE 10 shows that CIL patients had significantly better motor ability when compared to the Controls). The CIL patients and the Control group performed at a similar level on all the intellectual measures (see TABLE 2 and TABLE 3).

(b) MS v. CONTROLS

The mean scores and standard deviations of the MS and Control groups are given in TABLE 2. The MS group had significantly poorer scores on FSIQ and PIQ. In order to examine these measures within groups in relation to motor ability, FSIQ and PIQ were compared between Physically Independent subjects and subjects using a Walking Stick or Wheelchair <u>within</u> each subject group. No significant difference was found on these IQ measures within either group (see TABLE 14(a)). Verbal IQ (VIQ) was not significantly different when MS patients were compared to Controls.

(c) MS v. CIL

The MS group had significantly poorer levels of motor ability compared to the CIL group (see TABLE 10) and the MANOVA procedure was, therefore, applied in order to take

this motor variable into account when making a group comparison on FSIQ and PIQ (see TABLE 2 for means and standard deviations). MS and CIL patients performed at a similar level on these IQ measures when motor ability was accounted for (see TABLE 3). The CIL patients' mean scores (TABLE 2) were significantly higher for VIQ (see TABLE 3).

(2) IQ DEFICIT

A measure of deterioration of intellectual functions was calculated for each subject by subtracting tested FSIQ from NART IQ Equivalent (a measure that is considered to be a good estimate of premorbid IQ): this yielded an 'IQ Deficit Score' for each subject.

TABLE 1 presents the means and standard deviations of this measure for the three subgroups of the CIL group; there was no significant difference across the three subgroups on this measure.

(i) Group Comparisons

The means and standard deviations for the IQ Deficit score are presented in TABLE 2: the MS group's Deficit score is significantly higher than the Controls' and when motor ability is taken into account the CIL group also have significantly higher IQ Deficit scores than the Controls

(TABLE 3).

Within the MS Group, the IQ Deficit Score did not differ significantly between those patients who were Physically Independent and those who required mobility aids; this result was similar for the CIL group (TABLE 14(a)).

(ii) Relationship with MRI Analysis

(a) MS Group

Correlations of the IQ Deficit measure (IQ) with MRI measures are presented in TABLE 5 for this group: these positive correlations were not significant.

(b) CIL Group

The IQ Deficit measure correlated positively with both MRI measures (TABLE 6) but not to a significant degree. When a statistical comparison was made on IQ Deficit between those 38 patients with abnormal scans and the 9 with normal scans no significant difference was found ($z=.70$; $p=.50$).

(3) ANALYSIS OF IQ DEFICIT VIA GRADING PROCEDURE

The IQ Deficit score was assigned grades based on the results of the Control group: TABLE I(i) displays the percentage of each group scoring within each grade.

(i) Group Comparisons

As can be seen from TABLE I(i), proportionately the MS group had almost four times the number of individuals scoring in the Deficient Grade as the Controls did: the difference between MS patients and Controls with regard to IQ Deficit grades was significant (TABLE 4). The CIL group scored within the Deficient Grade more than twice the rate that the Controls did: again this difference between the CIL patients and Control subjects on IQ Deficit grades was significant (TABLE 4). Both experimental groups had a much higher percentage of individuals scoring in the Poor Grade when compared to the Control Group.

This analysis demonstrates that the performance level with regard to the IQ Deficit measure is different for each group: the Controls have the highest percentage of individuals performing efficiently, next best is the CIL group, and the MS group have the lowest percentage of individuals performing efficiently (see TABLE 4).

(ii) MRI Analysis and IQ Deficit Performance Grades

(a) <u>MS Group</u>

The mean scores of the Total Scan Score for the group of individuals scoring within each IQ Grade were examined and it was found that those scoring within the Deficient Grade

obtained the highest mean (TABLE 8). This descriptive analysis suggests that those individuals who performed least well on the IQ Deficit measure had more lesions on MRI assessment. However, Chi square analysis of IQ Deficit Performance Grades with MRI Quartile Grades did not indicate a significant association between the two (see TABLE 7).

(b) CIL Group

Those CIL patients scoring within the Poor grade had more lesions on MRI than those scoring within any other Grade (TABLE 9). This pattern of results would seem to indicate that IQ Deficit is not related to degree of brain lesions within the CIL group. This is borne out by a Chi square analysis of IQ Deficit Performance Grades with MRI Quartile Grades which is not significant (TABLE 7) and there was no significant difference on IQ grades between those with abnormal scans (N=38) and those with normal scans (N=9) ($z=.30$; $p=.80$).

C) Conclusions

Premorbid intellectual functioning is similar for the two patients groups and the controls.

(1) MS Group

This group performed at a significantly poorer level with regard to Performance IQ, Full Scale IQ and the IQ Deficit measure when compared to Controls. These deficits could not be explained by poor level of motor ability. Those MS patients with the poorest IQ Deficit scores had more lesions on MRI than MS patients with more efficient intellectual functioning: indicating that increased number of brain lesions is associated with deficient scores on intellectual assessment. However, for the MS group as a whole, overall intellectual functioning does not significantly correlate with amount of lesions present in the brain on any analyses carried out.

(2) CIL Group

The pattern of results for the CIL patients demonstrate a similarity in performance to MS patients on FSIQ, PIQ and on the IQ Deficit measure when motor ability is taken into account. Furthermore, when motor ability was taken into account, the CIL group differed significantly to the Controls on the IQ Deficit measure. This deficit did not seem to be strongly related to degree of lesions in the brain.

TABLE I(i)

PERCENTAGE OF GROUP IN EACH IQ GRADE

GROUP		GRADE			
		0-Good	1-Fair	2-Poor	3-Deficient
DEF MS	(N=58)	21.4	17.9	41.1	19.6
CIL	(N=48)	33.3	27.1	29.2	10.4
CONTROLS	(N=46)	54.3	28.3	13.0	4.3

2. MEMORY FUNCTIONS

A) Method

(1) Recognition Memory for Words (RMW)

This test was administered according to the standard procedure; the raw score (i.e. number correct out of 50) was converted to an age corrected score (Warrington, 1984). This test consisted of 50 high frequency words as stimuli and 50 distracter words drawn from the same pool. The retention task requires the subject to read the recognised word from a list of the stimulus words paired with the distracter words (Warrington, 1984).

(ii) Recognition Memory for Faces (RMF)

This test was administered and scored as the RMW (Warrington, 1984). The test stimuli consists of 50 black and white photographs of unfamiliar male faces and 50 distracter faces (also male) drawn from the same pool. In the retention task, the subject was required to indicate recognition by pointing to the appropriate photograph.

These two memory tests (RMW and RMF) were chosen in order to examine both verbal and visual memory (respectively) via tasks that were equally demanding in terms of complexity. Administering both tests allows comparison of the two memory types in this population.

B) Results

(1) GROUP COMPARISONS

(a) CIL v. CONTROLS

The mean scores and standard deviations for the memory assessment are presented in TABLE 2: the performance of the CIL group was not significantly different to the Control Group's (see TABLE 3).

(b) MS v. CONTROLS

The MS patients performed similarly to the Controls on Verbal Memory assessment (see TABLE 2) but obtained significantly lower scores on Visual Memory Assessment (TABLE 2 and TABLE 3).

(c) MS v. CIL

Performance on the Verbal Memory task was not significantly different for the two experimental groups while on the Visual Memory task the MS group obtained significantly poorer scores (TABLE 2 and TABLE 3).

(2) RELATIONSHIP WITH MRI ANALYSIS

(a) MS Group

This group's performance on the Verbal Memory and Visual Memory tasks correlated negatively to a significant degree with amount of lesions in the Periventricular area and with total scan score (see TABLE 5): indicating that as

Memory ability of the MS patients decreased so the amount of lesions in the brain increased.

(b) CIL Group

No significant correlations were obtained between Memory performance and any MRI scan measure for the CIL group (see TABLE 6). When memory scores were compared between CIL patients with normal scans (N=9) and CIL patients with abnormal scans (N=38) no significant differences were obtained (Verbal Memory - $z=.10$, $p=.92$; Visual Memory - $z=.40$, $p=.71$).

(3) RELATIONSHIP WITH DISEASE FACTORS

(a) MS Group

There was no significant difference between MS patients in relapse at the time of testing and MS patients not in relapse at the time of testing on Verbal or Visual Memory performance. While performance on Verbal Memory was not related to Years of Active Disease within the MS group, Visual Memory performance negatively correlates with number of years of Active Disease to a significant degree ($tau= .32$, $p= .02$).

(b) CIL Group

There was no significant difference between CIL patients in relapse at the time of testing and CIL patients not in relapse at the time of testing with regard to Memory test

performance.

(4) ANALYSIS OF MEMORY ABILITY VIA GRADING PROCEDURE

The Verbal Memory score and the Visual Memory score were assigned grades based on the results of the Control group: TABLE II(i) displays the percentage of each group scoring within each Verbal Memory Grade and TABLE II(ii) displays the same for the Visual Memory Grade.

(i) Verbal Memory Analysis Via Grading Procedure:

(a) Group Comparisons

The three groups of subjects performed similarly on the Verbal Memory test but the grading procedure allows one to examine their pattern of results in more detail. As can be seen in TABLE II(i) 7 patients with MS (12.5% of the group) scored within the Deficient Grade while only 2 CIL patients and 1 Control did. This difference between groups, however, was not significantly different overall on Verbal Memory grades (see TABLE 4).

(b) MRI Analysis and Verbal Memory Performance Grades

1 - MS Group

The pattern of results presented by examining the mean Total Scan Scores within each Verbal Memory performance Grade for MS patients show that the two poorest grades had the two highest Scan Score means (TABLE 8). This pattern of results suggests that there is a propensity for those

with poor verbal memory scores to present with a higher degree of brain lesions within the MS group. This association between Verbal Memory performance grades and MRI Quartile grades is not significant (see TABLE 7).

2 - CIL Group

Scan scores within the CIL group are low for those scoring within the Fair Grade for Verbal Memory and evenly distributed on a higher level across the other three grades (TABLE 9). The pattern of results for CIL patients does not suggest a strong relationship between verbal memory performance and amount of brain lesions: association between performance grades and MRI Quartile Grades is not significant (TABLE 7).

(c) Deficient Verbal Memory Group and Physical Ability

TABLE II(iii) displays the means of the motor ability assessment score (ADL) within each Verbal Memory grade for the MS group. Those MS patients with deficient Verbal Memory scores have the poorest mean ADL score. This is also true for the Controls but not for the CIL group: the controls with the poorest Verbal Memory scores have the worst physical ability assessment scores.

(d) Brief Descriptions of the Deficient Verbal Memory Groups

1 - MS Patients

One male and six females had deficient verbal memory scores. The mean age of the deficient verbal memory group was 33.4 (5 years younger than the whole MS group's mean age) and the means on Full-Scale, Verbal and Performance IQ were 85, 89 and 82 respectively (18, 16 and 18 points lower, respectively, than the whole MS group's means).

2 - CIL Patients

Two males aged 46 and 48 (10 and 12 years older than the CIL group's mean age) had deficient verbal memory scores within the CIL subject group. Full-scale, Verbal and Performance IQ was significantly lower than the CIL group's mean for one of these men (13, 16 and 7 points down respectively) and the second man's scores were significantly higher than the CIL group's mean (4, 8 and 15 points up respectively).

(ii) Analysis of Visual Memory Via Grading Procedure:

(a) Group Comparisons

Twelve MS patients scored within the Deficient Grade for Visual Memory while only 1 CIL patient and 3 Controls did. The pattern of results highlights the fact that one quarter of the CIL patients scored within the Poor Grade on Visual Memory compared to thirteen percent of the

Controls in the same grade (TABLE II(ii)). The difference between the CIL group and the Controls is not significant on Visual Memory with regard to distribution across the performance grades but the MS group's pattern of scores is significantly poorer than the CIL group's and also the Controls' on Visual Memory (see TABLE 4).

(b) MRI Analysis and Visual Memory Performance Grades

1 - MS Group

A clear pattern emerges when the scan scores of MS patients are examined within their Visual Memory performance grades: MS patients scoring within the Deficient Grade for Visual Memory had a mean Total Scan Score that was almost three times the mean obtained by MS patients scoring within the Good Grade for Visual Memory (TABLE 8). This result pattern indicates a strong association between poor visual memory and increased amount of brain lesions within the MS group. This association is significant for MS patients when examined via the relationship between Visual Memory performance Grades and MRI Quartile Grades (TABLE 7).

2 - CIL Group

CIL patients scoring within the Poor Grade on Visual Memory had the highest Total Scan Score mean of the group (TABLE 9). There is no clear pattern of results within the CIL group to suggest a strong association between

lesions on MRI and visual memory performance: MRI Quartile Grades are not significantly associated with Visual Memory performance grades (see TABLE 7).

(c) Deficient Visual Memory Group and Physical Ability

TABLE and II(iv) displays the mean scores of the groups on Activities of Daily Living (ADL) assessment within each Visual Memory grade and it can be observed from these presentations that MS patients with poor Visual Memory are more disabled than the rest of the group. This is also true for the Controls, but not for the CIL group: those Controls with the poorest Visual Memory scores have a higher disability level than the rest of the Controls.

(d) Brief Descriptions of the Deficient Visual Memory Groups

1 - MS Patients

There were 3 males and 9 females with a mean age of 39.5 (one year younger than whole MS group's mean age) scoring with deficient visual memory within the MS group. MS patients with deficient Visual Memory had mean Full-scale, Verbal and Performance IQ's of 98.8, 101.7 and 95.3 respectively (5, 4 and 5 points lower, respectively, than the whole MS group's means on the same measures).

2 - CIL Patient

This was a 37 year old female (one year older than the CIL group's mean age) whose Full-scale, Verbal and Performance IQ's were 100, 97 and 105 respectively (that is, 8, 12 and 1 points down from the CIL group's respective means): she was the only CIL patient with deficient Visual Memory.

C) Conclusions

Verbal Memory was similar across the three groups with no significant differences obtained.

(1) MS Group

MS patients had significantly poorer Visual Memory when compared to the CIL patients and the Controls. Within the MS group Performance on the Visual Memory task was related to number of Years of Active Disease; this was not so for Verbal Memory ability. Neither Verbal nor Visual Memory ability was affected by the MS patient's exacerbation status at the time of testing. Performance on both Verbal and Visual Memory was related to amount of brain lesions for patients with MS, suggesting that memory ability deteriorates with increased lesions on MRI within this group. Examination of MS patients with deficient scores on Verbal memory suggests that poor IQ is associated: it would seem also that MS patients with deficient memory have a greater degree of physical disability.

(2) CIL Group

The CIL group's performance on both memory assessments was similar to that of the Controls, though their pattern of scores were different as presented within the graded structure: in general the attainment of CIL patients on the Memory Assessments was poorer than the Controls, with no significant differences observed, and better than the MS patients (significantly so for Visual Memory). No significant association was found between CIL patients' memory ability and the amount of brain lesions. Exacerbation status at the time of testing was not related to memory performance within the CIL group. CIL patients with deficient memory performance did not have a higher degree of physical disability.

TABLE II(i)

PERCENTAGE OF GROUP IN EACH VERBAL MEMORY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	55.4	16.1	16.1	12.5
CIL	N=48	54.2	18.8	22.9	4.2
CONTROLS	N=46	60.9	19.6	17.4	2.2

TABLE II(ii)

PERCENTAGE OF GROUP IN EACH VISUAL MEMORY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	21.4	21.4	35.7	21.4
CIL	N=48	39.6	33.3	25.0	2.1
CONTROLS	N=46	52.2	28.3	13.0	6.5

TABLE II(iii)

MEAN ADL SCORE IN EACH VERBAL MEMORY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	1.3	1.4	3.1	9.3
CIL	N=48	1.9	.9	1.6	.5
CONTROLS	N=46	4.2	4.6	1.5	5.0

TABLE II(iv)

MEAN ADL SCORE IN EACH VISUAL MEMORY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	0.0	1.7	3.9	4.7
CIL	N=48	1.0	.4	4.1	0.0
CONTROLS	N=46	5.3	1.7	2.7	6.0

3. ABSTRACTING ABILITY

A) Method

Nelson's Short Wisconsin Card Sorting Test (WCST)

This modified version of the WCST was administered and scored according to the standard procedure recommended by Nelson (1976). This test consisted of one set of 4 stimulus cards and two sets of 24 response cards which required the subject to sort the response cards under the stimulus cards according to a consistent attribute (e.g. Colour, Shape or Number).

This test of nonverbal abstracting ability has been validated as a test of frontal lobe functioning (Nelson, 1976). The total number of errors made on this test was the measure of abstracting ability used in this study.

B) Results

(1) GROUP COMPARISONS

(a) CIL v. CONTROLS

The difference between the CIL patients and the Controls on abstracting ability (means and standard deviations are presented in TABLE 2) was not significant (see TABLE 3).

(b) MS v. CONTROLS

When compared to the Controls the MS patients had significantly poorer scores on the abstracting ability assessment (see TABLES 2 and 3).

(c) MS v. CIL

The performance of the MS patients on the abstraction task was significantly below that of the CIL patients (see TABLES 2 and 3).

(2) RELATIONSHIP WITH MRI ANALYSIS

(a) <u>MS Group</u>

The performance of the MS group on the Abstracting Ability task did not correlate significantly with any of the MRI measures (see TABLE 5).

(b) <u>CIL Group</u>

The CIL group's performance correlated significantly with their Total Scan Score (TABLE 6) . This correlation was positive indicating that the higher the error score the more lesions were observed in the brain. CIL patients with normal scans (N=9) were compared to CIL patients with abnormal scans (N=38) on the abstraction task: there was no significant difference on scores obtained ($z = 1.0$, $p = .3$).

(3) ANALYSIS OF ABSTRACTING ABILITY VIA GRADING PROCEDURE

(i) Group Comparisons

Twenty percent of the MS group scored within the Deficient Grade on abstracting ability assessment (TABLE III). The pattern of results on examination of the percentage scoring within each abstracting ability grade highlights the MS group's poor performance and the similarity between the CIL group and the Controls'. The poorer performance of the MS group on this abstraction task is significant when compared to the CIL patients and also to the Controls, while no significant difference was observed between the latter two groups (see TABLE 4).

(ii) MRI Analysis With Abstracting Ability Grades

(a) MS Group

Although the highest Total Scan Score mean is obtained by MS patients scoring within the Deficient Abstracting Ability Grade, the pattern of results examined by Grade indicate that the amount of brain lesions does not seem to be strongly associated with performance on the abstraction task (TABLE 8). This abstraction measure result does not significantly associate with MRI Quartile Grades (see TABLE 7).

(b) CIL Group

The Total Scan Score mean for CIL patients scoring within the Poor Abstraction Grade is almost twice that of any other mean observed in the other Grades (TABLE 9). The two highest Scan Score means occur within the two poorest abstraction function grades suggesting that increased amount of brain lesions is associated with poor performance for the CIL group. However, association between this measure on abstraction and MRI Quartile Grades is not significant (TABLE 7).

C) <u>Conclusions</u>

(1) MS Group

MS patients performed at a level significantly below that of CIL patients and Controls on the Abstracting Ability task. This poor performance by the MS group was not related to amount of lesions present in the brain.

(2) CIL Group

Although the CIL group's performance on the Abstracting Ability task was similar to that of the Controls it appeared to be associated with amount of lesions in the brain. The more lesions observed on scan the more errors were scored on Abstracting Ability.

TABLE III

PERCENTAGE OF GROUP IN EACH ABSTRACTING ABILITY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	22.2	18.5	38.9	20.4
CIL	N=48	41.7	29.2	27.1	2.1
CONTROLS	N=46	52.2	23.9	21.7	2.2

4. ATTENTION FUNCTIONS

A) Method

The following tests were chosen to measure attention functions because they do not rely on educational levels, intellectual capacity or motor ability to be completed successfully. In addition, they take a short time to administer and complete.

(i) Letter Counting Speed Test (LCST)

This test was based on a letter cancellation task (Willison et al, 1980). It consisted of a page of 90 letters (19 each of 'A's and 'B's, 18 of 'C's and 17 each of 'D's and 'E's) in large print, arranged randomly in 12 rows of 5 columns. The score obtained was the time taken to count the number of 'A's on this page.

(ii) Vigilance Test (VT)

This test was adapted from a vigilance task provided by Kaplan (personal communication). It consists of a random presentation of 5 groups of 20 letters, presented one per second on a prepared audio tape (with no time interval between the letter groups). All the letters of the alphabet were used. Imbedded in this random presentation was the alphabet in its conventional order: the first 5 letters randomly imbedded in group 1; second

5 letters in group 2, etc.. The subject was required to make an agreed sign (usually tapping a finger or a pencil) when they heard the first letter of the alphabet; then when they heard the second letter of the alphabet, and so on until the letter 'Z' was reached. Prior to testing each subject was asked to say the alphabet to ensure that they knew it, and were then given a practice run (also on tape) of 20 letters with the first five letters of the alphabet imbedded therein. Once the subject completed the practice run and understood what was required of them, the tape of the test proper was run. As soon as a subject made an error, either by responding to the wrong letter (a false positive error), or by missing the correct letter (a false negative error), the tape was stopped and the tester made known the error to the subject and reminded them of the last letter responded to, and which letter they should now be listening for. The total number of errors was recorded and constitutes the score obtained on this test.

Both tests necessitated only a knowledge of the alphabet: the LCST examined visual attention while the VT required sustained auditory attention for a minimum of 100 seconds. Distractibility (i.e. inattention) is thought to significantly increase the time taken to complete the LCST, and to significantly increase the amount of errors

obtained on the VT.

B) Results

(1) GROUP COMPARISONS

(a) CIL v. CONTROLS

The means and standard deviations for the attention assessment are presented for the two groups in TABLE 2: the poorer mean of the CIL group on Visual Attention was not significantly different to the Controls (see TABLE 3). However, the CIL group obtained significantly more errors on the Auditory Attention task when compared to the Controls (see TABLE 3).

(b) MS v. CONTROLS

The means and standard deviations on the attention assessment for both groups are presented in TABLE 2: the MS group's poorer scores are significantly different to the Control's on the two attention measures, as can be observed in TABLE 3.

(c) MS v. CIL

The MS group's poorer scores on Auditory Attention (TABLE 2) are not significantly different to the CIL group's (TABLE 3) while their scores on the Visual Attention task are significantly poorer than the CIL group's (see TABLE 3).

(2) RELATIONSHIP WITH MRI ANALYSIS

(a) MS Group

The MS group's performance on the Visual Attention task did not significantly correlate with any MRI measure (see TABLE 5). However, Auditory Attention error scores significantly correlated with increased amount of lesions in the Periventricular region and with Total Scan Score for MS patients (see TABLE 5).

(b) CIL Group

The CIL group's performance on the Visual Attention task did not significantly correlate with any MRI measure. Errors on the Auditory Attention test, however, were found to significantly increase with increased amount of lesions in the Periventricular region and with Total Scan Score for CIL patients (TABLE 6). CIL patients with normal scans (N=9) were compared to CIL patients with abnormal scans (N=38) on the attentional tasks and there were no significant differences between these groups on either measure (Visual attention: $z= 1.1$, $p= .3$; Auditory attention: $z= .12$, $p= .91$).

(3) ANALYSIS OF ATTENTION ABILITY VIA GRADING PROCEDURE

The Visual Attention score and the Auditory Attention score were assigned grades based on the results of the Control Group: TABLE IV(i) displays the percentage of each

group scoring within the Visual Attention grade and TABLE IV(ii) displays the same for the Auditory Attention grade.

(i) Visual Attention Analysis Via Grading Procedure:

(a) Group Comparisons

The Controls and the CIL patients were not significantly different on Visual Attention but the grading structure allows a more detailed examination of each group's performance: only 27% of the CIL group scored within the Good Grade while 52% of the Control group did. This difference between the two groups on this Visual Attention measure is not significant (see TABLE 4). The MS group's poor performance when compared to the Controls on Visual Attention is illustrated with 43% of MS patients scoring within the Poor Visual Attention Grade and 20% of MS patients scoring within the Deficient Visual Attention Grade (see TABLE IV(i)). This difference on the Visual Attention measure between MS patients and Controls is significant; as is the difference between the MS group and the CIL group on Visual Attention (see TABLE 4).

(b) MRI Analysis and Visual Attention Performance Grades

1 - MS Group

The pattern of results presented by examining the mean Total Scan Scores within each Visual Attention Performance Grade for the MS group show that there is little

difference between grades on this MRI measure (see TABLE 8). This Visual Attention measure did not significantly correlate with MRI Quartile Grades for the MS group (see TABLE 7).

2 - CIL Group

As can be seen in TABLE 9, CIL patients with Deficient Visual Attention Scores have a Total Scan Score mean (21.3) that is more than twice that of CIL patients scoring within any of the better Visual Attention Grades. The pattern is variable in that CIL patients scoring within the Good Visual Attention Grade have the second highest Total Scan Score mean (10.6) and the lowest Scan Score mean (7.5) occurs within the Poor Visual Attention Grade for the CIL group . The relationship between this Visual Attention measure and MRI Quartile Grades is not significant for CIL patients (see TABLE 7).

(ii) Auditory Attention Analysis Via Grading Procedure:

(a) Group Comparisons

The majority of the CIL group scored within the Poor Grade for the Auditory Attention task (see TABLE IV(ii)) highlighting their poorer performance level when compared to the Controls. The difference between these CIL patients and Controls on this Auditory Attention measure is significant (see TABLE 4). The CIL group's pattern of results on the Auditory Attention task is similar to the

MS group's (see TABLE IV(ii)) and is not significantly different on statistical analysis (see TABLE 4). The majority of MS patients score within the Poor grade on the Auditory Attention task and their scores are significantly different when compared to the Controls on this measure (see TABLE 4).

(b) MRI Analysis and Auditory Attention Performance Grades

1 - MS Group

Examination of the pattern of results presented in TABLE 8 showing mean Total Scan Score within Auditory Attention Performance grades for the MS Group indicates that those in the poorest grades (2 and 3) have the highest scan scores. However, the relationship between this Auditory Attention measure and MRI Quartile grades is not significant (see TABLE 7).

2 - CIL Group

Presentation of Total Scan Score means within the Auditory Attention Performance Grades for CIL patients (see TABLE 11) suggests that there is a relationship between poor auditory attentional performance and amount of brain lesions. CIL patients scoring within the Good Auditory Attention Grade have the lowest mean Scan Score and CIL patients with Deficient Auditory Attention performance have the highest mean Scan Score. The relationship

between this Auditory Attention measure and MRI Quartile Grades for the CIL group is not, however, significant (see TABLE 7).

C) Conclusions

(1) MS Group

MS patients performed poorly on Visual Attention when compared to the Controls and to the CIL group. However, this poor Visual Attention did not significantly correlate with any MRI measure for the MS group. Auditory Attention performance of the MS group was not significantly different to the that of the CIL group, though MS patients were significantly poorer than the Controls. Auditory Attention errors significantly related to amount of brain lesions within the MS group.

(2) CIL Group

CIL patients' Visual Attention scores did not significantly differ to the Controls on statistical analysis, though when Visual Attention Performance Grades were examined the poor performance of the CIL group was observed. No firm relationship was observed between Visual Attention ability and amount of brain lesions within the CIL group. Auditory Attention was significantly poorer in the CIL group when compared to the Controls and correlated significantly with increased amount of brain lesions for CIL patients.

TABLE IV(i)

PERCENTAGE OF GROUP IN EACH VISUAL ATTENTION GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	11.1	25.9	42.6	20.4
CIL	N=48	27.1	37.5	27.1	8.3
CONTROLS	N=46	52.2	26.1	17.4	4.3

TABLE IV(ii)

PERCENTAGE OF GROUP IN EACH AUDITORY ATTENTION GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	20.8	22.6	35.8	20.8
CIL	N=48	25.0	22.9	42.8	8.3
CONTROLS	N=46	47.8	30.4	19.6	2.2

5. NAMING ABILITY

A) Method

Grading Naming Test (GNT)

This test was administered according to the standard procedure (McKenna and Warrington 1983), in order to obtain a measure of naming ability. This is an object naming test consisting of 30 black and white line drawings, each presented in the order of difficulty. The score obtained was the number correctly named.

This test was chosen as an assessment of language functioning as reduced efficiency in retrieving the name of an object can be the first and only indication of impairment of such functions and this test attempts to sample the more vulnerable items on the boundary of the individual's naming vocabulary (McKenna and Warrington 1983).

B) Results

(1) GROUP COMPARISONS

The means and standard deviations for each group on the Naming task are presented in TABLE 2: there were no significant differences between any of the groups (see TABLE 3).

(2) RELATIONSHIP WITH MRI ANALYSIS

(a) MS Group

MS patients' Performance on the Naming Ability task significantly correlated with lesions in the Periventricular Region and with the Total Scan Score (see TABLE 5).

(b) CIL Group

CIL patients' Performance on the Naming task does not significantly correlate with any MRI measure (see TABLE 6). When Naming ability was compared between CIL patients with normal scans (N=9) and CIL patients with abnormal scans (N=38) there was no significant difference ($z = .8$, $p = .4$).

(3) ANALYSIS OF NAMING ABILITY VIA GRADING PROCEDURE

(i) Group Comparisons

The pattern of results on the Naming task within the grading structure (see TABLE V) highlights the similarities between the three groups. It is only within the Deficient Naming Grade that one can see some differences: 9% of the MS group and 10% of the CIL group score at the Deficient level compared to only 2% of the Controls. However, there was no significant difference between the groups on this measure of Naming ability (see TABLE 4).

(ii) MRI Analysis and Naming Ability Performance Grades

(a) MS Group

The highest Total Scan Score mean occurs within the Fair Naming Ability Grade for MS patients (see TABLE 8) while the lowest Scan Score mean occurs within the Deficient Naming Ability Grade. The relationship between this Naming Ability measure and MRI Quartile Grades is not significant within the MS Group (see TABLE 7).

(b) CIL Group

The highest Total Scan Score mean occurs within the Fair Naming Ability Grade for CIL patients while the lowest Scan Score mean is within the Deficient Naming Ability Grade (see TABLE 11): a pattern that is similar to that of the MS Group for this measure. The relationship between this Naming measure and MRI Quartile Grades is not significant for the CIL group.

C) Conclusions

Although the MS and CIL patients had more individuals with Deficient scores on the Naming task compared to the Controls, there were no significant differences between any of the groups. Low scores on naming ability were significantly related to increased amount of brain lesions for the MS group; no significant correlations between Naming Ability and MRI were observed within the CIL group.

TABLE V

PERCENTAGE OF GROUP IN EACH NAMING ABILITY GRADE

GROUP		GRADE			
		0-GOOD	1-FAIR	2-POOR	3-DEFICIENT
DEF MS	N=58	47.3	27.3	16.4	9.1
CIL	N=48	52.1	22.9	14.6	10.4
CONTROLS	N=46	37.0	30.4	30.4	2.2

6. COGNITIVE EFFICIENCY

A) Method

The Cognitive Efficiency Score was obtained by summing the individual function grades for each subject; full details of this procedure are described in the Statistics Section of this report. In the case of the Visual Attention assessment, where data was lacking on some subjects in each group, the grade was assigned for that function on individuals with no Visual Attention data by a prorating procedure. This prorating procedure consisted of summing the grades for the rest of the functions and dividing the sum by the number of functions added: this was done for each subject without Visual Attention data and provided a prorated grade on that measure for each such individual. This was in order to have a comparable Cognitive Efficiency Score for all subjects. In the analysis of differences between the groups on Cognitive Efficiency, those subjects who had undertaken Visual Assessment were examined as a subgroup separately; as well as comparison analyses involving the full samples of subjects.

B) Results

(1) GROUP COMPARISONS

(a) CIL v. CONTROLS

The CIL group's poorer scores, presented in TABLE 2, differed significantly to the Controls' (see TABLE 3).

(b) MS v. CONTROLS

The MS group's mean was poorer than the Controls' (see TABLE 2) and this difference was significant (see TABLE 3).

(c) MS v. CIL

Examination of the means and standard deviations for both groups (see TABLE 2) indicate that the MS group's Cognitive Efficiency is poorer; this difference between the MS and CIL patients is significant for the group as a whole but not significant when only those subjects who underwent the Visual Attention assessment are examined (see TABLE 3). CIL patients (those with Visual Assessment data) performed at a similar level to the MS group (those with Visual Assessment data) with regard to the Cognitive Efficiency score.

(2) RELATIONSHIP WITH MRI ANALYSIS

(a) <u>MS Group</u>

The MS group's overall Cognitive Efficiency correlated significantly with amount of brain lesions in the Periventricular Region and with Total Scan Score (see TABLE 5).

(b) <u>CIL Group</u>

Positive correlations of the Cognitive Efficiency Score with MRI measures within the CIL group (TABLE 6) are not

significant. When CIL patients with Normal scans (N = 9) were compared to CIL with Abnormal scans (N = 38) there was no significant difference on Cognitive Efficiency Scores (z= .07; p= .95).

(3) RELATIONSHIP WITH DISEASE FACTORS

(a) MS Group

The MS group's Cognitive Efficiency Score was found to positively correlate to a significant degree with Years of Active Disease (see TABLE 11). Years of Active disease positively correlates with Total Scan Score for MS patients (see TABLE 12). However, when MS patients who were in relapse at the time of testing were compared to MS patients who were not in relapse at the time of testing, no significant difference was observed on the Cognitive Efficiency measure (see TABLE 13).

(b) CIL Group

The CIL group were significantly different to the MS group with regard to Years of Active Disease (see TABLE 10). A negative correlation between Years of Active Disease and Cognitive Efficiency was not significant within the CIL group (see TABLE 11). A comparison was made between CIL patients in relapse at the time of testing and CIL patients not in relapse at the time of testing, and Cognitive Efficiency was not significantly different (see TABLE 13).

(4) RELATIONSHIP WITH PSYCHIATRIC FACTORS

(a) MS Group

The MS group had significantly poorer scores on the Clinical Interview Schedule (CIS) and the Beck Depression Inventory (BECK) when compared to the CIL patients and to the Controls (see TABLE 10). The CIS and the BECK correlated significantly with Cognitive Efficiency within the MS group (see TABLE 11). However, when comparisons were made between MS Psychiatric 'cases' and MS 'non-Psychiatric-cases', between depressed MS and non-depressed MS patients and between anxious MS and non-anxious MS patients, no significant differences were observed on Cognitive Efficiency (see TABLE 13).

(b) CIL Group

This group did not significantly differ to the Controls on the Clinical Interview Schedule Score (CIS) or the Beck Depression Inventory Score (BECK) (see TABLE 10). Both the CIS and the BECK significantly correlated with Cognitive Efficiency within the CIL group (see TABLE 11). However, there were no significant differences on Cognitive Efficiency between CIL psychiatric 'cases' and CIL 'non-Psychiatric-cases'; between CIL depressed and CIL non-depressed patients or between CIL anxious and CIL non-anxious patients (see TABLE 13).

(5) RELATIONSHIP WITH FATIGUE

(a) MS Group

Fatigue was a measure within the Clinical Interview Schedule and when MS patients rated as 'Non-fatigued' (that is, scoring 0 or 1 on the four-point scale) (N = 18) were compared to MS patients rated as 'Fatigued' (scoring 2 or more) (N = 35) no significant difference was observed on Cognitive Efficiency ($z = .05$; $p = 1.0$).

(b) CIL Group

Those CIL patients who were judged as 'Fatigued' (N = 13) had significantly poorer Cognitive Efficiency Scores when compared to CIL patients rated as Not Fatigued (N = 35) ($z = 1.9$; $p = .05$). Fatigued CIL patients were compared to Fatigued Controls (N = 11) and no significant difference on Cognitive Efficiency was observed ($z = 1.0$; $p = .31$); however, when CIL 'Not Fatigued' patients were compared to 'Not Fatigued' Controls (N=34), Cognitive Efficiency was significantly poorer for the Non-fatigued CIL group ($z = 2.6$; $p = .009$).

(6) RELATIONSHIP WITH MOTOR ABILITY

The motor assessment Activities of Daily Living (ADL) is the measure considered here in relation to the psychometric assessments.

(a) MS Group

ADL was similar for the MS and Control groups (see TABLE 10). The ADL motor measure correlated significantly with Cognitive Efficiency within the MS Group (see TABLE 11), however when MS patients who were physically independent were compared to MS patients using mobility aids no significant difference was observed on overall cognitive ability (see TABLE 14(a)). TABLE 14(b) displays group comparisons on Cognitive Efficiency within those subjects who were physically independent, and within those subjects who were not: the MS patients, within both subgroups, remain significantly poorer than Controls. Physically independent MS patients have significantly poorer cognitive efficiency when compared to physically independent CIL patients.

(b) CIL Group

The CIL group is significantly more able on the ADL motor measure when compared to the MS group and to the Controls (see TABLE 10). ADL significantly correlates with Cognitive Efficiency within the CIL group (see TABLE 11). When CIL patients who are physically independent were compared to CIL patients using mobility aids, Cognitive Efficiency was significantly different (see TABLE 14(a)); though the small sample size of the Disabled subgroup must be noted. Furthermore, those CIL patients who used mobility aids were significantly worse on Cognitive

Efficiency than those Controls using mobility aids (see TABLE 14(b)): again sample size must be noted.

(7) ANALYSIS OF COGNITIVE EFFICIENCY VIA GRADING PROCEDURE

Grades were assigned to the Cognitive Efficiency scores on the basis of the Control Group's results on this measure; this was carried out according to the procedure described in the Statistics section of this report.

(i) Group Comparisons

The percentage of each group scoring within each Cognitive Efficiency grade is presented in TABLE VII: This grading structure illustrates the stepwise progression of performance level, with performance being significantly better as one goes from MS Group to the CIL Group, and from the CIL Group to the Controls. This is confirmed to some extent by statistical analysis (see TABLE 4) with the Controls performing significantly better than the CIL patients and the CIL patients performing better (though not significantly) than the MS patients.

(ii) MRI Analysis and Cognitive Efficiency Level Grades

(a) <u>MS Group</u>

The mean Total Scan Scores progress higher from Grade 0 to Grade 3 on Cognitive Efficiency for the MS group (see TABLE 8): MS patients with Deficient scores on Cognitive

Efficiency have the highest Scan Score mean. The relationship between this Cognitive Efficiency measure and MRI Quartile Grades is not significant, however, as can be seen in TABLE 7.

(b) CIL Group

TABLE 9 presents the means and standard deviations of the Total Scan Score within each Cognitive Efficiency Grade for this group: CIL patients with the highest Scan Scores have the poorest level of cognitive efficiency. The relationship between this Cognitive Efficiency measure and MRI Quartile Grades is not significant within the CIL group (see TABLE 7).

C) Conclusions

(1) MS Group

The MS group's cognitive efficiency was poorer than the CIL group's and significantly poorer than the Controls. MS patients' poor cognitive efficiency was significantly related to increased amount of brain lesions in the Periventricular areas of the brain. Level of motor ability, psychiatric state, fatigue and disease factors did not seem to account for MS patients' poor performance.

(2) CIL Group

Cognitive Efficiency was significantly poorer in the CIL group when compared to the Controls: this was especially

so when both groups were presenting with dependency on mobility aids; or no fatigue. It must be noted that when subgroups are examined within the CIL group the sample size necessarily decreases and some 'within factor' analyses for this group are perhaps more indicative than conclusive.

TABLE VI

PERCENTAGE OF GROUP IN EACH COGNITIVE EFFICIENCY GRADE

GROUP		GRADE			
		0-GOOD (0-4)	1-FAIR (5-7)	2-POOR (8-10)	3-DEFICIENT (11-21)
DEF MS	N=58	7.5	32.1	26.4	34.0
CIL	N=48	22.9	35.4	27.1	14.6
CONTROLS	N=46	47.8	26.1	21.7	4.3

7. SPEED OF COGNITION

A) Method

Response latencies on the Recognition Memory Tests and the Graded Naming Test were obtained using a digital Sports Stopwatch that recorded in milliseconds. This stopwatch allowed one to 'freeze' the time at any point in the procedure in order to record it, while actual timing continued. This particular function of the stopwatch was used for both the Memory and the Naming latencies.

(1) Recognition Memory Latency Measurements

On the Verbal Memory Test Timing was started as soon as the subject began responding to the list of paired words, and on the Visual Memory Test timing began as soon as the first pair of photographs was exposed to the subject. Time was recorded halfway through the responses (after the 25^{th} response) and after the last response (the 50^{th} one) for both memory tests yielding:

a) 1st half latency, and

b) 2nd half latency

for Verbal and Visual Memory for each subject. These two latency measures were added together [**a) + b)**] for the Verbal Memory Test and for the Visual Memory Test. The sum obtained was divided by two on each Test [**a) + b) / 2 = overall latency measure**] to yield per subject:

i) the latency measure for Verbal Recognition Memory and

ii) the latency measure for Visual Recognition Memory

Timing was recorded in two halves on each test in an attempt to reduce the potentially confounding effects of minor interruptions (e.g. a sneeze): by then dividing the sum of the halves' times by two an average latency measure was obtained for the whole of each test.

(2) Object Naming Latency Measurement

Timing was recorded separately for each object presented to the subject: as soon as the picture of the object was exposed to the subject the stopwatch was started; as soon as the subject responded time was 'frozen' and recorded. The stopwatch was stopped as soon as the correct response was given. If the correct response was not forthcoming or a 'Don't Know' answer was given, then the time recorded was that for the first response made by the subject (the 'frozen' time that was recorded).

Each subject's correct response latencies were added together and the sum was divided by the number of correct responses made by that subject. This was the Object Naming Latency measure for each subject.

Whenever timing was disrupted by major interruptions (or two or more minor ones) then that subject's timing data were excluded from the study.

B) Results

1) ASSOCIATION BETWEEN SPEED AND ACCURACY

a) MS Group

Accuracy scores on Verbal Memory, Visual Memory and Naming Ability negatively correlated significantly with their respective latency measures: indicating that reduced accuracy on these measures was related to slower response latencies (see TABLE VI (1)).

b) CIL Group

As can be seen in TABLE VI (1) the CIL group's accuracy score on Naming Ability negatively correlated significantly with the latency measure. No significant correlation was observed between Verbal or Visual Memory accuracy and their respective latency measures for CIL patients.

c) Control Group

Both memory accuracy measures negatively correlated with their respective latencies to a significant degree in the Control group; however, Naming Ability accuracy did not correlate with naming latencies (see TABLE VI (1)).

2) GROUP COMPARISONS ON LATENCY MEASURES

a) CIL v. CONTROLS

The CIL group's recognition memory latencies were slower than that of the Controls (see TABLE 2) but the difference

between the two groups was significant only for Visual Memory latencies (see TABLE 3). Naming Ability latency was similar for the CIL patients and the Controls (see TABLES 2 & 3).

b) MS v. CONTROLS

The means and standard deviations on the memory latencies and naming latencies are presented in TABLE 2: the latency measures of the MS group were significantly slower than the Controls' for each test (see TABLE 3). Given that the MS Group had significantly poorer scores on Visual Memory accuracy, and that poor scores correlate significantly with slow times, only accuracy scores of 9 and above on the Visual Memory measure were examined to compare latencies: the difference between MS and Controls on Visual Memory latency remained significant (TABLE 3).

c) MS v. CIL

The MS group's latency measures on the memory and naming tests were slower than those of the CIL group's (TABLE 2). This difference was significant for Verbal Memory latency and Naming latency. The MS group had significantly poorer scores on Visual Memory and so comparison of latencies on this test was applied to accuracy scores 9 and above only. On accuracy scores of 9 and above on Visual Memory the latencies of the MS and the CIL patients were similar (see TABLES 2 & 3).

3) ANALYSIS OF ACCURACY AND LATENCY VIA GRADING PROCEDURE GROUP COMPARISONS

Quartile grades were assigned to each latency measure on the basis of the Control group's latency results: this procedure is fully described in the Statistics section of this report. The latency quartile grades were examined in conjuction with the Recognition Memory Accuracy Grades and the Naming Ability Accuracy Grades.

a) CIL v. CONTROLS

(i) Latencies analysed via grading procedure

Verbal Memory latencies as a graded measure and Naming Ability latencies as a graded measure did not significantly differ between CIL subjects and Controls, however, Visual Memory latencies as a graded measure was significantly poorer for the CIL group (see TABLE 4). This demonstrates that significantly more CIL patients had slow latencies on Visual Memory assessment when compared to the Controls.

(ii) Interaction of Accuracy with Latencies via grading procedure

TABLES VI (2),(3),(4)B and C display the interaction of Accuracy with latency measure for Verbal Memory (2), Visual Memory (3) and Naming Ability (4) for the CIL (B) and Control (C) Groups. On Recognition Verbal and Visual Memory, and Naming Ability, the pattern of interaction

between accuracy and latency measure was significantly different for the CIL patients when compared to the Controls (see TABLES VI (2),(3) and (4)D).

b) MS v CONTROLS

(i) Latencies analysed via grading procedure

The graded latencies measures on both memory tests and the naming test were significantly different between MS patients and Controls (see TABLE 4).

(ii) Interaction of Accuracy with Latencies via grading procedure

TABLES VI (2),(3) and (4)A display the pattern of interaction between accuracy and latency for the MS group on Verbal Memory (2), Visual Memory (3) and Naming Ability (4): it can be seen that most of this group cluster around the 'Slow' speed categories. The association between accuracy and latency was significantly different for the MS group when compared to the Controls on Verbal and Visual Recognition Memory and on Naming Ability (see TABLES VI (2),(3) and (4)D).

c) MS v. CIL

(i) Latencies analysed via grading procedure

The MS group obtained significantly poorer grades on the three Cognitive Speed measures when compared to the CIL group (see TABLE 4).

(ii) Interaction of Accuracy with Latencies via grading procedure

The associations between accuracy and latency differed significantly for the MS group when compared to the CIL patients on Verbal and Visual Memory and on Naming Ability (see TABLES (2)D to (4)D).

4) GOOD ACCURACY ACCOMPANIED BY SLOW RESPONSES

TABLE VI (5) displays the number of individuals within each group who obtained high accuracy scores but were slow responders. These individuals were examined in more detail and no pattern was found which grouped them in any significant way: only one individual was accurate but slow on all three tests and this was a CIL patient with a normal scan (i.e. no observable lesions on MRI); physically independent; with IQ Deficit, Visual and Auditory Attention scores within the 5^{th} to 25^{th} percentile range (Grade 2 on each function). Poor IQ or attention scores were not consistently observed in the rest of the group.

Within the MS group those individuals with accurate scores but slow latencies on Naming and Verbal Memory obtained the highest Total Scan Scores (see TABLE VI (5)). Within the CIL group, apart from the one 'normal-scan' subject (who scored accurately but slowly on the three tests), accurate but slow subjects obtained Total Scan Scores that

ranged from 7 up to 22 (near or well above the CIL Group's mean Scan Score of 9.9).

C) Conclusions

1) MS Group

The MS group perform significantly more slowly than the Controls on Memory and Naming tests even when the accuracy scores are similar.

It would seem that as accuracy worsens within the MS group then time taken to respond is likely to increase; however, there are significantly more individuals scoring well but with poor speeds in this group. The pattern of interaction between accuracy and speed is significantly different to that of Controls or that of CIL patients. When compared to the Controls the MS group have significantly more individuals with Accurate but Slow scores on Naming and Verbal Memory. On Visual Memory significantly more MS patients have Slow and Deficient scores when compared to the Controls.

2) CIL Group

The CIL group perform similarly to the Controls with regard to Naming Ability latency and Verbal Memory latency but were significantly faster than the MS group on these latency measures. The CIL group's Visual Memory Latency is similar to the MS group's when accuracy on this test is

similar; but when accuracy is similar to Controls the CIL patients are significantly slower on Visual Memory latencies.

Cognitive speed would seem to be unrelated to accuracy within this group on both Memory tasks, while better scores on Naming are related to faster response latencies.

The CIL group's interaction between accuracy and speed is significantly different to that of the Controls and to that of the MS Group. When compared to Controls on Naming Ability significantly more CIL patients were Fast and Accurate; while on Verbal and Visual Memory significantly more CIL patients were Slow but Accurate. When compared to the MS group on Naming Ability significantly more CIL patients were Fast and Accurate; while on Verbal Memory significantly more MS patients were Slow and Accurate when compared to the CIL group. The interaction of accuracy and speed for Visual Memory differed significantly between the MS and CIL patients as the MS group had significantly more individuals who were slow with deficient visual memory scores. On Visual Memory there were more individuals within the CIL group who were Accurate but Slow than within either the MS group or the Control group.

3) Control Group

Cognitive speed on both memory tests is related to accuracy within this group, but naming accuracy does not relate to naming response latency.

TABLE VII (1)A

WITHIN GROUP CORRELATIONS OF ACCURACY WITH SPEED

Using Kendall tau scores (and p values)

	MS GROUP		CIL GROUP		CONTROL GROUP	
	tau	p	tau	p	tau	p
VERBAL MEMORY SCORE WITH SPEED	-.60	.0000*	-.17	.06	-.29	.004*
VISUAL MEMORY SCORE WITH SPEED	-.54	.0000*	-.05	.34	-.25	.009*
NAMING ABILITY SCORE WITH SPEED	-.27	.004*	-.24	.01*	-.10	.18

* = statistically significant

TABLE VII (1)B

WITHIN GROUP CHI SQUARE ANALYSIS OF ACCURACY GRADE WITH SPEED QUARTILE

(expected frequencies = no association)

	MS GROUP		CIL GROUP		CONTROL GROUP	
	chi	p	chi	p	chi	p
VERBAL MEMORY GRADE WITH SPEED QUARTILE	31.7	.0000*	9.2	.01*	6.0	.05*
VISUAL MEMORY GRADE WITH SPEED QUARTILE	134.2	.0000*	44.7	.0000*	4.5	.10
NAMING ABILITY GRADE WITH SPEED QUARTILE	15.4	.001*	16.9	.001*	.70	.70

* = significantly different to expected frequencies

TABLE VII (2)A

VERBAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN MS GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	3	3	7	16	60.4
	Grade 1				7	14.6
	Grade 2				7	14.6
	Grade 3				5	10.4
% of group		6.3	6.3	14.6	72.9	100

TABLE VII (2)B

VERBAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN CIL GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	3	5	7	10	54.3
	Grade 1	3	3	1	2	19.6
	Grade 2	2	1	1	7	23.9
	Grade 3				1	2.2
% of group		17.4	19.6	19.6	43.5	100

TABLE VII (2)C

VERBAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN CONTROL GROUP

Score Grade	Speed Quartile Grades: Grade 0	Grade 1	Grade 2	Grade 3	group %
Grade 0	10	8	3	7	60.9
Grade 1	1	2	3	3	19.6
Grade 2		2	5	1	17.4
Grade 3				1	2.2
% of group	23.9	26.1	23.9	26.1	100

TABLE VII (2)D

CHI SQUARE ANALYSIS ON VERBAL MEMORY RESULTS BETWEEN GROUPS

Group Analysis	Source Analysis	Chi Square Score	Degrees of Freedom	p value
MS v Controls	Score by Speed	23.2	2	.0001*
	Group by Score by Speed	37.7 - 23.2= 14.5	2	.001*
	Total	37.7	5	.0001*
MS v CIL	Score by Speed	32.5	2	.0001*
	Group by Score by Speed	40.9 - 32.5= 8.4	2	.02*
	Total	40.9	5	.0001*
CIL v Controls	Score by Speed	7.4	2	.05*
	Group by Score by Speed	15.2 - 7.4= 7.8	2	.02*
	Total	15.2	5	.01*

TABLE VII (3)A

VISUAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN MS GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0		2	3	7	24.5
	Grade 1			1	8	18.4
	Grade 2			1	17	36.7
	Grade 3			1	9	20.4
% of group		0	4.1	12.2	83.7	100

TABLE VII (3)B

VISUAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN CIL GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	1	1	6	11	41.3
	Grade 1			6	10	34.8
	Grade 2			5	5	21.7
	Grade 3				1	2.2
% of group		2.2	2.2	37.0	58.7	100

TABLE VII (3)C

VISUAL MEMORY - SCORE GRADE BY SPEED QUARTILE WITHIN CONTROL GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	9	6	4	5	52.2
	Grade 1	2	4	3	4	28.3
	Grade 2		1	4	1	13.0
	Grade 3		1		2	6.5
% of group		23.9	26.1	23.9	26.1	100

TABLE VII (3)D

CHI SQUARE ANALYSIS ON VISUAL MEMORY RESULTS BETWEEN GROUPS

Group Analysis	Source Analysis	Chi Square Score	Degrees of Freedom	p value
MS v Controls	Score by Speed	85.3	2	.0001*
	Group by Score by Speed	137.7 - 85.3= 52.4	2	.0001*
	Total	137.7	5	.0001*
MS v CIL	Score by Speed	145.2	2	.0001*
	Group by Score by Speed	179.9 - 145.2= 34.7	2	.0001*
	Total	179.7	5	.0001*
CIL v Controls	Score by Speed	7.3	2	.05*
	Group by Score by Speed	49.2 - 7.3= 41.9	2	.0001*
	Total	49.2	5	.0001*

TABLE VII (4)A

NAMING ABILITY - SCORE GRADE BY SPEED QUARTILE WITHIN MS GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	6	3	10	7	52.0
	Grade 1		4	5	5	28.0
	Grade 2			3	4	14.0
	Grade 3		1	1	1	6.0
% of group		12	16	38	34	100

TABLE VII (4)B

NAMING ABILITY - SCORE GRADE BY SPEED QUARTILE WITHIN CIL GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	6	12	4	2	52.2
	Grade 1	2	2	4	3	23.9
	Grade 2			3	3	13.0
	Grade 3		2	3		10.9
% of group		17.4	34.8	30.4	17.4	100

TABLE VII (4)C

NAMING ABILITY - SCORE GRADE BY SPEED QUARTILE WITHIN CONTROL GROUP

		Speed Quartile Grades				
		Grade 0	Grade 1	Grade 2	Grade 3	group %
Score Grade	Grade 0	6	4	3	4	37.0
	Grade 1	4	3	2	5	30.4
	Grade 2	3	4	5	2	30.4
	Grade 3			1		2.2
% of group		28.3	23.9	23.9	23.9	100

TABLE VII (4)D

CHI SQUARE ANALYSIS ON NAMING ABILITY RESULTS BETWEEN GROUPS

Group Analysis	Source Analysis	Chi Square Score	Degrees of Freedom	p value
MS v Controls	Score by Speed	7.4	2	.05*
	Group by Score by Speed	16.1 - 7.4= 8.7	2	.02*
	Total	16.1	5	.01*
MS v CIL	Score by Speed	23.6	2	.0001*
	Group by Score by Speed	32.3 - 23.6= 8.7	2	.02*
	Total	32.3	5	.0001*
CIL v Controls	Score by Speed	11.3	2	.01*
	Group by Score by Speed	17.6 - 11.3= 6.3	2	.05*
	Total	17.6	5	.01*

TABLE VII (5)

NUMBER OF INDIVIDUALS WITHIN EACH GROUP

WITH GOOD ACCURACY (SCORES) ACCOMPANIED BY

SLOW RESPONSES (SPEEDS)

	MS GROUP	(mean Scan Sc.)	CIL GROUP	(mean Scan Sc.)	CONTROLS	(mean Scan Sc.)
On Naming	7	(23.6)	2	(5.5)	4	(0)
On Verbal Memory	16	(19)	10	(8.8)	7	(1)
On Visual Memory	7	(5.4)	11	(8.6)	5	(0)
On Naming and Verbal Memory	4	(21.3)	2	(5.5)	0	(-)
On Naming and Visual Memory	1	(2)	1	(0)	1	(-)
On Verbal and Visual Memory	2	(4.5)	3	(11)	2	(0)
On Naming, Verbal and Visual Memory	0	(-)	1	(0)	0	(-)

TABLE 1

Mean Scores in Patients with Clinically Isolated Lesions

	Optic Neuritis (N=14)	Brain Stem (N=16)	Spinal Cord (N=18)	(Kruskal-Wallis) x^2	
IQ deficit	2.1 (6.6)	4.3 (8.0)	0.4 (7.5)	2.43	
Verbal memory	12.9 (1.8)	11.8 (2.8)	12.1 (2.6)	.66	
Visual memory	11.2 (3.2)	11.6 (2.7)	11.1 (3.0)	.16	
Abstracting ability	5.4 (3.6)	5.7 (3.9)	8.7 (7.6)	1.20	NS
Visual attention	15.8 (2.8)	14.3 (4.4)	18.0 (7.2)	2.4	
Auditory attention	1.3 (1.8)	2.3 (1.5)	2.8 (4.2)	4.03	
Naming ability	21.6 (3.7)	21.4 (4.8)	22.6 (3.7)	.68	

NS - not significant.

Standard deviation in brackets.

TABLE 2

MEAN SCORES (and Standard Deviations) OF PSYCHOMETRIC MEASURES

	MS GROUP (N=58)	CIL GROUP (N=48)	CONTROLS (N=46)
Nart IQ Equivalent	110.1 (8.7)	110.8 (7.0)	108.9 (7.9)
Full Scale IQ	103.7 (12.2)	108.5 (9.9)	109.7 (9.9)
Verbal IQ	105.1 (12.1)	109.7 (10.6)	109.4 (11.2)
Performance IQ	100.5 (13.1)	106.2 (10.9)	108.3 (9.7)
IQ Deficit	6.8 (10.8)	2.2 (7.4)	-.7 (8.4)
Verbal Memory	11.0 (3.9)	12.2 (2.5)	12.5 (2.0)
Visual Memory	7.9 (4.4)	11.3 (2.9)	11.8 (3.5)
Abstracting Ability	11.8 (9.1)	6.7 (5.6)	5.8 (5.2)
Visual Attention	20.7 (10.1)*	16.2 (5.4)**	14.1 (3.4)***
Auditory Attention	3.1 (3.8)	2.2 (2.9)	1.2 (2.1)
Naming Ability	22.2 (3.9)	22.0 (4.1)	21.7 (3.0)
Cognitive Efficiency	9.7 (4.7)	7.2 (3.3)	5.3 (2.9)
	* N = 41	** N = 28	*** N = 45
MEANS (AND STANDARD DEVIATIONS) OF COGNITIVE SPEED (in seconds):			
Verbal Memory Speed	93.8 (45.0)	71.6 (23.2)	63.9 (15.9)
Visual Memory Speed	144.5 (60.0)	115.2 (29.7)	92.9 (20.0)
...On scores of 9+	110.3 (16.9)	111.6 (24.3)	90.8 (18.8)
Naming Ability Speed	2.6 (1.3)	2.2 (0.6)	2.2 (0.7)

TABLE 3

GROUP COMPARISONS ON ALL PSYCHOMETRIC MEASURES

Using Mann-Whitney z scores and MANOVA f scores with p values

	CIL v. CONT		MS v. CONT		MS v. CIL	
	z(f)	p	z(f)	p	z(f)	p
Nart IQ Equivalent	1.1	.29	.93	.35	.12	.91
Full Scale IQ	(f)1.1	.3	2.4	.02*	(f)3.2	.08
Verbal IQ	.28	.77	1.4	.16	2.1	.03*
Performance IQ	(f)2.5	.12	3.1	.005*	(f)3.0	.09
IQ Deficit	(f)5.5	.02*	4.1	.0000*	(f)3.1	.09
Verbal Memory	.47	.64	1.4	.15	1.3	.18
.....Speed	1.6	.12	4.8	.0001*	3.2	.001*
Visual Memory	1.4	.18	4.5	.0000*	4.2	.0000*
.....Speed	4.5	.0000*	4.0	.0001*#	.4	.67$
Abstracting Ability	.86	.39	3.9	.0001*	3.5	.0005*
Visual Attention	1.7	.09	4.7	.0000*	2.4	.02*
Auditory Attention	2.7	.007*	3.5	.0004*	1.5	.14
Naming Ability	1.2	.23	1.4	.17	.1	.92
.....Speed	.3	.8	2.0	.04*	2.0	.04*
Cognitive Efficiency	2.7	.008*	4.8	.0000*	3.3	.001*
!!!	2.9	.005*	4.5	.0000*	1.4	.20 !!!

* = statistically significant / (f) = Manova taking account of ADL score

!!!On those who undertook visual attention N= MS-41; CIL-28; CONTROLS-45!!!

#N=MS- 22; CIL- 41; CONT- 40 / $N=MS- 22; CIL- 41; CONT-41 - 9+ scores only

TABLE 4

GROUP COMPARISONS ON ALL PSYCHOMETRIC GRADES

Using Mann-Whitney z scores and p values

	CIL v. CONT		MS v. CONT		MS v. CIL	
	z	p	z	p	z	p
IQ Deficit	2.5	.01*	4.3	.0000*	2.4	.02*
Verbal Memory	.80	.42	.95	.34	.55	.56
.....Speed	1.6	.11	4.6	.0000*	3.0	.003*
Visual Memory	1.1	.27	3.9	.0001*	3.6	.0003*
.....Speed	4.4	.0000*	5.9	.0000*	2.6	.01*
Abstracting Ability	.93	.35	3.9	.0001*	3.7	.0002*
Visual Attention $	1.6	.11	4.6	.0000*	2.2	.03*
Auditory Attention	3.0	.003*	3.8	.0001*	1.6	.10
Naming Ability	1.1	.28	.83	.41	.78	.44
.....Speed	.2	.83	2.2	.03*	2.3	.02*
Cognitive Efficiency	2.5	.01*	4.8	.0000*	2.6	.01*
!!!	2.9	.004*	4.4	.0000*	1.3	.20 !!!

* = statistically significant

$ carried out only on patients who had undertaken visual attention assessment so that MS N=41; CIL N=28; CONTROLS N=45.

!!! carried out on those patients who undertook the visual attention test only: N= MS-41; CIL-28; CONTROLS-45 !!!

TABLE 5

CORRELATIONS OF MRI AND PSYCHOMETRIC MEASURES WITHIN MS GROUP

Using Kendall tau scores

(and p values)

	TOTAL SCAN SCORE		PERIVENTRICULAR SCORE	
	tau	p	tau	p
IQ DEFICIT	.10	.14	.11	.12
Verbal Memory	-.20	.03*	-.22	.02*
Visual Memory	-.32	.005*	-.34	.0003*
Abstract/Abil.	.02	.41	.02	.43
Visual/Atten.	-.002	.49	-.01	.45
Auditory/Att.	.18	.04*	.21	.02*
Naming Abil.	-.19	.02*	-.19	.02*
Cog/Effic/Sc.	.23	.01*	.26	.005*
	N = 57		N = 56	

* statistically significant

TABLE 6

CORRELATIONS OF MRI AND PSYCHOMETRIC MEASURES WITHIN CIL GROUP

Using Kendall tau scores

(and p values)

	TOTAL SCAN SCORE		PERIVENTRICULAR SCORE	
	tau	p	tau	p
IQ DEFICIT	.11	.14	.09	.19
Verbal Memory	.02	.44	-.04	.36
Visual Memory	-.07	.25	-.10	.18
Abstract/Abil.	.18	.05*	.16	.07
Visual/Atten.	.01	.46	.03	.43
Auditory/Att.	.20	.04*	.29	.005*
Naming Abil.	-.03	.41	.004	.49
Cog/Effic/Sc.	.16	.07	.17	.06
	N = 37		N = 35	

* statistically significant

TABLE 7

MRI TOTAL QUARTILES WITH PSYCHOMETRIC GRADES WITHIN EXPERIMENTAL GROUPS

CHI ANALYSIS WITH P VALUES

	MS GROUP		CIL GROUP	
	Chi	p	Chi	p
IQ DEFICIT	3.9	.92	10.0	.40
VERBAL MEMORY	9.3	.41	11.6	.24
VISUAL MEMORY	19.1	.03*	11.7	.23
ABSTRACTING ABILITY	10.4	.32	10.8	.29
VISUAL ATTENTION	9.5	.40	14.6	.10
AUDITORY ATTENTION	9.7	.37	11.1	.27
NAMING ABILITY	12.5	.19	15.9	.07
COGNITIVE EFFICIENCY	9.6	.38	11.0	.30

* statistically significant

TABLE 8

MS GROUP - MEANS (and Standard Deviations) OF TOTAL SCAN SCORE WITHIN PSYCHOMETRIC GRADES

	GRADE 0-Good		GRADE 1-Fair		GRADE 2-Poor		GRADE 3-Deficient	
	MEAN	(s.d.)	MEAN	(s.d.)	MEAN	(s.d.)	MEAN	(s.d.)
IQ DEFICIT	22.7	(13.0)	21.3	(10.5)	21.6	(13.7)	28.5	(13.7)
VERBAL MEMORY	21.4	(11.3)	17.1	(11.1)	31.7	(12.8)	27.3	(15.2)
VISUAL MEMORY	10.5	(8.1)	22.5	(8.6)	28.6	(12.1)	27.2	(13.7)
ABSTRACTING ABILITY	20.6	(11.8)	24.1	(9.8)	22.1	(14.3)	26.6	(15.8)
VISUAL ATTEN.	24.3	(10.9)	22.9	(16.9)	22.9	(12.3)	22.7	(11.8)
AUDITORY ATT.	21.3	(10.4)	19.7	(11.7)	23.6	(14.6)	29.4	(13.4)
NAMING ABILITY	22.0	(12.4)	27.3	(14.7)	26.3	(7.4)	21.8	(19.2)
COGNITIVE EFFICIENCY	16.0	(7.6)	18.5	(11.6)	25.4	(12.9)	27.8	(13.9)

TABLE 9

CIL GROUP - MEANS (and Standard Deviations) OF TOTAL SCAN SCORE WITHIN PSYCHOMETRIC GRADES

	GRADE 0-Good		GRADE 1-Fair		GRADE 2-Poor		GRADE 3-Deficient	
	MEAN	(s.d.)	MEAN	(s.d.)	MEAN	(s.d.)	MEAN	(s.d.)
IQ DEFICIT	6.6	(6.3)	9.5	(8.9)	15.6	(15.3)	6.4	(8.1)
VERBAL MEMORY	10.8	(9.8)	5.6	(6.4)	11.1	(15.5)	11.0	(1.4)
VISUAL MEMORY	8.7	(6.4)	8.1	(8.4)	14.6	(16.8)	3.0	*
ABSTRACTING ABILITY	6.7	(6.1)	8.5	(7.1)	16.2	(16.3)	10.0	*
VISUAL ATTEN.	10.6	(13.9)	8.4	(7.9)	7.5	(8.1)	21.3	(13.1)
AUDITORY ATT.	5.2	(4.1)	11.8	(8.5)	10.1	(12.4)	18.3	(16.1)
NAMING ABILITY	7.3	(9.0)	14.6	(7.1)	14.3	(18.9)	6.0	(5.8)
COGNITIVE EFFICIENCY	6.7	(4.8)	7.8	(7.6)	9.0	(9.9)	21.1	(18.7)

* N = 1

TABLE 10

GROUP COMPARISONS ON A) DISEASE FACTORS B) PSYCHIATRIC MEASURES and C) PHYSICAL ABILITY

Using Mann-Whitney z scores and p values

	CIL v. CONT		MS v. CONT		MS v. CIL	
	z	p	z	p	z	p
A) YEARS of ACTIVE DISEASE	N.A.		N.A.		6.1	.0000*
B) Clinical Interview Schedule Score	.43	.67	5.4	.0000*	4.2	.0000*
Beck Depression Inventory Score	.81	.42	4.5	.0000*	3.2	.001*
C) Activities of Daily Living Score	2.0	.05*	.27	.80	2.8	.005*

* = statistically significant

TABLE 11

WITHIN GROUP CORRELATIONS OF COGNITIVE EFFICIENCY SCORE WITH

A) DISEASE FACTORS B) PSYCHIATRIC MEASURES

and C) PHYSICAL ABILITY

Using Kendall tau scores (and p values)

	MS GROUP		CIL GROUP		CONTROL GROUP	
	tau	p	tau	p	tau	p
A) YEARS of ACTIVE DISEASE	.32	.01*	-.06	.27	NA	
B) Clinical Interview Schedule Score	.17	.04*	.20	.03*	.20	.04*
Beck Depression Inventory Score	.23	.02*	.28	.007*	.08	.23
C) Activities of Daily Living Score	.37	.0006*	.21	.04*	- .19	.06

* = statistically significant

TABLE 12

WITHIN GROUP CORRELATIONS OF TOTAL SCAN SCORE WITH

A) DISEASE FACTORS B) PSYCHIATRIC MEASURES

and C) PHYSICAL ABILITY

Using Kendall tau scores (and p values)

	MS GROUP		CIL GROUP		CONTROL GROUP	
	tau	p	tau	p	tau	p
A) YEARS of ACTIVE DISEASE	.40	.003*	NA		NA	
B) Clinical Interview Schedule Score	.01	.50	.09	.21	.07	.36
Beck Depression Inventory Score	.12	.43	.05	.32	.15	.24
C) Activities of Daily Living Score	.23	.02*	.10	.20	-.18	.22

* = statistically significant

TABLE 13

COGNITIVE EFFICIENCY SCORE - WITHIN DISEASE FACTOR AND WITHIN PSYCHIATRIC FACTOR COMPARISONS FOR EACH SUBJECT GROUP

Mann-Whitney z scores and p values

	MS GROUP		CIL GROUP		CONTROL GROUP	
	z	p	z	p	z	p
In Relapse v.						
Not In Relapse	1.5	.14	1.4	.16	2.7	.006*
Number	17 v. 35		17 v. 29		31 v. 14	
Psychiatric						
'Case' v.	1.7	.10	.9	.40	2.1	.04*
'Non-Case'$						
Number	23 v. 30		8 v. 40		2 v. 43	
Depressed v.						
Not Depressed $	.02	.98	1.2	.23	2.2	.03*
Number	17 v. 36		10 v. 38		5 v. 40	
Anxious v.						
Not Anxious $	.0	1.0	.70	.50	1.3	.20
Number	14 v. 39		13 v. 35		4 v. 41	

$ Based on the Clinical Interview Schedule

* statistically significant

TABLE 14(a)

PHYSICAL ABILITY FACTOR COMPARISONS WITHIN EACH SUBJECT GROUP

Mann-Whitney z scores and p values

INDEPENDENT PHYSICALLY v. USING WALKING STICK OR WHEELCHAIR

		FULL SCALE IQ	PERFORMANCE IQ	IQ DEFICIT	COGNITIVE EFFICIENCY	TOTAL SCAN SCORE
MS GROUP	N	38 v 20	38 v 20	38 v 20	34 v 19	38 v 18
	z	.23	.36	.84	1.5	2.0
	p	.82	.72	.40	.15	.04*
CIL GROUP	N	43 v 5	43 v 5	43 v 5	43 v 5	43 v 5
	z	1.5	1.4	.40	2.4	1.6
	p	.14	.17	.72	.02*	.11
CONTROLS	N	27 v 19	27 v 19	27 v 19	27 v 19	14 v 4
	z	.70	.16	1.0	1.8	.80
	p	.50	.90	.32	.08	.44

* statistically significant

TABLE 14(b)

GROUP COMPARISONS ON COGNITIVE EFFICIENCY SCORE

WITHIN PHYSICAL ABILITY GROUPS

Mann-Whitney z scores and p values

	CIL v CONTROLS		MS v CONTROLS		MS v CIL	
	N = 43 v 27		N = 34 v 27		34 v 43	
	z	p	z	p	z	p
PHYSICALLY INDEPENDENT SUBJECTS ONLY	.90	.40	2.8	.006*	2.4	.02*
	N = 5 v 19		N = 19 v 19		N = 19 v 5	
	z	p	z	p	z	p
USING W/STICK OR WHEELCHAIR ONLY	3.1	.002*	3.9	.0001*	.18	.90

* statistically significant

CHAPTER V

DISCUSSION

1. DISCUSSION OF METHOD

The range of psychometric assessment procedures employed in previous research, coupled with the spectrum of severity with regard to the neurological status of the MS patients studied, have resulted in contradictory findings in most areas. Some earlier studies are further confounded by the lack of standardisation with regard to the classification of the disease of MS; and some later studies have included patients with Probable MS in their subject samples. The present study examines patients with Clinically Definite MS following the criteria recommended by Poser et al (1983).

The present study included examination of patients with Optic Neuritis, Brain Stem Disorder and Spinal Cord Syndrome as these conditions represented possible precursors to the development of MS and are certainly features observed in the presentation of MS. It was established in the present investigation that the three groups of patients, Optic Neuritis, Brain Stem Disorder and Spinal Cord Syndrome, did not differ significantly on any cognitive measure. They were examined, therefore, as

one group for the purposes of analysis of results and constitute the Clinically Isolated Lesion (CIL) group.

Analysis of results in the present study included examination of each patient's performance level on each cognitive measurement by dividing the performance level into four categories based on the results of the Control Group. The performance levels of the Control Group closely matched that expected by the normal population on tests with validated norms. The Control Group tested, therefore, was a good representative sample of the normal population with regard to level of cognitive functioning.

The four categories were based on the percentile levels of the Controls Group's scores for each test: all subjects with scores above the Control Group's 50^{th} percentile were assigned to Grade 0 (Good Grade); with scores between the 25^{th} and 50^{th} percentiles to Grade 1 (Fair Grade); with scores between the 5^{th} and 25^{th} percentiles to Grade 2 (Poor Grade); and those with scores at or below the Control Group's 5^{th} percentile were assigned to Grade 3 (Deficient Grade).

The graded structure was demonstrated to be a sensitive measure: on the IQ Deficit measure (before controlling for Motor Ability) the CIL patients did not differ to the Controls on the basis of analyses on conventional scores

(p=.06); however, the difference reached statistical significance on IQ Deficit **Grades** (Motor Ability not controlled for).

This graded structure allowed one to examine the number of individuals scoring at a particular level within each cognitive measurement, and enabled the investigator to compare the groups' patterns of cognitive abilities. Furthermore, it was possible to sum across the graded measures and obtain an **overall** 'Cognitive Efficiency' score for each subject: the Grades obtained by each individual were added together to provide a single index of cognitive efficiency. In addition, one could look at individuals scoring within a particular performance grade and examine this subgroup with regard to other measures obtained (e.g. the lesion score of Deficient Grade IQ individuals within the MS group).

The measure of overall 'Cognitive Efficiency' begs the question: What is 'Cognitive Efficiency' - measured in this way? Firstly, it may be the summation of some deficit replication. That is to say, more than one test may be tapping one and the same cognitive ability. Secondly, the 'Cognitive Efficiency' measure may, on the other hand, be the total of multiple specific deficits. The second important question to consider is: Does this method of measuring 'Cognitive Efficiency' point the way to a more sensitive measure? Future research is necessary

to clarify the answer to the first question posed: whether this is a measure of 'g', a general cognitive factor, or a measure of the plurality of specific deficits. As to the second question posed, the present findings suggest that it is a sensitive measure: it distinguishes quantitatively between each subject group and seems to be, as will be discussed below, an indicator of disease progression in the present study.

MRI lesion scores were also graded into four categories for each of the MS and CIL groups, based on the quartiles of each group's own scores: Grade 0 (Lowest) was assigned to each group's scores that occurred below the 25^{th} percentile; Grade 3 (Highest) was assigned to each group's scores that occurred above the 75^{th} percentile; with Grades 1 and 2 assigned respectively to scores in the two middle quartiles. These Quartile Grades were assigned on the basis of the group's own lesion scores because there is no "expected norm" with regard to MS lesion scores or CIL lesion scores.

The same procedure to obtain Quartile Grades was applied to the results of the cognitive speed measures, except that in this case the grades assigned were based on the quartile levels of the speeds obtained by the Control group. The Controls' timing results provided an "expected norm" on which to base the grades from Best (Grade 0) to

Worst (Grade 3) for the MS and CIL patients.

Quartile Grades were obtained on lesion scores and speed results in order to provide compatible data with which it was possible to examine their interactions with the graded cognitive assessment scores for each group. Nonparametric statistics were employed to analyse this ordinal data with the Chi Square statistic applied to examine interactions between Graded scores.

2. DISCUSSION OF INDIVIDUAL TEST RESULTS

(1) Intellectual Functions

Previous studies have concluded that patients with Multiple Sclerosis (MS) have deficits in IQ (Parsons et al, 1957; Reitan et al, 1971; Canter, 1951); the present findings confirm the results of some previous studies, demonstrating deficits in the MS group with regard to IQ. Previous research on IQ assessment of patients with MS have discussed their findings with reference to specific subtests of the Wechsler Adult Intelligence Scale (WAIS) and similar batteries. This was, in general, in order that deductions might be made with regard to localising and describing selective deficits (e.g. Diers and Brown, 1950 citing the Digit Span subtest; Peyser et al, 1980 citing the Similarities subtest; and Ivnik in 1978 cites the Information and Vocabulary subtests).

The present study has tried to assess selective deficits with assessments designed to attend to each function, and has not examined the pattern of WAIS results for this purpose. The analysis of the pattern of WAIS subtests is considered to be of value in diagnosing selective deficits associated with a focal lesion (Warrington et al, 1986) and, therefore, would not seem to be an appropriate method to employ with a group of patients presenting with widespread and diffuse lesions of the kind documented in MS (Ikuta and Zimmerman, 1976). Furthermore, discussion of specific subtests of the WAIS was of value in the absence of concurrent measures of disability, anxiety and premorbid functioning: performance on some subtests was considered to offer information about these three aspects of an individual's functioning.

The present study provides information about the MS group with regard to level of physical ability, anxiety and premorbid intellectual functioning on the basis of assessments designed to measure these functions. Therefore, the present discussion considers the pattern of results obtained by a number of cognitive measures for each patient group and does not rely on examination of specific WAIS subtests.

Verbal IQ was demonstrated to be intact in the present sample of MS patients, confirming the results of Peyser et

al (1980) and Jambor (1969). However, Full Scale IQ and Performance IQ were significantly impaired in the present group of MS patients and performance was not different for those patients with increased physical disability.

The only distinguishing factor of those MS patients with severe IQ deficit was the increased amount of brain lesions observed on Magnetic Resonance Imaging (MRI) when compared to the rest of the group. A study published since the completion of the present investigation (Rao et al, 1989a) partly supports the present findings: Rao and his colleagues' investigation concludes that there is a strong association between Verbal IQ performance and lesion presentation on MRI. It must be noted that 11% of Rao et al's (1989a) sample were patients with Probable MS. Analysis of results in the present study demonstrates that IQ deficit is associated with more lesions on MRI, however there is little evidence to support an association between Verbal IQ level and total brain lesion score within the present MS group (Verbal IQ was found to be associated with lesions in the Temporal area, but not with overall total lesion score, as may be seen from the TABLES in Appendix 5 and Appendix 6).

Patients with Clinically Isolated Lesions (CIL) performed at a level similar to the Controls with regard to Full Scale IQ, Performance IQ and Verbal IQ (Callanan et al,

1989). However, when premorbid levels of functioning and physical ability levels were taken into account, the CIL patients had significantly greater IQ Deficit when compared to the Controls.

Previous research concluded that patients with Optic Neuritis may be cognitively impaired (Lyon-Caen et al, 1986): nine patients with Optic Neuritis were cognitively assessed and six were considered 'impaired'. This subject sample was small, however, and was compared to a heterogeneous group of patients, some of whom were likely to have been brain-damaged: no conclusions were drawn about intellectual impairment as only three subtests of the WAIS were administered in Lyon-Caen et al's study (1986).

Analysis of results in the present study demonstrates that over sixty percent of the MS group, and thirty-nine percent of the CIL group, had an IQ Deficit score that was obtained by only seventeen percent of the Control group. Twenty percent of the MS group and ten percent of the CIL group had a severe IQ Deficit: a performance level expected by only four percent of the normal population. This IQ Deficit was not different for MS patients with a severe disability; though the twenty percent with severe deficient IQ did have more brain lesions when compared to the rest of the group.

An association between IQ Deficit and amount of MRI lesions was not observed within the CIL group, though those CIL patients within the 'Poor' IQ Deficit grade had more brain lesions than individuals scoring within any of the other three IQ grades.

The performance level of the CIL patients, when broken down into the four categories, demonstrates an intermediate degree of IQ deficit when compared to the Controls' and the MS group's. The presence of diffuse lesions observed on MRI within this CIL group (Ormerod et al, 1987) is similar to the pattern observed for patients with MS. Secondly, there is a similarity to the MS group with regard to some neurological features, and thirdly there is evidence of increased intellectual impairment. These similarities between the MS group and CIL patients present a picture that supports the hypothesis that a percentage of CIL patients will go on to develop MS. This study has so far demonstrated the fact that CIL patients, with what might be the early stages of a demyelinating disease such as MS, are already performing at a level significantly worse than that expected by the norm with regard to intellectual functions.

(2) Recognition Memory Ability

(a) Verbal Recognition Memory

With regard to Verbal Recognition Memory the present MS group perform at a level similar to that of the Controls, confirming the results of some previous studies that concluded that Verbal Recognition Memory is intact in this group (Carroll et al, 1984). However, some other previous research has suggested that poor memory performance is related to high disability levels (Baldwin, 1952; Beatty and Gange, 1977; Vowels, 1979). Although this previous research concentrated mostly on verbal learning tasks and verbal free recall tasks, the present group of MS patients who scored within the Deficient grade for Verbal Recognition Memory were examined with regard to physical ability and any other factors. Those MS patients with deficient Verbal Recognition Memory have the highest lesion scores, are more disabled and have poorer IQ scores.

As the present Verbal Recognition Memory test could not be directly affected by motor function the present results indicate that amount of brain lesion present is the most pertinent factor: lowered performance on Verbal Recognition Memory was related to increased amount of brain lesions within the MS group in the present investigation.

This finding is further evidence supporting the claim made by previous researchers that memory functions, like motor functions, are particularly vulnerable to the demyelination process (Beatty and Gange, 1977). Another explanation for this correlation between memory and motor ability is that both memory and motor signs are produced by a similar distribution of plaques within the CNS (Rao et al, 1984).

Previous research has also suggested that impairment on recognition memory was demonstrated only in patients with chronic progressive MS as opposed to recently diagnosed patients (Elpern et al, 1984) but the present study demonstrates that performance on Verbal Recognition Memory was not related to length or status of disease activity. This finding confirms the work of Grant and his colleagues (1984) suggesting that memory impairment is not confined to long-term chronic MS patients.

While the MS group in the present study did not differ to the Controls with regard to Verbal Recognition Memory overall, a higher percentage of the MS group obtained deficient scores on the Verbal Recognition Memory assessment: 12.5% of the MS group had Deficient Verbal Recognition Memory and only 2% of Controls scored at this deficient level.

CIL patients did not differ to the Controls or the MS group with regard to Verbal Recognition Memory. Only 4% of the present CIL group obtained Deficient Verbal Recognition Memory scores: their performance was not related to lesion score, disease activity, physical ability or IQ levels. This result with regard to CIL patients does not support the findings of Lyon-Caen et al (1986) which reports observing abnormal verbal memory in their group of Optic Neuritis patients, although it is unclear what percentage of the sample studied (N=9) presented with verbal memory impairment. Furthermore, the memory tests employed by Lyon-Caen et al (1986) were tests of recall and not recognition tasks.

(b) Visual Recognition Memory

Visual Recognition Memory was significantly poorer for the present MS group when compared to the Controls, supporting some of the previous research on this patient population (Rao et al, 1984). However, results of previous investigations seem to be contradictory with regard to Recognition Memory ability in MS patients, with some studies suggesting that this type of memory ability (i.e. recognition memory) is intact in this group (Carroll et al, 1984) and other studies qualifying the presence of recognition memory impairment with the conclusion that it occurs only in patients with chronic-progressive MS (Elpern et al, 1984).

Clearly, this issue required clarification and it seemed possible that more than one type of recognition memory was under study in previous investigations, and that confusion about the kind of test material employed could be responsible for contradictory conclusions. The results of the present study suggest that impairment of Recognition Memory is a feature of MS not, however, for verbal material, but for visual material (i.e. pictures rather than words).

It would appear that failure to retrieve material for MS patients occurs on tasks using both verbal and visual stimuli. However, this would seem to be with regard to Free Recall tasks, not to Recognition tasks. The present findings indicate that Visual Recognition Memory is impaired for patients with MS but Verbal Recognition Memory is not. This observation is not compatible with the diffuse, bilateral lesions observed on MRI of MS patients and it must be hypothesised that Verbal Recognition Memory is a function which, under these conditions, would seem to be more resistant to the effects of widespread demyelination.

MS patients' Visual Recognition Memory was related to amount of brain lesions and to number of years of active disease: those patients with a higher amount of lesions demonstrated on MRI and increased number of years of

active disease performed less well on Visual Recognition Memory. Unlike the pattern observed for Verbal Recognition Memory, it would seem that years of active disease relates to Visual Recognition Memory performance in a significant way. This finding suggests that there is the possibility of cumulative damage resulting from increased disease activity which, combined with an increase in the amount of MRI lesions, affects in an adverse way Visual Recognition Memory.

Twenty-one percent of the present MS group had Deficient scores on Visual Recognition Memory: this subgroup had higher brain lesion scores and a greater degree of physical disability when compared to the rest of the group. These were the only two factors that distinguished this MS subgroup from MS individuals in any of the other Visual Recognition Memory performance grades.

Motor function could not be directly related to Visual Recognition Memory (as the task did not require any motor involvement) and so the conclusion, as with Verbal Recognition Memory, is that both motor and recognition memory are subsumed by a similar distribution of demyelination plaques in the CNS. This finding confirms the early work of Baldwin (1952) and the later research conclusions of Rao and his colleagues (1984).

Although a larger percentage of the CIL group had 'Poor' Visual Recognition Memory when compared to the Controls, the CIL patients' **overall** performance was similar to the Control group's. The CIL patients' Visual Recognition Memory was significantly better than the MS group's. Again, these findings do not support the statement of 'abnormal memory ability' reported in Optic Neuritis patients by Lyon-Caen and colleagues (1986). Recognition memory ability would appear to be intact in patients with CIL: a difference in the pattern of deficit as compared to MS patients. If one hypothesises that CIL patients possibly represent a very early stage in the disease of MS, then it must be concluded that the assessment of recognition memory ability is not a sensitive measure at this early stage. Tests of memory recall are, possibly, more sensitive a measure for CIL patients as seems to be indicated by previous research results (Lyon-Caen et al, 1986).

Discussion of recognition memory ability in patients with CIL and in patients with MS is not complete in the present study without mention of the other dimension measured: cognitive speed. The speed of processing on the recognition memory tasks was included in the measures in the present investigation and will be discussed in detail below.

(3) Abstracting Ability

Abstracting ability has been reported in early studies as being intact in patients with MS (Ross and Reitan, 1955; Knehr, 1962); impaired in patients with MS (Parsons et al, 1957; Jambor, 1969) and mildly impaired in patients with MS (Reitan et al, 1971). Again, conclusions are contradictory due to the variety of tests administered and the unreliable disease classification used.

Most later studies, however, consistently report that patients with MS are impaired with regard to abstracting ability (Peyser et al, 1980; Elpern et al, 1984; Rao et al, 1984; Rao and Hammeke, 1984; and Heaton et al, 1985), especially nonverbal abstraction and in particular with respect to perseverative tendencies (Rao, 1986; Rao et al, 1989a).

The literature on abstracting ability in MS patients suggests using a test that allows the analysis of error patterns (Rao, 1986) and the Modified Wisconsin Card Sorting Test (MWCST) is such a measure. However, in the present investigation where this test was used, no difference was found between the perseverative error patterns and other types of errors made: the final measure used was the total number of errors obtained. On the basis of this analysis the MS group performed significantly worse than the Controls, and worse than the

CIL patients, with regard to abstracting ability.

The present finding confirms the conclusions of the bulk of previous research in this area. This impairment in Abstracting Ability, however, was not related to amount of lesions in the brain for MS patients in the present study. In a recently published study the performance of a group of MS patients was demonstrated to be predicted by Total Lesion Area on MRI (Rao et al, 1989a). However, Rao et al's study did not present evidence for a strong correlation between Abstracting Ability and MRI lesions but stated that overall cognitive efficiency strongly related to MRI lesions in a group of MS patients of whom 11% had a diagnosis of probable MS (Rao et al, 1989a). Furthermore, in Rao et al's recent study the error index used from the Wisconsin CST was different to that used in the present study.

Twenty percent of MS patients in the present study obtained deficient abstracting ability scores and this subgroup had the highest scan scores when compared to the rest of the MS group, which does, in part, support the findings of Rao et al's study (1989a). However, the present study's MRI results over all the other Abstracting Ability performance grades in the MS group did not indicate a strong relationship between the two.

The present finding with regard to an absence of correlation between Abstracting Ability and MRI within the MS group may be explained by the comment in a previous report which suggests that the ability to form abstract concepts is affected by the level of distractibility and impulsiveness of the patient at the time, rather than to any disease factor as such (Rao 1986). It must be noted, however, that the present CIL group had deficient Auditory Attenional ability (suggesting some level of distractibility was present) and yet were not deficient on Abstracting Ability. Furthermore, a significant percentage of the CIL group had poor Visual Attention while only two percent of CIL patients obtained deficient scores on Abstracting Ability. It would seem, therefore, that attentional ability and abstracting ability are not closely related or causally related in the present study.

Dysfunctional abstract reasoning is thought to be related to impairment in the frontal lobes (Vowels and Gates, 1981; Cicerone et al, 1983): MRI of patients with MS in the present study do not suggest major involvement of the frontal lobes: MS patients' mean frontal lobe score is 2.1, the third lowest mean lesion score obtained. Twenty-six percent of the present group of MS patients were assessed as having no evidence of any MRI lesions in the frontal lobes. This finding is contrary to evidence in a recent report which states that ten out of twelve MS

patients (83%) under investigation showed frontal lobe release signs in the lower extremities (Franklin et al, 1989). The mean of the Total Frontal Lesion score (which includes the Frontal Horns brain area) of the present MS Group was 5.3, and 86% of the group demonstrated lesions on MRI in this area. It may be that one has to look at a wider frontal area of the brain than just the frontal lobes when considering an attempt to localise deficits in MS patients.

The CIL patients in the present study were not impaired with regard to abstract reasoning, though it was observed that the greater the number of errors on the abstracting ability task the higher the lesion score obtained. It is suggested that assessment of abstracting ability would not seem to be a sensitive measure for what might be the very early stages of MS.

(4) Attentional Ability

Published reports of deficits in attentional ability that had been systematically studied in patients with MS were not known prior to the commencement of the present investigation. As fatigue is a common subjective complaint of MS sufferers and might result in inattention and distractibility it was considered of interest to examine whether deficits of visual or auditory attention were present in patients with MS and in CIL patients. A

recently published study (Rao et al, 1989a) examined 53 patients with definite or probable MS with three tests designed to assess concentration and attention. The attention tests used were a reaction time measure, a memory scanning measure and the Paced Auditory Serial Addition Test (PASAT): these tests were administered as part of a large battery of cognitive assessment. It is unclear what percentage were impaired on the attention tests: 36% of the group were demonstrated to be impaired over the whole of the cognitive assessment. The MRI measure that was demonstrated to be the best predictor of performance on the attention tests was the size of the Corpus Callosum: an MRI measure that was not used in the present study. This previous research (Rao et al, 1989a), due to the different measures of Attentional ability and MRI analysis employed, cannot be directly compared to results in the present study but provide support for the notion of attentional deficits in MS patients.

(a) Visual Attention

The MS patients had significantly slower visual attention ability when compared to the Controls and when compared to the CIL group. Although the CIL group did not differ to the Controls overall with regard to Visual Attention ability, examination of their performance when broken down into the graded categories demonstrates that a larger percentage of CIL patients (35% of the group) scored

within the Poor and Deficient grades when compared to Controls. This finding confirms the presence of attentional deficits in patients with MS, supporting some previous research in this area (Rao et al, 1989a), and suggests that patients who are possibly in the early stages of the disease also show some evidence of this deficit.

Neither the MS group's Visual Attention ability nor the CIL group's was observed to be related to amount of lesions in the brain: this finding is contrary to that in previous investigations (Rao et al, 1989a). It may be that, while Visual Attention ability is impaired for MS patients, it is not directly related to the disease but is a result of the fatigue level that may be present. This fatigue level could be due to factors other than degree of lesions in the brain.

(b) Auditory Attention

The MS group were significantly impaired with regard to Auditory Attention ability and this dysfunction was demonstrated to be related to increased amount of brain lesions. This result is supportive of the findings in a recent study (Rao et al, 1989a). The CIL group's performance was similar to that of the MS group: CIL patients were significantly impaired with regard to Auditory Attention ability and this dysfunction was

demonstrated to be related to higher MRI lesions. Fifty-six percent of the MS group and fifty-one percent of the CIL group scored within the Poor and Deficient grades for Auditory Attention ability, while only twenty-two percent of the Controls performed at these deficient levels. This result would seem to demonstrate that impairment in auditory attention is a strong feature in MS patients and one that, if the CIL group are hypothesised to represent an early stage of MS, manifests itself early on in the disease. Furthermore, this dysfunction in auditory attention would seem to be directly related to the amount of lesions present in the brain: it cannot be related directly to physical ability as the Auditory Attention task did not require motor involvement and the CIL group were not impaired to a great extent with regard to motor ability.

The present study's results on Auditory Attention, it's independence of disability level, and it's correlation with MRI are supportive of the findings published in a recent study on attentional deficits in MS (Rao et al, 1989a).

(5) Naming Ability

Reports of focal lesions producing language dysfunction in MS are rare and confounded by the absence of pathological confirmation of MS and the validity of the diagnostic

criteria employed. Jambor's study, in 1969, was not a systematic investigation of language function in MS patients but did conclude that naming ability was impaired in that sample of MS patients. Jambor's MS sample was restricted to persons under the age of 40 and the present study attempts to examine naming ability in a wider age range, in patients with a range of neurological severity. The present investigation demonstrates that nine percent of the MS group obtained deficient scores on an object naming task: the MS group, as a whole, did not differ significantly to the Controls on this measure.

The CIL group performed similarly to the MS group in that they did not differ to the Controls but a larger percentage of CIL patients obtained deficient scores: ten percent of CIL patients scored within the deficient range while only two percent of the Control group did the same.

The present findings would seem to suggest that object naming ability is not a sensitive measure for the population of patients with MS or with CIL, but nevertheless, a small percentage of such patients do present with impairment of this naming function. This result highlights the need to examine patients in greater numbers who represent a range of MS factors such as neurological severity, disease progression and age. In 1985 Heaton and colleagues suggested that language

dysfunction seemed to occur in patients with chronic-progressive MS only; the present study does not confirm this result though a systematic investigation of language dysfunction is necessary to be more conclusive. A recent study examined expressive language function in definite MS and probable MS patients and concludes that two MRI measures, Total Lesion Area and size of the Corpus Callosum, were good predictors of this expressive language dysfunction (Rao et al, 1989a).

Although the results in the present study suggest that object naming ability correlates with lesions in the brain for the MS group, those MS individuals with deficient object naming scores have the lowest mean lesion score when compared to the rest of the group.

No relationship between object naming and lesion score was demonstrated within the CIL group. Dysfunction in naming ability, and it's relationship to degree of brain lesions, in MS patients and patients with CIL has yet to be firmly demonstrated.

Discussion of object naming ability in patients with MS and in the CIL group is not complete in the present study without examination of the dimension of speed. Object naming latencies were measured for the present groups and will be discussed below.

3. DISCUSSION OF COGNITIVE EFFICIENCY

Seven cognitive measures were obtained on the three groups in the present study, covering a wide range of neuropsychological functioning. Each individual's performance on each function measure was assigned a 'Grade' based on set percentile levels of the results of the Control group: **Grade 0** indicates the **'Best'** performance level and **Grade 3** indicates the **'Worst'**. Each function, therefore, had a single index score which was comparable to the single index scores of all the other function measures. This enabled the investigator to examine two important factors: firstly, the pattern of deficit within each group; and secondly, by summing the seven function 'Grades' for each individual and obtaining a single overall score, the overall cognitive efficiency of each group. No previous studies known to the investigator have examined the functioning of MS patients with these methods.

The pattern of deficit within each group will be discussed below in the General Discussion.

The second important factor to be discussed is the overall cognitive efficiency of each group. Level of cognitive efficiency, as measured in the present study, quantitatively distinguishes between the two experimental groups, MS and CIL. The group with the highest Cognitive

Efficiency Score, and therefore the poorest overall cognitive efficiency, was the MS group. The MS patients' cognitive efficiency was demonstrated to be poorer than that of the CIL patients and significantly poorer than that of the Controls. The cognitive efficiency of the CIL group was significantly poorer than that of the Controls; this finding places their performance level between that of the MS group and that of the Controls.

The reduced cognitive efficiency of the MS group was demonstrated to be related to increased amount of brain lesions. This finding confirms the conclusion made in a recently published study (Rao et al, 1989a) where a relationship between overall cognitive efficiency and MRI measures was presented. Furthermore, the cognitive efficiency of the MS group in the present investigation was demonstrated to be related to number of years of active disease, though MS patients who were in relapse at the time of testing did not have poorer scores than those MS patients who were not in relapse.

Rao et al's recent study (1989a) concludes that cognitive dysfunction was independent of disease course and duration of illness. However, it is not clear what was measured to represent 'duration of illness'; if it was length of time since diagnosis then it is a different measure to the one used in the present study for 'years of active disease'.

The present study's findings suggest that number of years of active disease, that is the number of 12-month periods during which relapse or evidence of a further episode/s of disease activity was recorded, is related to cognitive efficiency in patients with definite MS.

Increased MRI lesions in the brain may affect the number of episodes of disease activity, and also would seem to increase the likelihood of reduced cognitive efficiency. MS patients are not, it seems, cognitively INefficient when in relapse, but likely to be less efficient cognitively the more years of active disease they have had. It is suggested that reduced cognitive efficiency in MS patients may be the result of cumulative damage in the brain, which may be manifested by increased disease activity.

Although the psychiatric data in the present study confirm the presence of psychiatric problems in some patients with MS, it was demonstrated that reduced cognitive efficiency was not related to any psychiatric factor. In previous research certain test components have been omitted in the study of MS patients because the test was thought to be sensitive to the presence of anxiety (Peyser et al, 1980): present findings, which include the same test previously omitted by researchers, do not demonstrate a difference between those MS patients assessed as 'anxious' and those

MS patients assessed as not anxious. Furthermore, fatigue was demonstrated to be unrelated to the overall level of cognitive efficiency in the present group of MS patients.

Previous research presents evidence that, in the MS population, motor impairment is related to reduced cognitive efficiency with regard to IQ (Goldstein and Shelley, 1974) and with regard to memory (Beatty and Gange, 1977). However, other previous studies conclude that severity of disability was not correlated with cognitive efficiency, especially with regard to IQ (Marsh, 1980). The present findings with regard to the MS group confirm a strong correlation between cognitive efficiency and motor disability and so would seem to confirm the conclusions of the Goldstein and Shelley (1974) investigation. A comparison was made, therefore, in the present group of MS patients between the cognitive efficiency of those who were assessed as disabled and the cognitive efficiency of those assessed as physically able: no difference was found. The MS group's cognitive efficiency was not, it seems, causally related to motor ability: a finding that confirms the work of Marsh (1980) and the conclusions of a more recent study by Rao et al (1989a).

As both cognitive and motor efficiency were demonstrated to be related to degree of MRI lesions within the present

MS group, it is suggested that these two ability levels are equally affected by amount of brain lesions. This hypothesis would support the possibilities raised by Beatty and Gange in their study in 1977 with regard to memory and motor ability.

The cognitive efficiency of the CIL group was not demonstrated to be related to degree of lesions in the brain; nor were number of years of active disease or exacerbation status at the time of testing correlated with level of cognitive efficiency. Psychiatric factors and fatigue were also eliminated and demonstrated to have no effect on the cognitive efficiency of the CIL group. The main factor that remains significant is poor physical ability: those CIL patients who were physically disabled (N=5) had reduced cognitive efficiency. These results are particularly interesting in the light of the fact that the CIL group as a whole were not impaired on Motor Ability. It would seem that the very small percentage of CIL patients who were physically disabled represent a group that are more impaired overall.

The cognitive efficiency level of each subject was graded according to the percentile results of the Control group as described previously: this enabled examination of the percentage of individuals in each group performing at 'Poor' (Grade 2) or 'Deficient' (Grade 3) levels with

regard to overall cognitive efficiency.

The results in the present study are very similar to those found in previous research. Rao et al's (1989a) investigation concluded that 36% of their sample of MS patients presented as cognitively impaired; the present study's findings demonstrate that 34% of the MS group are deficient with regard to overall cognitive efficiency and a further 26% present with 'Poor' cognitive efficiency. Further confirmation of Rao et al's findings are demonstrated in the present study by the examination of Total Lesion score for those MS individuals within each cognitive efficiency grade: those MS patients with deficient cognitive efficiency have the highest Total Lesion scores.

Fifteen percent of the CIL group demonstrated deficient cognitive efficiency and this subgroup obtained the highest Total Lesion scores. A further 27% of the CIL group demonstrated 'Poor' cognitive efficiency and this subgroup obtained the second highest Total Lesion scores.

In Conclusion:

The present findings support the bulk of previous research demonstrating that patients with clinically definite MS present with impairment of intellectual functions, Visual Recognition Memory, Abstracting Ability and attentional

functions. It was further demonstrated that Verbal Recognition Memory and Naming Ability were intact in the present group of MS patients which confirms the findings of some previous studies. With the exception of Abstracting Ability and Visual Attention ability, cognitive impairment in the MS group was demonstrated to be associated with increased amount of lesions observed on MRI. The MS group's overall cognitive efficiency was significantly worse than the Controls', and poorer than the CIL patients', and this deficiency was related to higher brain lesion scores.

The present study suggests that the cognitive efficiency of the CIL group is on an intermediate level between that of the MS group and the Controls, as is their brain lesion score. While the CIL group's cognitive efficiency was not related to amount of MRI lesions it was, however, demonstrated that those CIL patients with reduced cognitive efficiency had more brain lesions and an association was observed with physical disability. This finding would seem to suggest that, if CIL patients represent an early stage in the disease of MS, those patients at this early stage who present with poor physical ability are more likely to demonstrate reduced cognitive efficiency. However, it must be noted that 42% of the CIL group had Poor or Deficient cognitive efficiency while only 10% of the group were disabled.

4. DISCUSSION OF SPEED OF COGNITION

The present study examined the response latencies on performance in memory and naming ability for all subjects. Latency measures were obtained in order to investigate the relationship between speed and accuracy for patients with MS and CIL. This is not known to have been attempted in any previous studies. Furthermore, response latencies allowed the examination of performance on a different dimension for abilities considered 'intact' in MS patients and whether this dimension of speed was a sensitive measure early in the disease process. Finally, there has been discussion in previous studies on the 'Cortical' versus 'Subcortical' dementia debate with regard to the disease of MS (Albert et al, 1974; Rao 1986; Caine et al 1986; and Filley et al, 1989) and measuring response latencies was considered of interest in the light of this and other previous research (Rao et al, 1989b). The 'Cortical' versus 'Subcortical' dementia issue will be discussed fully below in the General Discussion.

(a) Speed of Cognition

The MS group presented, in the present study, with significantly slower latencies on Verbal and Visual

Recognition Memory and Naming Ability. This finding is despite the fact that accuracy scores on Verbal Recognition Memory and Naming were similar to Controls'. Visual Recognition Memory latencies were significantly slower for the present MS group even on average, and above average, accuracy scores when compared to Controls'. This evidence of slowed cognition confirms previous research in MS (Rao et al, 1989b) but extends the finding to abilities that are considered, and measured, to be 'intact'.

CIL patients presented, in the present study, with significantly slower latencies on Visual Recognition Memory when compared to the Controls, despite similar accuracy scores on this measure. The CIL group's Visual Recognition Memory latencies were, in fact, similar to those of the MS group on average and above average accuracy scores. This finding suggests that slowed processing occurs in what might be early stages of the disease in patients with high lesion scores on MRI. Again, on both measures, MRI lesions and Visual Recognition Memory, the CIL group occupy an intermediate position in relation to the Controls and the MS group. With regard to Visual Recognition Memory the CIL patients are similar to the Controls on accuracy scores, and

similar to MS patients on the latency measure. Latency measures, not known to have been applied to this group of patients in previous research, would seem to be a sensitive measure in the early stages of a demyelinating disease.

Assessment of Visual Attention in the present study involves a timing process so attentional processes are considered in relation to speed of cognition. The CIL Group were not significantly different to the Controls on Visual Attention speeds and yet were significantly slower on Visual Recognition Memory. Furthermore, the CIL group were not significantly slower than the Controls on Naming Ability and Verbal Recognition Memory, yet obtained significantly worse Auditory Attention scores. It is suggested, therefore, that speed of cognition is different to attentional ability with regard to the measurements in the present study.

The findings in the present study suggest that cognitive speed is sensitive to the demyelinating process and would seem to be affected before accuracy of function is reduced. Within the CIL group it is demonstrated that speed of processing and accuracy of function is intact for

Verbal Recognition Memory and Naming Ability: however, at a much later stage, in individuals diagnosed with MS, speed of processing on both functions is adversely affected, while accuracy remains intact. With regard to Visual Recognition Memory, accuracy of function would seem to be reduced only at the later stage of the disease process (i.e. in MS patients) while speed of this function appears to be adversely affected in both the early (i.e. CIL group) and later stages of the disease process. Up to now, it is only accuracy that has ever been measured on Memory within this population.

(b) Relationship between Speed and Accuracy

The relationship between speed and accuracy in patients with MS is not well understood. It has been demonstrated that the time taken for normal adult subjects to name pictures of objects was linearly related to the frequency of the object-names in print (Oldfield and Wingfield, 1964; and 1965) and this result was also reported for patients with localised cerebral lesions (Newcombe et al, 1964) and dementing patients (Barker and Lawson, 1968). These previous findings suggest that the aphasic group differed only in degree from that of the normal group.

The present study's findings suggest that MS patients' accuracy scores on memory and naming ability are related to their response latencies. It is not possible to conclude, however, that this relationship is a function of word frequency in the present study as the object-names used in the Naming Ability test are all of low frequency. Furthermore, the words used in the Verbal Recognition Memory test are all of high frequency, and there are no words employed in the Visual Recognition Memory Test.

With regard to the MS population, it is perhaps of more interest to examine this relationship between speed and accuracy in more detail, disregarding, within the objectives of the present study, the role that word frequency has to play. The relationship between speed and accuracy within the MS group suggests that those patients with the highest accuracy had the quickest response latencies, though there were exceptions to this as will be discussed below.

This finding with regard to the present MS group was not demonstrated for the present group of Controls: the control group's accuracy scores on Naming Ability did not significantly correlate with their response latencies on

that measure (perhaps because the word frequency was similar across all object-names, see above). As both the MS group and the controls did not differ on the accuracy of naming ability, this finding cannot by explained by overall poor accuracy on the part of the MS group: this result may, therefore, be a factor of slowed processing within the MS group.

The relationship between speed and accuracy in patients with CIL in the present study is somewhat different to the pattern demonstrated in the MS group and in the Controls. CIL patients' accuracy scores on naming were related to the response latencies for that measure; this finding is similar to that demonstrated within the MS group but different to that of the Controls. Accuracy scores on naming, as stated above, are similar for the three groups; suggesting that slowed processing is also a factor in the CIL group's performance on naming ability.

With regard to Verbal and Visual Recognition Memory, however, the CIL group's accuracy was not related to their respective latency measures: a different result to that demonstrated within the MS group and within the Controls. What these findings signify may be clarified by a closer

examination of the interaction between accuracy and speed within each group.

The present study, therefore, examined the interaction between accuracy and speed, via a grading procedure based on the Control group's quartiles, in order to elucidate the patterns observed within each group. It was demonstrated that the interaction between accuracy and speed on memory and naming were different for the three groups. Most of the MS group, despite comparable accuracy scores on Verbal Recognition Memory and Naming Ability, cluster around the 'slow' speed categories. Again, the CIL group hold an intermediate position with regard to these analyses: CIL patients cluster around the 'slow' speed categories to a lesser degree when compared to the MS patients but to a greater degree when compared to the Controls on Verbal Recognition Memory.

Dissociation between speed and accuracy was observed: it was demonstrated that more MS individuals had accurate scores accompanied by slow latencies on naming and Verbal Recognition Memory. It would seem that, with regard to functions demonstrated as 'intact' within the MS group, there is evidence, nevertheless, of slowed processing.

This deficit with respect to speed is definite but may only be detected with careful neuropsychological examination of the kind undertaken in the present study. Slowed processing in MS patients has been reported in previous studies (Elsass and Zeeburg, 1983; Carroll et al, 1984; Rao et al, 1989b) but has either included a motor component in the tasks examined or did not examine the speed of memory processing and it's relationship to accuracy. The present study presents evidence of slowed processing in MS patients on functions considered and demonstrated to be intact. Furthermore, these findings are associated with high lesion scores on MRI for the MS patients.

The CIL group have significantly more individuals with accurate Visual Recognition Memory scores accompanied by slow latencies: these CIL patients also present with high lesion scores on MRI. Dissociation between speed and accuracy on Visual Recognition Memory is, therefore, demonstrated in CIL patients. It may be that in what might be considered to be the early stages of the disease process Visual Recognition Memory deficits are more subtle and related to speed of processing and dissociation between speed and accuracy, rather than to clear and

demonstrable deficits in accuracy. Again, a follow-up investigation would help to clarify whether those CIL individuals with slowed cognitive processing go on to develop MS.

One further point of interest is that the only subject to obtain accurate but slow responses on all three functions (Verbal and Visual Recognition Memory and Naming) is a CIL patient whose MRI was considered normal. Follow-up of this particular individual would be of great interest; were environmental factors operating during the present assessment? Or was the present cognitive assessment detecting dysfunction before detectable lesions could be observed on MRI?

There is some evidence in the present study to suggest that slowed processing accompanied by high accuracy may be specific to certain functions and not necessarily a general deficit for all MS patients. None of the MS group had highly accurate but slow responses on all three measures examined in the present study. Furthermore, ten MS individuals (17.3%) had highly accurate scores accompanied by slow latencies on Verbal Recognition Memory only, and not on the other two functions measured in this

way. Similarly, four MS individuals (6.9%) were accurate but slow **only** on the naming task, and two (3.5%) were accurate but slow **only** on the Visual Recognition Memory task. These individuals represent a small percentage of the whole group; however, the finding may be of important heuristic value. The highest brain lesion scores were observed for those MS patients with accurate but slow responses on Naming and Verbal Recognition Memory: this finding suggests that disease activity within the brain does have an effect on functions considered by the bulk of previous research to be 'intact' in this group (Goldstein and Shelley, 1974; Staples and Lincoln, 1979; Elpern et al, 1984; Carroll et al, 1984; Rao et al, 1984).

In Conclusion:

The present study examined the response latencies on performance in memory and naming ability for all subjects. The findings indicate that slowed cognitive processing is a feature of MS confirming previous research (Rao et al, 1989b) and further, demonstrating slowness on functions generally considered intact in MS. Dissociation between speed and accuracy was observed for some MS patients and this was associated with high brain lesion scores.

The present CIL group demonstrated slowed cognitive processing with regard to Visual Recognition Memory functions, and dissociation between speed and accuracy was also observed on this measure for CIL patients.

It is further suggested that reduced cognitive speed, on Visual Recognition Memory in particular, may be a precursor, in the demyelinating disease under consideration, to reduced speed **and** reduced accuracy of function. Measuring cognitive speed is suggested to be a sensitive measure at all stages of the demyelinating disease process.

Conclusions on Discussion of Results with Regard to Cognitive Efficiency and Speed of Cognition

The present study's findings support the bulk of previous research demonstrating cognitive deficits in patients with MS. In addition, cognitive deficits were demonstrated in CIL patients. Cognitive speed was examined in a way not known to have been previously attempted: slowed cognitive processing was observed in patients with MS and in CIL patients.

The main differences on cognitive function accuracy between the experimental groups occurred in relation to Visual Recognition Memory and Abstracting Ability. However, CIL patients demonstrated similar slowed response latencies on Visual Recognition Memory when compared to patients with MS. The present findings do not demonstrate reduced speed for CIL patients in either Verbal Recognition Memory or in Naming Ability.

In general, the cognitive efficiency and cognitive speed of CIL patients is intermediate in relation to MS patients and Controls. This finding might be seen to support the notion that CIL disorders represent an early stage in the demyelinating process of MS, though follow-up and further detailed research would be more conclusive in this regard. It is suggested that if CIL patients do represent an early stage in the disease of MS, then those CIL patients with reduced physical ability, reduced Auditory Attention, poor Visual Attention and slowed Visual Recognition Memory are more likely to go on to develop MS: firstly, poor physical ability is associated with reduced cognitive efficiency for CIL patients and, in addition, poor attentional ability and slowed Visual Recognition Memory was demonstrated within this group. Secondly, these same

dysfunctions are observed to a greater degree in the present MS group. Further research, via follow-up studies, may clarify whether these dysfunctions in CIL patients are predictive of later development of MS.

5. GENERAL DISCUSSION

The range of neurological severity within the disease of MS, from the concept of 'benign' MS where no neurological disease was suspected in life, to the severe chronic-progressive MS accompanied by severe physical disability, would seem to require a particular investigative approach. The neuropsychological approach to investigating the disease of MS had, until relatively recently, tended to exclude MS patients that came into categories at either end of the spectrum of severity. This was to exclude patients with severe disability, a factor that might confound test results; and patients with 'unsuspected' or 'benign' MS were generally identified at postmortem studies which, of course, necessarily excluded them.

The present approach attempted to examine a range of demyelinating disease by studying patients with conditions that are thought to be possible precursors of MS and also patients with MS that represent as wide a range of neurological severity as possible.

MRI of patients with MS demonstrates widespread, diffuse and bilateral lesions that may be in different stages of evolution. Therefore, a neuropsychological approach that attempts to correlate specific deficits with localised lesion sites is not likely to meet with great success: to be conclusive about the effect of a particular lesion on any discrete cognitive function is very difficult given the presence of other widespread lesions in the brain, combined with the general finding of the presence of other cognitive deficits which may confound efficiency on any one psychometric measure. A recent related study suggests that recording event-related potentials may play a useful complementary role in the cognitive assessment of patients with MS (Newton et al, 1989) and future research could also address this issue.

The present neuropsychological investigation covers a wide range of cognitive function, including speed of memory and naming, in an attempt to clarify some of the contradictory evidence in the MS literature, with regard to recognition memory for example; and to examine the debate on 'Cortical' versus 'Subcortical' dementia in MS which is discussed fully below. Furthermore, as MS patients were not amenable to analysis that would examine localised

lesions with corresponding selective deficits, one of the objectives of the present study was to obtain an overall measure of cognitive efficiency that could be correlated with overall MRI lesions and provide information with regard to the number of individuals functioning at particular levels of ability. Vigorous attempts to take into account possible confounding variables such as age, sex, premorbid intellectual functioning, attentional level, psychiatric state, physical disability, visual acuity and fatigue were made. This was done by means of a matched control group and psychiatric and physical assessments on all subjects.

Factors such as age, sex, winter onset and the presence of oligoclonal bands in CSF in Optic Neuritis patients are proposed to be related to an increase in the risk of this group to go on to develop MS. The CIL group in the present study included Brain Stem Disorder patients and Spinal Cord Syndrome patients, two other conditions considered to be possible precursors of MS, and the present findings suggest that there may be cognitive factors that are predictive of disease progression. At this early stage of demyelinating disease, the question is whether CIL patients present with a cognitive deficit

pattern that is similar, albeit to a lesser degree of dysfunction, to that demonstrated in the present MS group.

A recently published study (Rao et al, 1989a) administered a large and wide battery of neuropsychological tests to a sample of 53 patients with a diagnosis of definite or probable MS and concluded that 36% of this MS sample were cognitively impaired. A statistical clustering method was employed in Rao et al's (1989a) study to divide the subject sample into those considered 'intact' cognitively and those considered cognitively 'impaired': the cognitive functions measured were examined in relation to MRI measures via the statistical method of regression analysis.

The methods used in the present study make possible the examination of each function measure separately in terms of what percentage of the group are dysfunctional and allow one to comment on the precise pattern of deficit observed with regard to both groups.

(1) <u>Pattern of Deficit Within CIL and MS Groups</u>

With regard to the pattern of deficit within the MS group, and within the CIL group, one can look at the percentage

of each group scoring in the two poorest grades (Grades 2 + 3: scores at or below the 25th percentile) for each function measure and observe which function the group performs best and which function the group performs least well.

The largest percentage of MS individuals performing in the two poorest Grades occurs on the Visual Attention task (70%) while for the CIL group the largest percentage performing poorly is on the Auditory Attention task (51.1%). However, it is interesting to note that performance on the IQ Deficit measure is very poor within both groups (60.7% of MS and 39.6% of CIL in Grades 2 + 3) when compared to each respective group's performance on the other measures, and performance on the Verbal Recognition Memory (28.6% of MS and 27.1% of CIL) and Naming Ability (25.5% of MS and 25% of CIL) measures are best within both groups.

There is a similarity then in the pattern of deficit demonstrated by the MS and the CIL groups: in fact, while performance on the Auditory Attention task is the CIL group's worst attainment level (51.1% in Grades 2 + 3) when compared to the other function measures, the

percentage of MS individuals scoring within these grades for Auditory Attention is very similar (56.6%).

The main differences between the two experimental groups that can be observed are with regard to Recognition Visual Memory (accuracy only), on which the MS group are impaired and the CIL group are not, and Abstracting Ability, on which, again, the MS group are impaired and the CIL group are not.

It is suggested that accuracy of Visual Recognition Memory and Abstracting Ability are likely to be affected only in the later stages of the disease process, or only mildly impaired in the early stages. This suggestion is based on the hypothesis that a portion of the CIL group represent an early stage in the disease of MS. Furthermore, the suggestion made would seem to be supported by the finding in the present study that, within the MS group Visual Recognition Memory (accuracy) was found to be significantly related to amount of MRI lesions and also significantly related to number of years of active disease. The CIL group had a significantly lower brain lesion score and significantly lower number of years of active disease.

MS patients with deficient Abstracting Ability did have the highest brain lesion scores and within the CIL group performance on the Abstracting Ability task was demonstrated to be related to MRI lesions. Therefore, the CIL group, given the lower lesion scores and lower number of years of active disease when compared to MS patients, might not be expected to obtain deficient scores on tasks that were demonstrated to be strongly related to both factors.

To be more conclusive with regard to the role of certain factors within the functioning of the CIL group, it is recommended that this group of CIL individuals be the subject group of a follow up investigation in order to establish the progress of neurological status and to re-test cognitive functioning. This proposed follow up investigation on the present CIL group may also clarify the present pattern of deficit and whether this pattern provides predictive information with regard to possible disease progression.

Accuracy of naming ability would seem to be intact for patients with CIL or with MS: dysfunction on naming accuracy and it's relationship to lesions measured on MRI

have yet to be firmly demonstrated. As argued in the introduction to this thesis, the MS research literature with regard to naming ability is either nonexistent or rather contradictory. Naming ability is intact in the present MS group, but the time taken to name an object is much longer than for Controls. This slowed cognitive processing is associated with increased number of brain lesions on MRI. Within the CIL group both accuracy and speed of Naming Ability is intact. At this stage of the disease process, neither the speed nor the accuracy of Naming Ability would seem to be a sensitive measure.

Recognition memory in MS research literature is also rather contradictory in that some studies suggest that it is impaired and other studies conclude that it is relatively intact. The present study suggests that recognition memory is affected, and that this dysfunction must be distinguished in terms of the type of deficit and the nature of the stimuli. Visual recognition memory is deficient with regard to accuracy and speed in the present MS group, and this is associated with lesions observed on MRI of the brain. Verbal recognition memory is also associated with MRI lesions in the MS Group, but the effect seems to be with regard to the speed of cognitive

processing and not in respect of accuracy. As deficits in memory speed may be too subtle to detect with the usual range of neuropsychological assessments, this may be the reason why it appears to have been overlooked in MS research up to now. This may account for some of the contradictory findings in the MS literature to date. Furthermore, the present results do not indicate that memory impairment is only a feature for patients with chronic-progressive MS, though it may be that memory is impaired for this group to a greater degree. Future research is needed to be more conclusive on this matter and to clarify the issue.

The disease of MS is frequently characterised by physical disability and this has been demonstrated to be related to a number of cognitive dysfunctions including intellectual deficits and memory deficits. Present findings do not support an association between intellectual deficits and physical disability, but confirm that MS patients with deficient verbal and visual recognition memory are more physically disabled. This is despite the fact that the present memory assessments did not require any motor involvement in their procedures. Such findings support previous suggestions that memory and motor functions are

equally vulnerable to the demyelination process: both memory and motor functions were demonstrated to be associated with increased lesions measured on MRI for MS patients.

With regard to CIL patients, it is of interest to note that those who are physically disabled, albeit a small number, do have reduced cognitive efficiency: so a similarity with the pattern demonstrated within the MS group is observed in this regard.

Attentional deficits are confirmed in patients with MS, and would seem to be related to disease progression. Auditory attention is deficient in patients in the early (CIL syndromes) and later (MS) stages of the demyelination process. This is supported by the finding that deficient auditory attention is related to increased number of lesions on MRI for patients with MS and CIL patients. However, visual attention deficit would seem to be a feature only of the later stages of the disease: significantly more CIL patients presented with poor visual attention when compared to the Controls' but MS patients demonstrated a greater degree of dysfunction on Visual Attention. Furthermore, the relationship between visual

attention and lesions on MRI is not established. Attentional deficits in the demyelination process may, therefore, be distinguished in terms of the modality of the stimuli and the stage of the patient in the disease process.

Overall cognitive efficiency is reduced even at the early stages of the disease process (CIL syndrome) and would seem to get progressively worse as the disease progresses (MS). Furthermore, in what might be considered to be the early stages of the disease, cognitive efficiency is not strongly related to lesion presentation on MRI but is associated with physical disability; although many more CIL patients were cognitively deficient than were physically disabled. As the disease progresses so cognitive efficiency deteriorates and is demonstrated, in patients with MS, to be related to increased lesions on MRI. Present findings demonstrate that a significant percentage of patients with MS present with deficient cognitive efficiency and this would seem to be independent of any factor other than the presence and number of lesions detected in the brain on MRI.

In summary, factors such as poor intellectual functioning, deficient auditory attention, poor visual attention and slowed visual recognition memory are present in the CIL group and in the MS group. Furthermore, accuracy of naming ability and verbal recognition memory are intact for both groups. The MS group have, in addition, deficits in accuracy of visual recognition memory and abstracting ability; and slowed processing in Verbal Recognition Memory and Naming Ability. This would seem to support the notion that MS patients are further on in the same disease process: indeed the relationship between accuracy of visual recognition memory and years of active disease would seem to support the proposal that this cognitive function deteriorates with disease progression. Although this suggestion is not borne out by recent research in the area (Rao et al, 1989a), it is possible that the measurement of disease duration is different in the present study.

(2) 'Cortical' versus 'Subcortical' Dementia Debate in MS

It has been suggested that because of the degree of cognitive deficit that has been demonstrated in MS patients, the term 'dementia' is an appropriate description for many patients with MS (Filley et al,

1989). The debate in previous research has addressed the issue of whether this 'dementia' is classified as 'Cortical' (that is, involving predominantly grey matter in the brain) or 'Subcortical' (involvement of white matter) (Rao et al, 1986). 'Cortical' dementia is used to describe disorders in which amnesia, aphasia, apraxia and agnosia are considered prominent features (Cummings et al, 1984). On the other hand, 'Subcortical' dementia is applied to conditions in which forgetfulness ("..not a true memory loss.. p.122), slowness, apathy and depression are predominant (Albert et al, 1974).

One explanation for the disturbance in timing within the MS group is that the disease of MS demonstrates lesions in the white matter on MRI; involvement of this brain area is considered to result in what is termed 'Subcortical' dementia, a disorder characterised by slow cognitive processing. It has been argued that the deficits observed in MS patients are consistent with deficits observed in disorders considered to be subsumed in the broad classification of subcortical dementia. The present study goes some way to supporting this argument: the present MS group demonstrate slow cognitive processing on all three of the cognitive functions that were timed. Furthermore,

subcortical dementia is considered to include the feature of "forgetfulness", while amnesia is subsumed under cortical dementia: the present MS group demonstrate intact accuracy of verbal recognition memory (though with slow response latencies) and deficient accuracy and speed on visual recognition memory.

Previous research has established a relationship between neuropsychological impairment and degree of white matter involvement demonstrated by MRI for patients with Chronic-Progressive MS (Filley et al, 1989; Franklin et al, 1989). Furthermore, a related study reported that MRI appearances in cases of dementia with Diffuse White Matter Disease resembled those of patients with advanced MS (Ormerod et al, 1984; and 1987). It is, therefore, suggested that patients with MS are likely to present with 'Subcortical' dementia. This suggestion has been put forward as being applicable to Chronic-Progressive MS patients, but the present study's findings apply to a group with a wider range of demyelinating disease.

Slowed processing is also observed in CIL patients but there is no suggestion that this group is 'dementing'; however, it may be that we can observe in this group

subtle deficits that resemble those of patients with 'Subcortical' dementia. Lesions in the white matter may be producing slowed responses in a group that is not neurologically impaired to the extent of warranting a diagnosis of MS. A related study (Ormerod et al, 1987) reported that over 50% of patients presenting with CIL had additional lesions on MRI at presentation. These increased signals on MRI in this group of CIL were, in the main, in the white matter of the brain.

The present study would seem then to support the notion that 'Subcortical' dementia, as characterised by slowed cognitive processing, is a feature of MS. Furthermore, it is suggested that this feature is usefully examined by means of a measure of response latencies on functions, regardless of whether those functions are generally considered 'intact' or not.

Examination of cognitive speed, therefore, seems to be of heuristic value in the 'Cortical' versus 'Subcortical' dementia debate in MS research. The present hypothesis, if correct, may predict the converse to be true in patients with predominantly cortical deficits: that poor or deficient accuracy scores would be accompanied by

normal latencies; for example, completing the memory or naming tasks within the Controls' normal speed range while obtaining deficient scores might be expected in patients with 'Cortical' dementia. Future research could address this issue of accuracy and it's relationship to speed in 'Cortical' dements.

In Conclusion:

The pattern of cognitive deficit would seem to be rather similar for CIL patients and MS patients, albeit the CIL Group are less dysfunctional overall. The main differences between the two groups are with regard to Visual Recognition Memory (accuracy) and Abstracting Ability. The explanation suggested to account for these differences is that these two functions are demonstrated to be strongly related to increased disease activity and/or amount of brain lesions, and so might not be expected to occur early in the disease process.

The present findings support previous research on the 'Cortical' versus 'Subcortical' dementia debate within MS: slowed processing may be related to white matter involvement and is observed in the present MS group. Subtle deficits in speed of cognitive processing have been

demonstrated and should form an important part of the focus of any future research in MS. Their clarification and detection are important in the management of MS, for the MS sufferer and his/her family. MS can have a number of so called 'hidden' features, for example - fatigue, tingling or numbness in limbs, which are particularly frustrating for MS sufferers who may not be well understood by significant others in their life. Subtle cognitive deficits are important to identify so that they do not form part of the burden of 'hidden' deficits for patients suffering with MS, and so that these cognitive deficits may be included in any management programs that are undertaken to help MS sufferers and their families.

The range of clinical severity in the disease of MS is reflected in the range of cognitive dysfunction demonstrated on assessment. It would appear that some degree of cumulative damage is operating on cognitive efficiency and longitudinal studies are recommended to be more conclusive. In addition, follow-up studies investigating the neurological status and cognitive efficiency of CIL patients may provide more conclusive results with regard to whether cognitive deficits predict disease progression, and which deficits have this predictive power, if any do.

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APPENDIX 1

OBSERVED AND EXPECTED FREQUENCIES FOR CHI SQUARE ANALYSIS ON ACCURACY AND SPEED

		NAMING ABILITY		VERBAL MEMORY		VISUAL MEMORY	
MS		Fast	Slow	Fast	Slow	Fast	Slow
50th% +	O	9	17	6	23	2	10
	E	9.25	9.25	14.6	14.6	12.8	12.8
25-50th%	O	4	10	0	7	0	9
	E	7.6	7.6	4.7	4.7	7	7
0-25th%	O	1	9	0	12	0	28
	E	8.15	8.15	4.7	4.7	4.8	4.8
CIL							
50th% +	O	18	6	8	17	2	17
	E	8.5	8.5	14	14	12	12
25-50th%	O	4	7	6	3	0	16
	E	7	7	4.5	4.5	6.5	6.5
0-25th%	O	2	9	3	9	0	11
	E	7.5	7.5	4.5	4.5	4.5	4.5
CONTROLS							
50TH% +	O	10	7	18	10	15	9
	E	8.5	8.5	14	14	12	12
25-50th%	O	7	7	3	6	6	7
	E	7	7	4.5	4.5	6.5	6.5
0-25th%	O	2	8	2	7	2	7
	E	7.5	7.5	4.5	4.5	4.5	4.5

APPENDIX 2

NUMBER OF INDIVIDUALS ON MEDICATION WITHIN EACH GROUP

	MS GROUP	CIL GROUP	CONTROL GROUP
STEROID	2	7	2
ANTISPASMODIC	5	4	NONE
ANTIDEPRESSANT	2	NONE	3
ANXIOLYTIC	6	2	1
Other Drugs*	29	12	27

* These were minor drugs available without prescription

APPENDIX 3

	MS		CIL		CONTROLS	
MEASURE	Mean	sd	Mean	sd	Mean	sd
Premorbid IQ	110.1	8.4	110.8	7.0	108.9	7.9
Full Scale IQ	103.7	12.2	108.5	9.9	109.7	9.9
Verbal IQ	105.1	12.1	109.7	10.6	109.4	11.2
Performance IQ	100.5	13.1	106.2	10.9	108.3	9.7
IQ Deficit	6.8	10.8	2.2	7.4	-.7	8.4
Subtests						
Arithmetic	10.8	3.0	11.9	2.9	11.6	2.8
Similarities	11.1	2.4	11.7	1.8	11.6	1.9
Digit Span	10.2	2.8	11.0	2.8	11.3	2.8
Vocabulary	11.5	2.0	11.7	1.9	11.5	1.6
Picture Comp.	10.0	2.6	10.8	2.2	10.7	2.1
Block Design	11.3	2.5	12.1	2.7	12.5	2.2
Picture Arr.	8.8	2.4	10.0	2.5	10.3	2.3

APPENDIX 4

	MS v. CIL		CIL v. CONTROLS		CONTROLS v. MS	
MEASURE	Z	p	Z	p	Z	p
subtests						
Arithmetic	2.3	.02*	.8	.42	1.2	.24
Similarities	1.3	.21	.12	.29	.73	.47
Digit Span	1.3	.2	.81	.42	1.94	.05*
Vocabulary	.37	.71	.19	.85	.02	.99
Picture Comp.	1.5	.12	.11	.91	1.2	.21
Block Design	1.1	.29	.88	.38	2.0	.04*
Picture Arr.	2.3	.02*	.61	.54	2.7	.007*

* p = statistically significant (DISABILITY NOT CONTROLLED FOR)

APPENDIX 5

p Values for CORRELATIONS within the DEFINITE MS GROUP - IQ and NMRI

	NMRI Measures						
MEASURE	Total Scan Score	Periv Score	Front Lobe	Temp Lobe	Front Score	Temp Score	Occip Score
Full Scale IQ	NS	NS	NS	.02	NS	NS	NS
Verbal IQ	NS	NS	NS	.04	NS	NS	NS
Performance IQ	NS	NS	NS	.01	NS	NS	NS
IQ Deficit	NS	NS	NS	.01	NS	NS	.05
subtests							
Similarities	NS	NS	NS	.03	NS	NS	NS
Digit Span	NS	NS	NS	NS	NS	NS	.03
Block Design	.03	.05	NS	.02	NS	.03	.003
Picture Arr.	.03	.01	.04	.008	.03	NS	NS
NS = NOT SIGNIFICANT							
No. Subjects with NO LESIONS in this AREA	1	2	15	52	8	23	11

APPENDIX 6

p Values for CORRELATIONS within the CIL GROUP - IQ and NMRI

	NMRI Measures					
MEASURE	Periv Score	Front Lobe	Temp Lobe	Pariet Lobe	Front Score	Temp Score
Full Scale IQ	NS	NS	NS	NS	NS	.04
Verbal IQ	.05	NS	NS	NS	NS	NS
Performance IQ	NS	NS	.05	NS	NS	NS
IQ Deficit	NS	.02	NS	.01	.02	NS
subtests						
Similarities	NS	NS	NS	.03	NS	NS
Picture Completion	NS	NS	NS	NS	NS	.04
NS = NOT SIGNIFICANT						
No. Subjects with NO LESIONS in this AREA	12	28	44	24	23	37

APPENDIX 7

p VALUES of CORRELATIONS between IQ MEASURES and PSYCHIATRIC RESULTS

DEF MS GROUP	CIS	CIS	CIS	CIS	BDI
MEASURE	Total Score	Fatigue	Anxiety	Elation	Depress
Full Scale IQ	.009	NS	NS	NS	.03
Verbal IQ	.007	NS	NS	NS	.007
Performance IQ	.04	NS	NS	NS	NS
Subtests					
Arithmetic	NS	NS	NS	NS	.05
Vocabulary	.05	NS	NS	NS	.03
Picture Comp.	.003	NS	NS	NS	NS
Block Design	NS	NS	.05	NS	NS

NS = Not Significant

APPENDIX 8

PERCENTAGE WITHIN EACH IQ GRADE ASSESSED AS 'NOT DEPRESSED'

	IQ GRADE			
GROUP	0-Good	1-Fair	2-Poor	3-Defic.
MS	90.9	70	76.2	88.9
CIL	85.7	100	92.3	100
CONTROL	95.8	91.7	100	100

APPENDIX 9

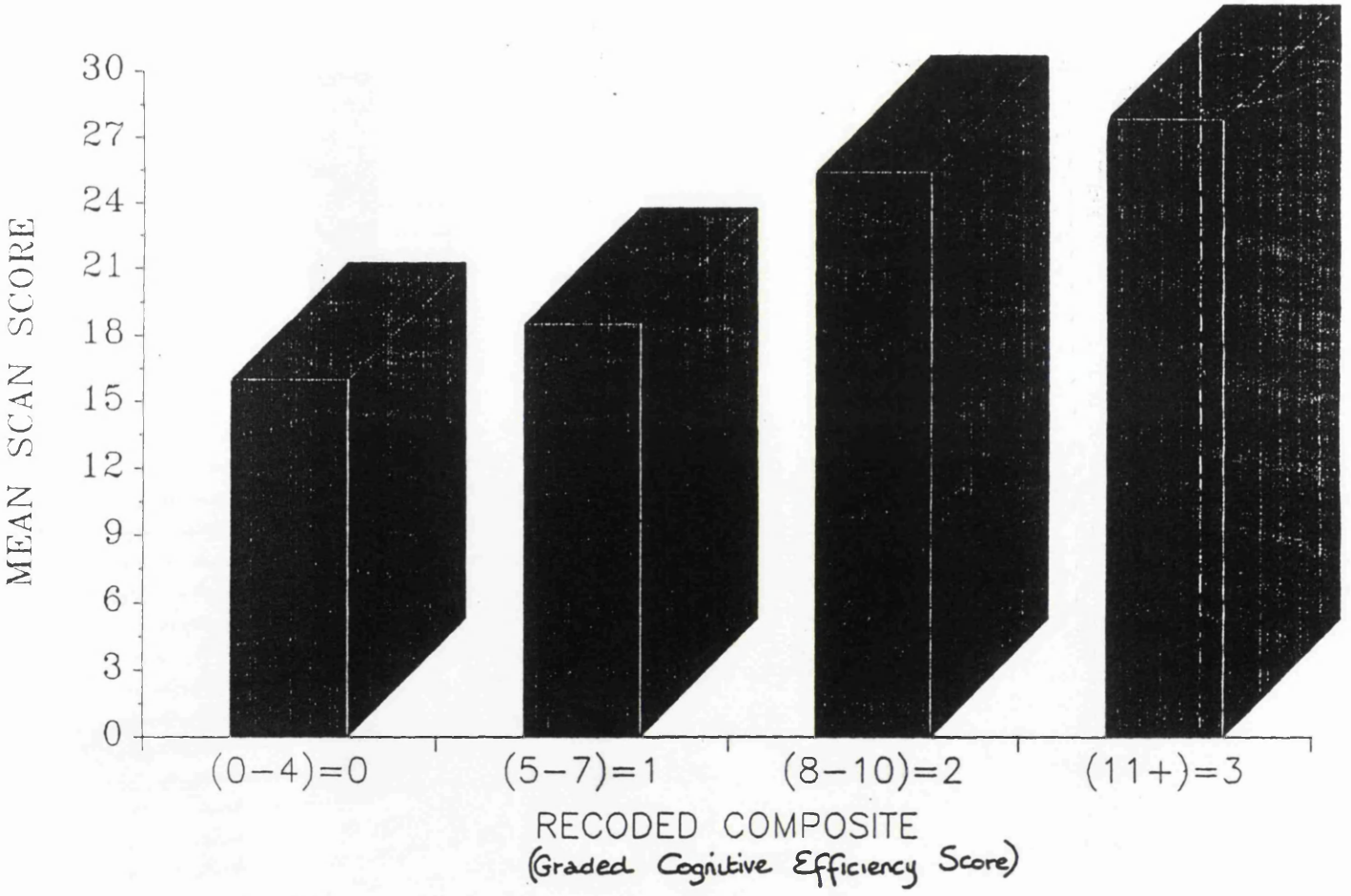
PERCENTAGE WITHIN EACH IQ GRADE THAT WERE NOT A 'CIS CASE'

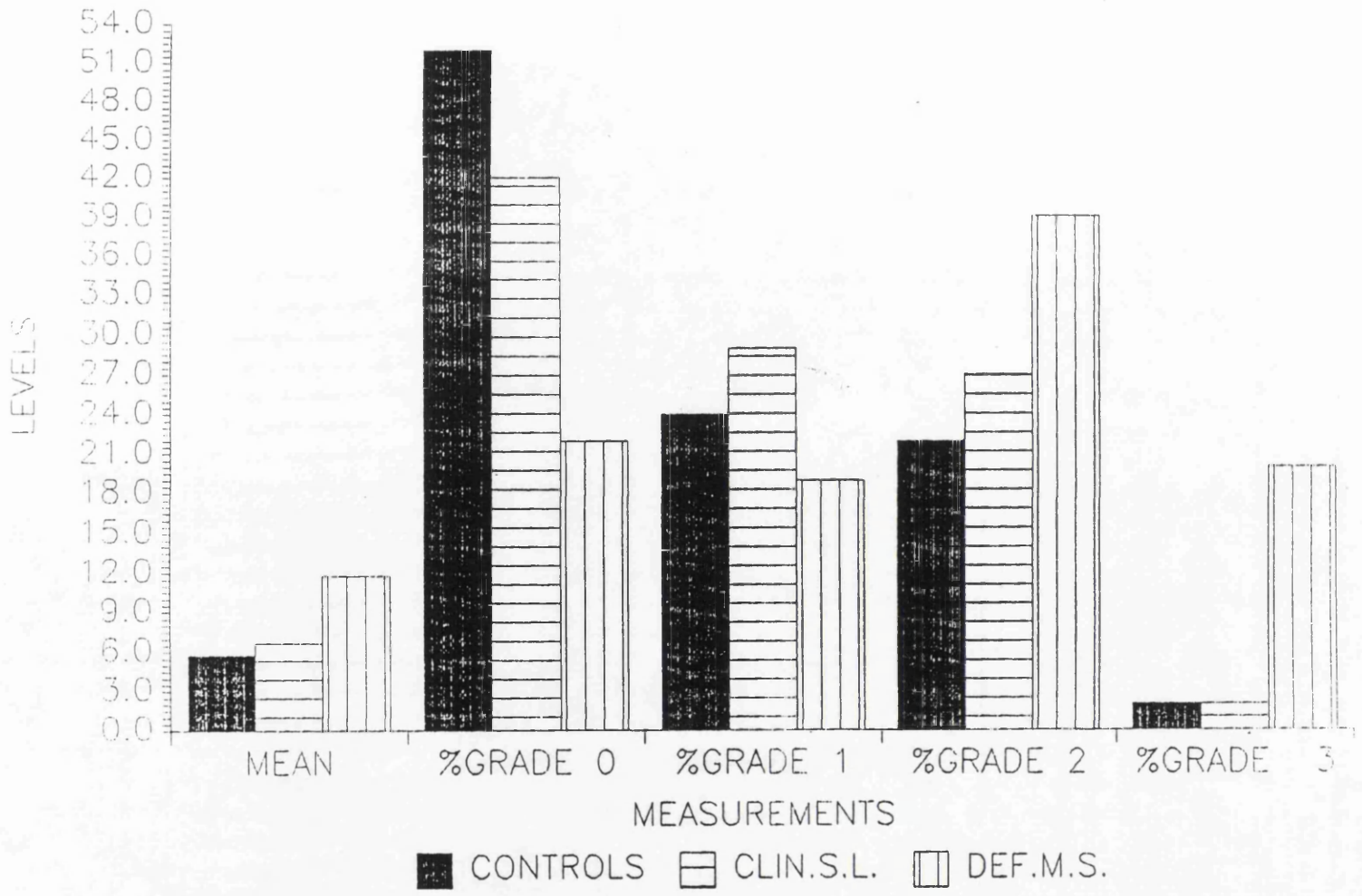
	IQ GRADE			
GROUP	0-Good	1-Fair	2-Poor	3-Defic.
MS	50	60	65.2	45.5
CIL	75	100	78.6	80
CONTROL	100	100	66.7	100

APPENDIX 10

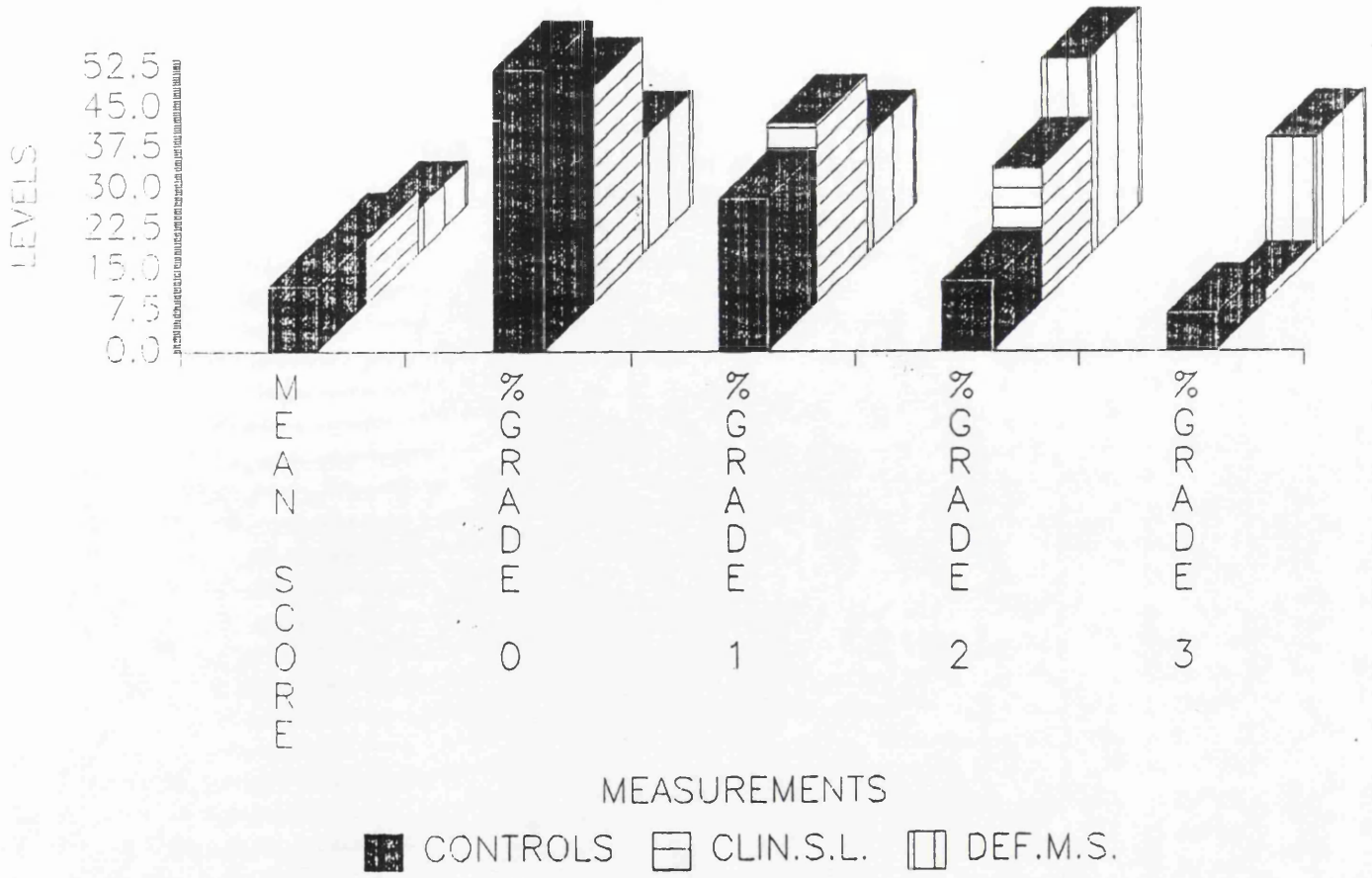
CIL GROUP	NORMAL SCAN		ABNORMAL SCAN	
	mean	std dev	mean	std dev
IQ DEFICIT	0.7	9.2	2.3	7.0
VERBAL MEMORY	12.3	1.9	12.1	2.6
VISUAL MEMORY	11.6	2.1	11.1	2.9
ABSTRACTING ABILITY	5.1	4.0	7.1	6.0
VISUAL ATTENTION	16.5	2.8	16.1	5.9
AUDITORY ATTENTION	1.7	1.0	2.3	3.2
NAMING ABILITY	20.4	5.1	22.2	3.8
OVERALL COGNITIVE ABILITY	7.1	2.4	7.2	3.5

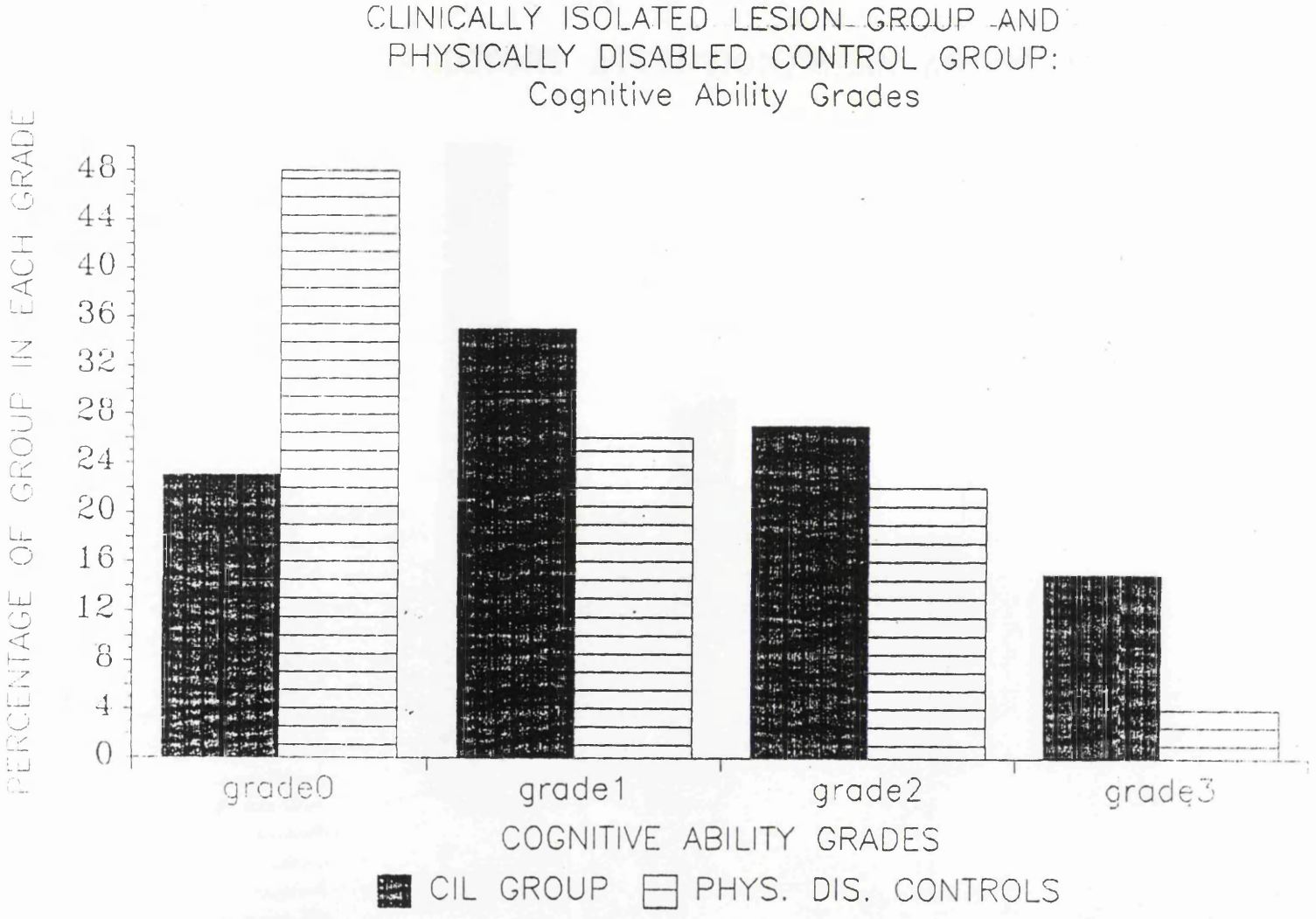
MEAN SCAN SCORE by RECODED COMPOSITE
DEFINITE MULTIPLE SCLEROSIS GROUP

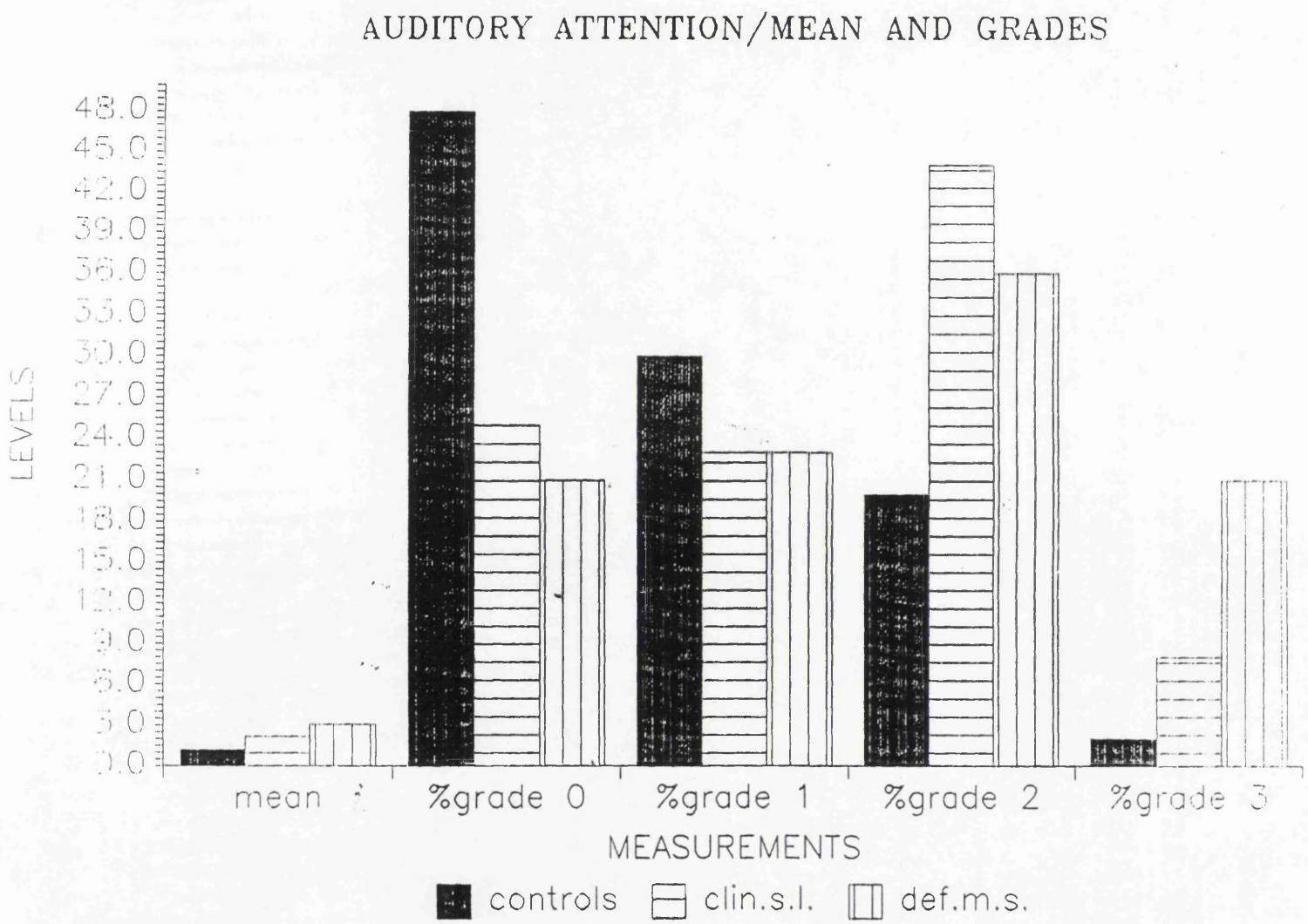


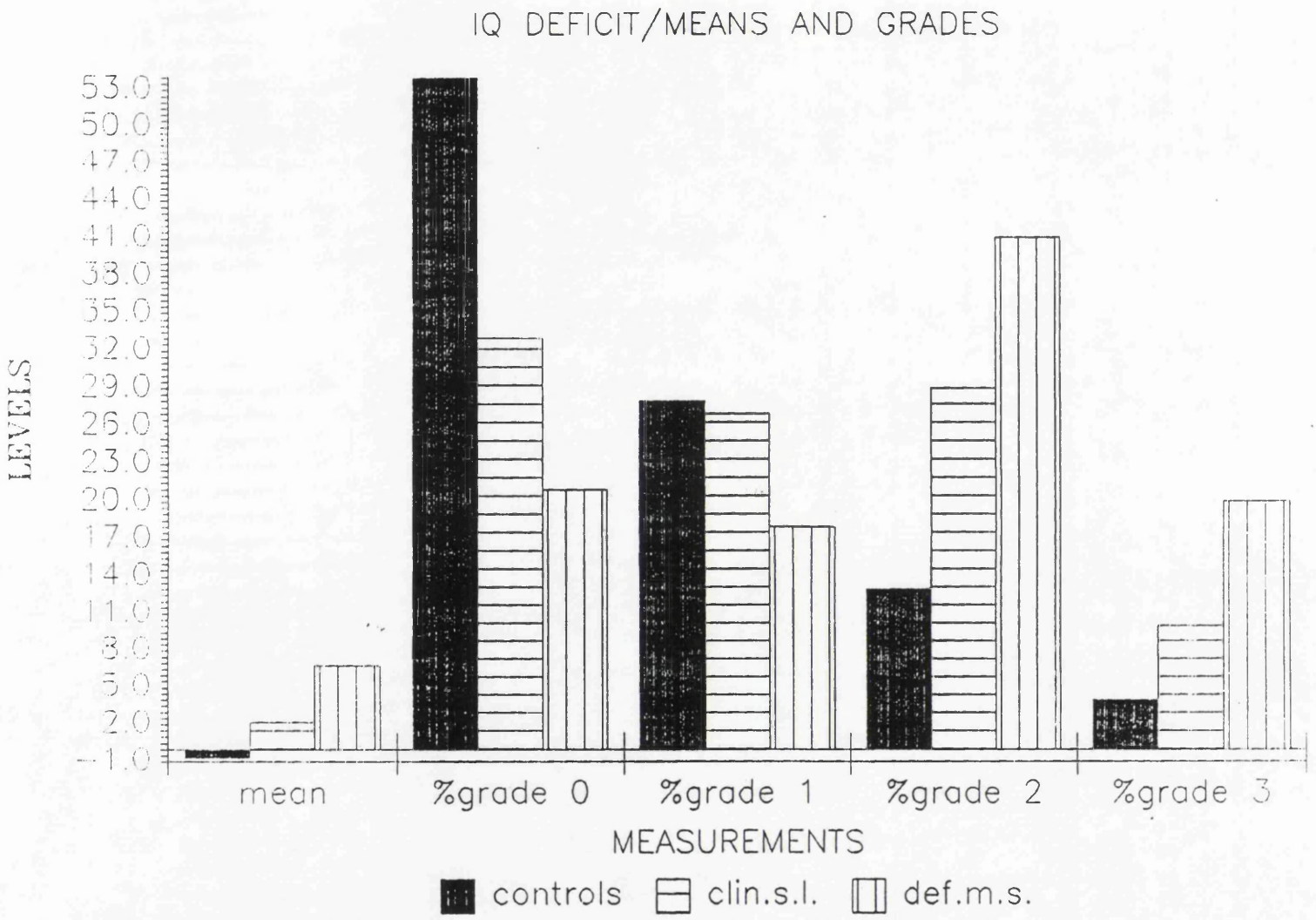

ABSTRACTING ABILITY/MEAN AND GRADES
LEVELS
54.0
51.0
48.0
45.0
42.0
39.0
36.0
33.0
30.0
27.0
24.0
21.0
18.0
15.0
12.0
9.0
6.0
3.0
0.0
MEAN
%GRADE 0
%GRADE 1
%GRADE 2
%GRADE 3
MEASUREMENTS
CONTROLS
CLIN.S.L.
DEF.M.S.

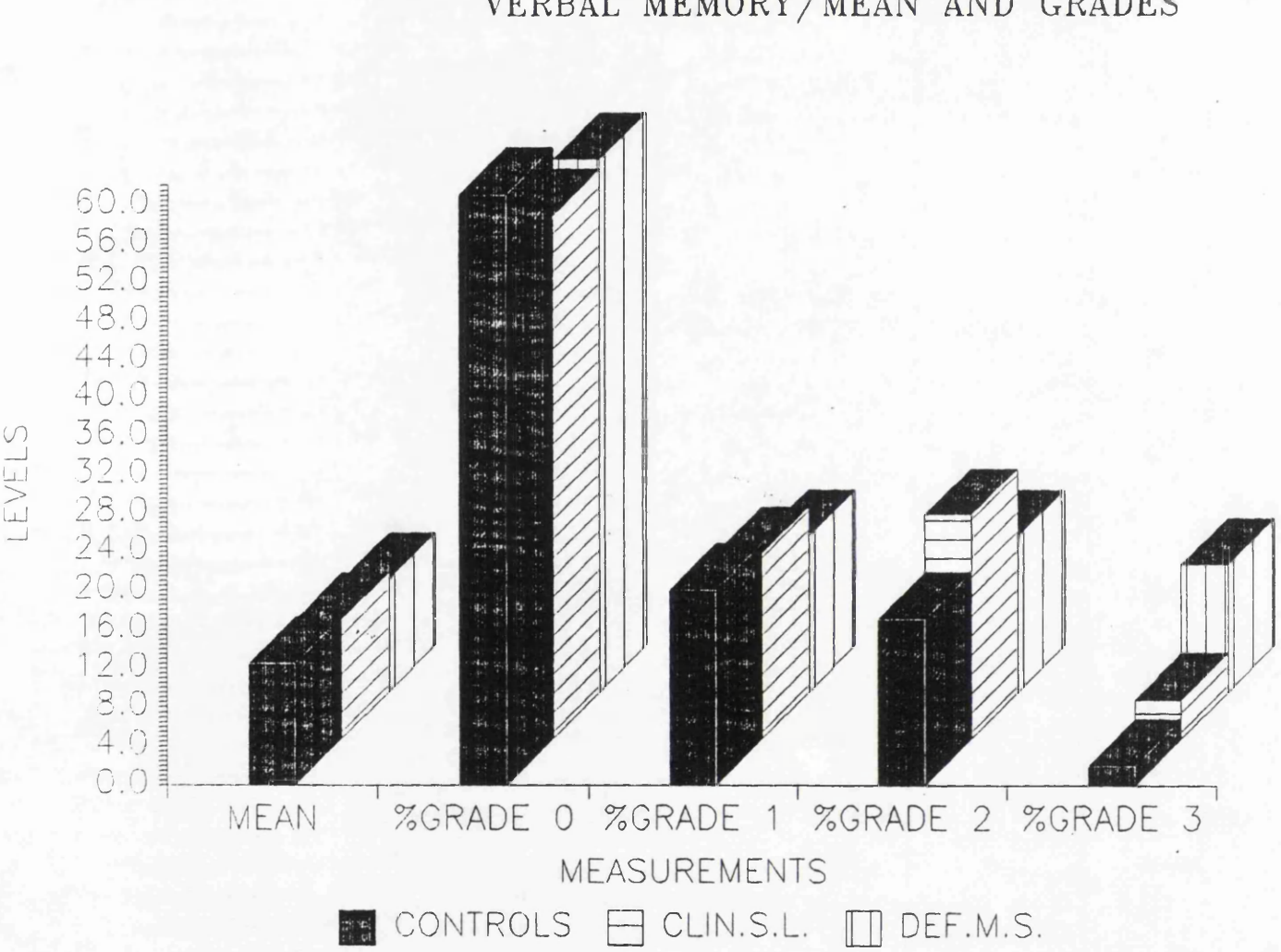
VISUAL MEMORY/MEAN AND GRADES



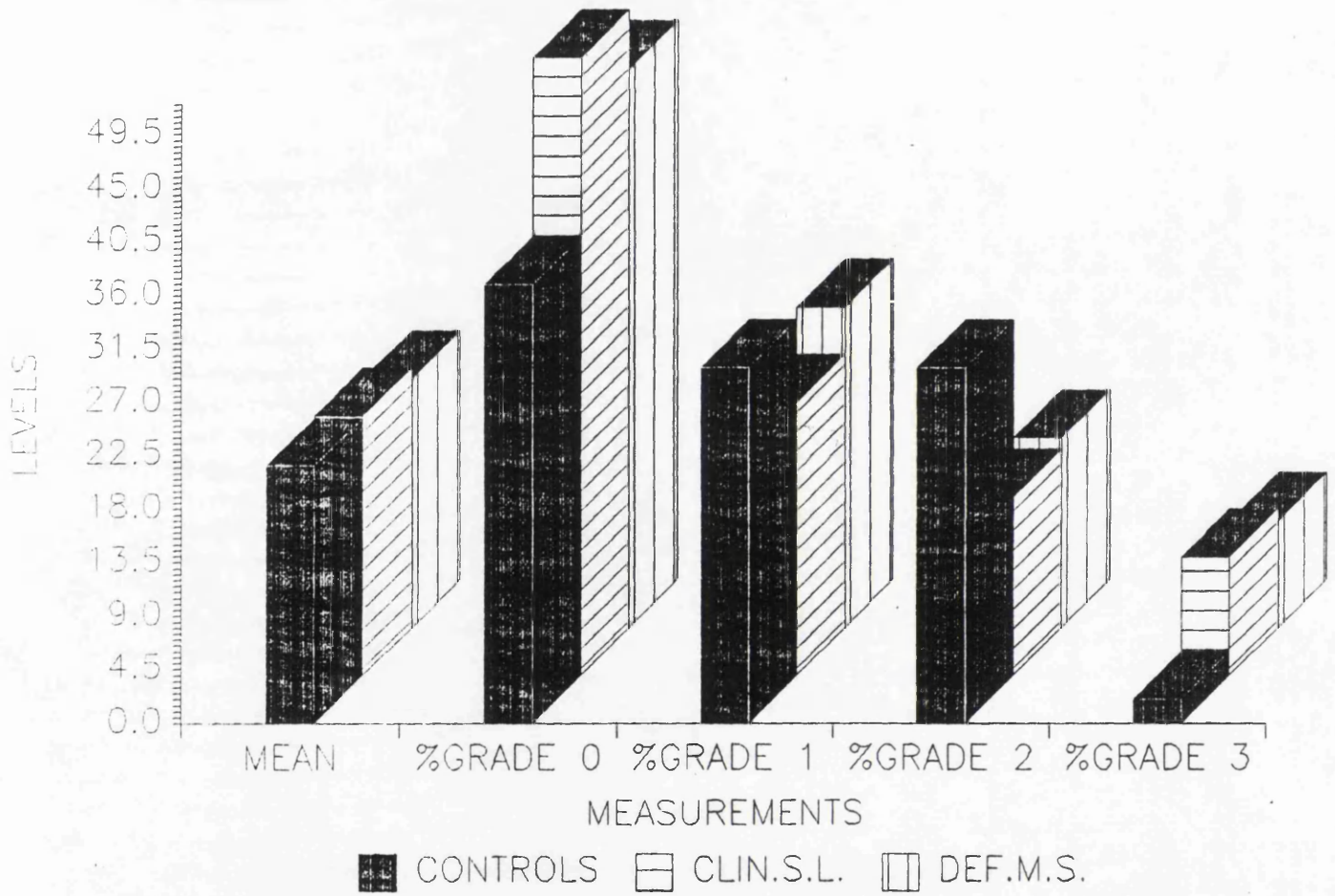

CLINICALLY ISOLATED LESION GROUP AND
PHYSICALLY DISABLED CONTROL GROUP:
Cognitive Ability Grades
PERCENTAGE OF GROUP IN EACH GRADE
48
44
40
36
32
28
24
20
16
12
8
4
0
grade0
grade1
grade2
grade3
COGNITIVE ABILITY GRADES
CIL GROUP
PHYS. DIS. CONTROLS


AUDITORY ATTENTION/MEAN AND GRADES
LEVELS
48.0
45.0
42.0
39.0
36.0
33.0
30.0
27.0
24.0
21.0
18.0
15.0
12.0
9.0
6.0
3.0
0.0
mean
%grade 0
%grade 1
%grade 2
%grade 3
MEASUREMENTS
controls
clin.s.l.
def.m.s.


IQ DEFICIT/MEANS AND GRADES
LEVELS
53.0
50.0
47.0
44.0
41.0
38.0
35.0
32.0
29.0
26.0
23.0
20.0
17.0
14.0
11.0
8.0
5.0
2.0
-1.0
mean
%grade 0
%grade 1
%grade 2
%grade 3
MEASUREMENTS
controls
clin.s.l.
def.m.s.


VERBAL MEMORY/MEAN AND GRADES
LEVELS
60.0
56.0
52.0
48.0
44.0
40.0
36.0
32.0
28.0
24.0
20.0
16.0
12.0
8.0
4.0
0.0
MEAN
%GRADE 0
%GRADE 1
%GRADE 2
%GRADE 3
MEASUREMENTS
CONTROLS
CLIN.S.L.
DEF.M.S.

NAMING ABILITY/MEAN AND GRADES



Cognitive Ability Grades