

PATTERNS OF COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS
AND THEIR RELATIONSHIP TO NEUROPATHOLOGY
ON MAGNETIC RESONANCE IMAGING

by

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Abstract

Recent reviews (Peyster & Poser, 1986; Rao, 1986) suggest that Multiple Sclerosis results in cognitive impairments in the areas of learning and memory, abstract reasoning, information processing efficiency, and, often, visual-spatial ability. Whether this pattern applies to the individual with MS is unclear. Due to the disseminated distribution of MS neuropathology, patients may undergo idiosyncratic cognitive changes dependent upon the site of white matter lesions. The present study explored this question using cluster analysis on the neuropsychological data from a group of mildly disabled MS patients (n = 177) and a well-matched control group (n=89). In a group of MS patients who were identified with unequivocal cognitive impairment, the resultant clusters indicated that MS does not result in a characteristic pattern of impairment. Two clusters were obtained that resembled the pattern described in the literature, while the majority of patients clustered into groups with specific deficits in one or two areas, with normal performance in others. In order to identify associations between cluster groups and lesion sites, frequency tables were constructed for the presence of a lesion on Magnetic Resonance Imaging in 24 brain sites. An association was obtained between two lesion sites and two cognitive tests. Visual-spatial impairment, as assessed by the Benton Visual Retention test, was associated with lesions in the genu of the corpus callosum and with more lesions throughout the corpus callosum. Impaired performance on Paired Associates, a test of learning and memory for novel verbal associations, was associated with a lesion in the deep white matter of the left parietal lobe. The results support the hypothesis that MS results in multiple patterns of cognitive impairment depending on the individual placement of white matter lesions. Identifying and characterizing the heterogeneity of the impairment may greatly increase our understanding of the role of myelin in cognition and the functions of white matter tracts in the brain.

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Chapter 1

Introduction

Current understanding of brain and behaviour relationships derives predominantly from knowledge of the effects of cortical or grey matter lesions. Recent research has extended this knowledge to include the cognitive sequelae of diseases that affect subcortical or deep grey regions of the brain, such as Parkinson's Disease and Huntington's Disease (Saint-Cyr, Taylor, & Lang, 1988). Relatively little is known, however, about the role of myelin in cognitive functioning. Indeed, many of the diseases associated with dementia such as Alzheimer's and Huntington's can result in extensive lesions to white matter. Multiple Sclerosis (MS) is of particular interest to cognitive psychologists because of the nature of its neuropathology. MS is characterized by the destruction of myelin, the white substance that protects and insulates axons. Myelination is an important parameter in the regional maturation of the nervous system. The myelination of functionally allied systems of fibres is synchronized in an orderly sequence and tempo (Yakovlev & Lecours, 1967). Since this process continues well into the years of maturity, myelination may play an essential role in plasticity of brain organization as new experiences are integrated. Research into the cognitive sequelae of MS may provide insight into the role of neuronal myelin in cognition.

MS is a progressive disease of unknown etiology affecting the central nervous system. It results in multiple focal areas of demyelination, with virtual sparing of cortical neurons until late in the disease process (Waxman, 1982). For the majority of patients, MS manifests itself as recurrent attacks of physical symptoms lasting anywhere from a few minutes to several weeks with intervening periods of remission. Prominent symptoms include generalized muscle weakness, proprioceptive sensory loss, and impairment in fine

motor coordination. For a given individual, the symptom pattern, course, and outcome of MS is extremely variable, making diagnosis and prognosis difficult.

Cognitive Changes in MS

Cognitive and emotional changes accompanying MS were acknowledged as far back as Charcot's lectures on the disease in 1877 (cited in Peyser & Poser, 1986). Early researchers noted emotional changes including depression, lability, euphoria, and denial, together with a general loss of intellectual ability (e.g. Cottrell & Wilson, 1926; Moxon, 1875). These changes, however, were considered a rare and relatively unimportant feature of MS, and if present, were assumed to occur only in later stages of the disease process when neuronal degeneration was extensive. MS continues to be described in the neurology literature almost exclusively as a motor/sensory disease (e.g., Hashimoto & Paty, 1986; Kandel & Schwartz, 1985; McKahn, 1982).

Recent investigations have established that MS may result in impairment on a variety of neuropsychological and intellectual tests. Impairment is not confined to late stages of the disease, but is evident in a substantial number of patients in relatively early or mild stages. In samples of patients with little functional disability, no current exacerbation of symptoms, and in whom no cognitive decline is evident on neurological examination, the incidence of impairment ranges from 30% to 50% (Ivnik, 1978; Klonoff, Clark, Oger, Paty, & Li, 1991). Indeed, for some patients, difficulty in memory and concentration may be the earliest and most prominent complaint (Young, Saunders, & Ponsford, 1976). Counterintuitively, the severity of impairment correlates poorly, if at all, with measures assumed to reflect severity of pathology, including degree of disability, age at diagnosis, years since onset of symptoms, or number of relapses (Baumhefner et al., 1990; Huber et al., 1987; Rao et al., 1985). The impairment is not adequately accounted for by psychological distress associated with chronic disease or other psychiatric conditions such as depression (Good, Clark, Oger, Paty, & Klonoff, 1992; Jambor, 1969; Peyser, Edwards, Poser, & Filskov, 1980).

Recent reviews (Peyser & Poser, 1986; Rao, 1986) emphasize cognitive changes in the areas of learning and memory, abstract reasoning, and information processing efficiency. Construction and visual-spatial ability are also frequently affected. While verbal skills and overlearned information tend to remain relatively intact, classic focal aphasia have been described in the literature, although rarely (Achiron, Ziv, Djaldetti, Goldberg, Kuritzky, & Melamed, 1992).

The most consistent finding is impairment in learning and memory for both verbal and visual novel information. The deficit is more likely to be seen on tests of recall rather than recognition (Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984), and is particularly evident when the information requires novel associations between previously unrelated materials (Carroll, Gates, & Rhodan, 1984; Klonoff et al., 1991). However, on tasks requiring immediate recall of short spans of information (such as Forward Digit Span), MS subjects perform similarly to controls (Grant, McDonald, Trimble, Smith, & Reed, 1984; Rao, Leo, & St. Aubin-Faubert, 1989).

In the area of abstract reasoning and problem solving, early studies indicated that tests of concept formation and rule learning may be impaired (e.g., Reitan, Reed, & Dyken, 1971), but this finding is inconsistent. Since 1980, most studies have obtained normal conceptual reasoning ability in groups of patients with relapsing-remitting disease course (Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Jennekens-Schinkel, van der Velde, Sanders, & Lanser, 1989), but impaired performance in chronic-progressive patients (Heaton et al., 1985; Rao et al., 1984). Overall, the preponderance of negative results indicates that conceptual reasoning is less likely than memory processes to be affected in MS.

More recently, investigators have focused on information processing efficiency in MS. Sufficient evidence exists to suggest that patients with MS may have particular difficulties in this area. Studies that included tests such as Word Fluency, Stroop Color-Naming, and Backward Digit Span have all indicated impaired performance in MS

compared to normal control groups, regardless of the disease course (Heaton et al., 1985; Klonoff et al., 1991; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). For example, a recent study by Rao and his colleagues (Rao, St. Aubin-Faubert, & Leo, 1989) examined MS patients' mental processing speed using the Sternberg paradigm. This task requires subjects to identify whether a probe is contained within a set of digits held in memory. Mean reaction time is plotted for digit sets of increasing length. The resultant slope of the line indicates speed of memory scanning that is uncontaminated by motor speed. Rao and his colleagues found that, while total number of errors did not differ between groups, MS patients obtained a mean memory scanning speed that was 47% slower than a matched control group.

Finally, performance on constructional and visual-spatial tasks (such as the WAIS-R Block Design) is often impaired in MS, but is confounded with motor speed and coordination that are inevitably disrupted in MS (Peyser & Poser, 1986). However, several studies that included tests without a speed/motor coordination component have found evidence for impairment in this area (Rao, Leo, Bernardin, & Unverzagt, 1991).

The Pattern of Impairment in MS

Taken together, the results of recent neuropsychological research identify cognitive impairment as an important aspect of MS. However, the particular pattern of impairment expected in an *individual* with MS is unclear. Ample evidence exists to suggest that cognitive impairment is not ubiquitous among MS patients. Performance on neuropsychological tests invariably ranges from superior to severely impaired. Several researchers have highlighted the increased variability of scores among MS patients when compared to controls (Klonoff et al., 1991; Rao, 1986), even in the absence of significant mean group differences (Jennekens-Schinkel et al., 1989). Statistically, the resulting increase in variance for the MS group decreases the likelihood of finding group differences using tests of mean differences, and makes the use of many multivariate procedures difficult (Clark & Ryan, 1993; Ryan, Clark, Klonoff, & Paty, 1993). The presence of

greater variability among test scores raises interesting hypotheses regarding the nature of cognitive impairment in MS.

One hypothesis is that the general pattern of impairment described above applies to most (or all) MS patients, and that group variability reflects individual differences in the *severity* of neuropathology. By this view, when cognitive impairment is present, a similar pattern will be manifest in all MS patients, but the degree of impairment will depend on factors such as the extent of demyelination. The assumption has been that, as with other neuropathological conditions such as Alzheimer's or Huntington's Chorea, a characteristic pattern of impairment exists in MS. For example, Rao (1990) has described MS as a prototypical "subcortical" dementia, highlighting a pattern of decreased speed of information processing, inefficient retrieval of previously learned material, and difficulty with abstract conceptualization, with intact verbal skills and an absence of "cortical" features such as aphasia, agnosia, or apraxia.

Alternatively, there may not be a characteristic pattern of cognitive deficit in MS. Prevailing theories of brain-behaviour relationships are based on a relatively invariant association between brain site and cognitive function. In MS, while demyelination occurs with high frequency in certain brain areas, patients have very different lesion distributions as assessed by brain imaging techniques such as Magnetic Resonance Imaging (MRI) (Hashimoto & Paty, 1986). Individuals may undergo idiosyncratic cognitive changes dependent upon the site, size, type, and distribution of the white matter lesions. For example, MS patients with a preponderance of lesions in the frontal lobes might exhibit a very different pattern of cognitive impairment than MS patients with a large percentage of lesions in the corpus callosum. Further, although a single lesion in MS may be discrete in terms of the area it occupies, it is likely to affect many cortical areas, since the myelinated tracts are comprised of axons from multiple and disparate areas of the cortex, making the invariance assumption untenable. Thus, group studies may mask a wealth of information due to averaging artifacts, since the inclusion of several differentially impaired subgroups

within a single sample could lead to the conclusion that MS results in mild impairment on virtually every cognitive test available, a view that accords well with the general impression expressed in recent reviews of the literature (Peyser & Poser, 1986).

In support of this position, Beatty (1992) has investigated whether Rao's characterization of MS as a subcortical dementia actually applies to the individual with MS. He argues that, while the group data indeed show deficits in typical "subcortical" areas, the pattern is evident in only a small percentage of individual patients. The majority of the MS patients would not be considered impaired in any area, while others have isolated deficits, such as in memory or abstract reasoning.

Neuropathological Correlates of Cognitive Impairment in MS

Consideration of the nature of the neuropathology in MS is an important aspect of understanding cognitive changes in MS. In recent years the advent of in vivo structural brain imaging techniques, such as computerized tomography (CT) and magnetic resonance imaging (MRI), have allowed the relationship between neuropathology and cognitive impairment in MS to be investigated. MRI is of particular interest because of its sensitivity to demyelinating lesions. MRI has been shown to be 10 times more sensitive than unenhanced CT in identifying lesions in MS. Although one cannot distinguish on normal MRI between areas of edema and areas of demyelination (Paty, 1990), the technique allows more precise localization and estimates of the extent of pathology evident at a particular time (Ormerod, du Boulay, & McDonald, 1986).

Neuroimaging studies have found a modest but consistent relationship between the extent of neuropathological changes and the severity of cognitive impairment. Most often these studies have used a global measure of pathology such as the total number of lesions weighted by size (Franklin, Heaton, Nelson, Filley, & Seibert, 1988), total area of lesion outlined on MRI scans (Baumhefner et al., 1990), or measurements of ventricular dilation that are presumed to reflect lesion load in the periventricular regions (Rao et al., 1985). For example, Franklin et al. (1988) correlated the total number of lesions weighted by size

on MRI with performance on various neuropsychological tests. Tests of learning and memory correlated modestly, with Pearson's correlation values ranging from .31 to .36, while tests with a motor speed component correlated somewhat higher, from .45 to .47.

It is difficult to interpret the results of studies using these global measures. For example, Rao et al. (1985) found that the maximum width of the third ventricle was the best predictor of global cognitive impairment, compared to other measurements such as the width of the lateral ventricles. They argued that dilation of the third ventricle is a good indicator of periventricular demyelination, and that lesions here disrupt the prefrontal- limbic white matter tracts thereby producing memory and conceptual deficits. However, it is difficult to understand why the same should not be true of dilation of the lateral ventricles, except if employing a circular argument. Such nonspecific indicators of neuropathology give little insight into the relationship between affected area and cognitive dysfunction, and one is sobered by the finding that the strongest relationships found are accounting for at best 20% to 22% of the variance on tests.

Expecting anything more than a modest relationship between such global measures is probably unwarranted given what is known about brain functioning in general, and physical symptoms in MS in particular (for discussion, see Clark et al., 1992). The situation would be analogous to a correlation between the amount of lesion load and ambulatory difficulty in MS patients. While larger numbers of lesions may increase the likelihood that one occurs in an area important to motor functioning, a single well-placed spinal or cerebellar lesion can totally incapacitate an individual (Peyser & Poser, 1986). Only by looking at factors including localization, size, and distribution of lesions can one begin to understand the effect of white matter lesions on cognition.

This view has been embraced by several recent papers that focus on demyelination within the corpus callosum (CC) (Huber et al., 1987; Pozzilli, Bastianello et al., 1991; Rao, Bernardin, Leo, Ellington, Ryan, & Burg, 1989). In one study, Rao, Leo, Haughton, St. Aubin-Faubert, and Bernardin (1989) found that the size of the CC

(presumably measuring amount of atrophy due to demyelination) predicted performance on measures of memory scanning speed, sustained attention, rapid problem solving, and mental arithmetic, tasks that are often affected in other "subcortical" dementias such as Huntington's Chorea. In contrast, total number of cortical lesions was the best predictor of recent memory, abstract reasoning, language ability, and visual-spatial problem solving, areas of cognition most closely associated with a classic "cortical" dementia, such as dementia of the Alzheimer's type. Unfortunately, CC atrophy was equally correlated with tests of verbal skill and judgement that should be "cortical" in nature, such as the Vocabulary and Comprehension subtests of the WAIS-R. As well, the CC is not the major site of pathology in Huntington's, so it is not clear why these two diseases should result in similar cognitive outcomes. The CC has been more often associated with inter-cortical transfer, as in the work of Sperry (for example, Sperry, Gazzaniga, & Bogen, 1969). Nevertheless, the finding of a correlation between CC atrophy and processing efficiency measures is interesting and warrants further investigation. More generally, the approach taken by Rao and his colleagues suggests that a more detailed assessment of the placement of lesions may be fruitful in predicting not only the overall severity of the MS patient's cognitive impairment, but the specific nature of the impairment as well.

Present Study

The purpose of the present study was to investigate the pattern of cognitive impairment in MS and its relationship to neuropathology. The Multiple Sclerosis Study at the University of British Columbia provided a unique opportunity to address this question. A large group of MS patients ($n = 177$), who met stringent diagnostic and research inclusion criteria, were tested on a battery of neuropsychological and intellectual tests. An important aspect of the study was the inclusion of a well-matched control group ($n = 89$) who underwent the same set of tests so that comparisons to a normative sample could be made. Lesion data from MRI scans, administered on the day of neuropsychological

testing, were available for 154 MS subjects and 66 control subjects. The images were coded for lesion presence in 50 predetermined sites.

Utilizing this extensive data base, the present study attempted to determine through statistical techniques the pattern (or patterns) of impairment in a group of clearly cognitively impaired MS patients. Given the individual nature of the neuropathology, we hypothesized that rather than one typical or characteristic pattern of MS, subgroups of patients with different profiles of impairments would be evident. While global measures of neuropathology may be associated with the presence of cognitive impairment, lesion placement and distribution should be important determinants in the pattern of cognitive impairment. That is, we hypothesized that individual patterns of impairment will be related to the area of lesion occurrence on MRI.

Before describing the methods, the following three chapters review current knowledge regarding the clinical and neurological aspects of MS (Chapter 2), the literature on cognitive impairment (Chapter 3), and research into associations between cognition and measures of neuropathology (Chapter 4).

Chapter 2

Neurological and Clinical Aspects of Multiple Sclerosis

This chapter reviews the clinical and neurological aspects of Multiple Sclerosis (MS), including disease characteristics, epidemiology, etiological hypotheses, and clinical scales used to describe MS disability. Laboratory tests and neuroimaging techniques used for diagnosis are reviewed. The role of myelin in normal signal conduction and the neuropathology associated with MS are also discussed.

Clinical Aspects

Course and prognosis. Seventy percent of MS patients experience a pattern of exacerbation and remission of symptoms, while the remaining thirty percent undergo chronic and unremitting deterioration from the outset. Age of onset is usually between 10 and 59 years. While MS is often referred to as a "debilitating" neurologic disease, in fact only a small proportion of patients, estimated at 20 to 25%, eventually become severely handicapped (Peyser & Poser, 1986). Many persons are able to carry out normal or near-normal lives. As well, in a significant number of patients, the disease becomes static and is considered arrested (Hashimoto & Paty, 1986). In a small number of well-documented instances from random autopsy series, the disease is never manifest symptomatically (Gilbert & Sadler, 1983; Herndon & Rudick, 1983). The demonstration of asymptomatic lesions through techniques such as MRI suggests that the disease may be more benign than is usually thought, and that the prognosis of the disease appears to be considerably better than has been believed in the past (Ebers, Paty, & Sears, 1984).

Even in those patients who continue to experience exacerbations, new attacks are not necessarily due to the production of new lesions, but may be the symptomatic expression of existing lesions through physiological alterations. These alterations include

heat or fever, changes in calcium concentration, dehydration, infection, emotional trauma, and stress (Peyser & Poser, 1986).

Characteristic symptoms and signs. The symptoms and neurological signs of MS tend to vary in nature and severity over time. At some point in the course of the disease, 75% of MS patients will experience ocular disturbance, muscle weakness, spasticity and hyperreflexia, a positive Babinski reflex, absent abdominal reflexes, dysmetria or intention tremor, and bladder disturbance; 50-75% of patients will experience visual nystagmus, gait ataxia, dysarthric speech, paresthesias, or alterations in vibratory or position sense (Poser, Presthus, & Horsdal, 1966). At any given time, however, the clinical picture for a patient is highly individual. Some of the neurological signs and symptoms that are characteristic of MS are briefly reviewed. A more comprehensive description of clinical onset patterns is described in Hashimoto and Paty (1986).

Optic neuritis (ON). ON is first manifest as pain behind the eye which is made worse by moving the globe, followed later by decreased visual acuity and a central field scotoma. Symptoms resolve spontaneously in 70 to 80% of patients, but cortical visual evoked potentials remain abnormal. Approximately six weeks after onset, optic nerve atrophy is apparent on examination. ON is the presenting symptom in 16% of patients with definite MS, and will occur in at least 60% of patients at some time. For patients who present with ON, the overall risk of developing MS is 35%, but increases with higher geographical latitudes (75% in the United Kingdom).

Internuclear ophthalmoplegia (INO). The patient experiences horizontal diplopia (double vision) due to a lesion in the medial longitudinal fasciculus (MLF). The MLF is a midline dorsal fiber tract connecting the lateral gaze center (the sixth nerve nucleus) and the contralateral third nerve nucleus in the midbrain. MS lesions are usually bilateral, hence diplopia occurs with lateral gaze in both

directions. Bilateral INO in young adults is almost pathognomic for MS.

Acute onset INO has a high recovery potential.

Trigeminal neuralgia (tic douloureux). A lesion at the fifth nerve root entry zone in the pons causes pain in areas of the trigeminal nerve distribution, particularly the face. The pain is severe, sharp and repeated, and is triggered by sensory stimulation of the area. Trigeminal neuralgia is rare in patients under age 50 unless they have MS.

Lhermitte's symptom. This symptom is brought on by forward neck flexion, and is manifest as an electric buzzing sensation that travels down the back and sometimes into the legs. The sensation sometimes travels downward into the arms, or reverses, rising upward from the lower back. Lhermitte's symptom arises from damage to the posterior columns of the cervical spinal cord. It is not specific to MS but occurs with many forms of cord compression damage.

Acute transverse myelitis (ATM). In its complete form, ATM results in loss of all sensory and voluntary motor function below the level of the functional cord transection. It is more likely in MS to see partial cord transection. The more acute the onset of the symptoms, the fuller and more rapid a recovery. Complete ATM carries with it a poor prognosis, often resulting in either complete paraplegia or significant residual impairments.

Useless hand of Oppenheim. The hand (or hands) become virtually useless because of a lack of tactile discrimination and movement feedback. All discriminatory sensory modalities are affected, including vibration, two-point discrimination, graphesthesia, stereognosis, and proprioception. This symptom is rarely seen in diseases other than MS. The lesion is most likely in the posterior columns of the lemniscal system, and is usually unilateral.

Paroxysmal symptoms. Seizures occur in 5% of patients with MS, which is twice the expected rate of seizures in the population. Other paroxysmal symptoms

include tonic spasms, positive sensations or paresthesias, and monocular blindness. It has been suggested that such paroxysmal symptoms are due to transverse ephaptic impulse spread (axonal cross-talk occurring within and across poorly insulated demyelinated tracts).

Facial myokymia. Facial myokymia is a sensation of twitching around the eyes and movement under the skin that is caused by single fiber and motor unit contractions in the musculature.

Radicular syndromes. Radicular numbness and pain is due to root entry lesions and is therefore similar to trigeminal neuralgia.

Heat sensitivity. MS patients show a characteristic temperature sensitivity. Fever or heat results in symptom exacerbation, even to the extent of quadriplegia.

Because the symptoms are dissipated when body temperature returns to normal, an episode of heat-induced symptoms has been called a pseudo-relapse. Heat typically results in visual blurring, diplopia, paresthesias, ataxia, and leg weakness. This sensitivity can be useful for diagnosis, since a patient will exhibit worsened symptoms after being immersed in hot water.

Neurophysiological research has shown that the reliability of impulse conduction in demyelinated fibers decreases with increased temperature (Waxman, 1982). Although the reason for this is not clear, it may explain heat-induced symptom exacerbation.

Other symptoms. Other symptoms that are less unique to MS, but nevertheless frequently experienced, include gait ataxia, dysarthria, incontinence, constipation, and muscle weakness.

Epidemiology and Genetics

Epidemiological studies have demonstrated that multiple factors, both genetic and environmental, must be implicated in the etiology of MS (for review, see Gonzalez-Scarano, Spielman, & Nathanson, 1986). The female to male ratio of MS prevalence is 3

to 2, but as age of onset increases, the frequency of male cases increases. The overall incidence of the disease is approximately 10 cases per 100,000, but this is complicated by a worldwide distribution that is influenced by both geographical latitude and racial origin. Generally, the colder the climate, the higher the incidence of MS. Areas of high prevalence (50 to 80 cases per 100,000) include north and central Europe, Canada, New Zealand, and parts of southern Australia. Unusually high prevalence is found in the Shetland and Orkney islands off the coast of Scotland, with 184 and 309 cases per 100,000, respectively (Pokanzer, Prenney, Sheridan, & Kundy, 1980). There are also areas of exceptionally low prevalence compared to other areas of similar climate. For example, Japan's incidence is low (<10 per 100,000), and MS is almost nonexistent among native Indian and Inuit in Canada (Hashimoto & Paty, 1986).

Migration studies show an unusual risk pattern. Immigrants moving from low risk to high risk areas assume the new risk of acquiring the disease if the move occurs before age 15. Over age 15, lifetime risk remains similar to their place of origin (Norman, Kurtzke, & Beebe, 1983). The second generation of immigrant families show similar rates of incidence to the country they are born into, regardless of the place of origin of their parents (Leibowitz, Kahana, & Alter, 1973). These findings suggest a third important etiological factor, namely, a developmental critical window in which environmental factors may exert an effect.

The heritability pattern of MS suggests some familial hereditary susceptibility. Ebers et al. (1986) reported a concordance rate for monozygotic twins of 30%, while concordance for dizygotic twins was 3%. Risk for all other first-order relatives was also 3%, which is still about 25 times greater than the general population in high-risk areas. Risk decreases as the degree of relatedness decreases.

Taken together, these findings have led researchers to consider a multi-factor etiological model that includes exposure to some environmental factor(s) during a critical

period of development. Susceptibility to environmental factors is mediated by both racial and familial genetic factors.

Neuropathology and Pathophysiology

CNS Myelin. CNS myelin is formed by a laminar spiral of oligodendroglial (OG) cell membrane that creates an insulating sheath around axons (Kandel & Schwartz, 1985). Each OG cell myelinates 20 to 40 sections of axons within its immediate vicinity. Segments of myelin from individual OG cells along a single axon are separated from each other, creating periodic interruptions referred to as the Nodes of Ranvier. Myelin, being derived from plasma membrane, is 70% lipid and 30% protein. Compared to gray matter, white matter is low in water content. Myelinated axons are typically thicker and longer than unmyelinated axons.

The myelin sheath is characterized by high electrical resistance and low capacitance, thereby acting as an effective insulation for the electrical currents that are propagated along the axon. The electrical signal in a myelinated axon is conducted by saltatory conduction, that is, the impulse jumps discontinuously from node to node rather than continuously along the axon. The action potential spreads passively along the myelinated sections, or internodes. At each node, repolarization occurs due to the high density of sodium channels situated there (10,000 per square micrometer at the nodes versus <25 per square micrometer along the internode). Potassium channels are found along the internodal membrane underneath the myelin or just beside the nodes. The role of these "leak" channels is unclear, but they are thought to contribute minimally to conductance. Saltatory conduction allows the myelinated axons to propagate signals with greater velocity, to conduct impulses at higher frequencies, and to expend less energy per impulse than in unmyelinated fibres.

Neuropathology in MS. MS is characterized by multiple focal lesions occurring throughout the white matter of the CNS (Prineas, Kwon, Cho, & Scharer, 1984). Lesions do not respect fiber tracts or other anatomical boundaries, but tend to be disseminated

throughout the CNS. The organization of CNS myelin lends itself to patchy loss. Microlesions are first produced by the loss of a single or several adjacent OG cells, which then combine into confluent, larger lesions. The earliest lesions are probably areas of inflammation with collections of lymphocytes, plasma cells, macrophages, and increased water content replacing hydrophobic myelin. Over time, the degree of inflammation decreases and the presence of astrocytes signal the beginning of gliosis. As gliosis continues, astrocyte processes proliferate causing fibrillary tangle plaques (Hashimoto & Paty, 1986). Water content also increases, although extracellular edema recedes. In later stages preservation of the axon is less consistent and, eventually, complete cell death occurs due to Wallerian degeneration (Hille, 1984).

Lesions occur most frequently at the optic nerve, the spinal cord, the periventricular region, and within the corpus callosum. In later stages of the disease, virtually no area of white matter is spared. To give an indication of the extent of neuropathology, Brownell and Hughes (1962) found 1,594 distinct lesions in 22 cases that came to autopsy. The majority of the plaques occurred in the white matter, but 26% were located at the junction of cortex and white matter, and a small number within the cortical and deep grey matter. Plaques within the grey matter have been described elsewhere as smaller and less well defined (Hashimoto & Paty, 1986).

Effects of demyelination. Demyelination of a single axon results in slower signal conduction and desynchrony of the signal due to differing amounts of demyelination along the length of the axon. As well, conduction block of high frequency signals may occur, since demyelinated axons cannot conduct signals fast enough so that high frequency signals tend to bunch up on one another (Waxman, 1982). Desynchrony of signals also occurs within a tract of axons, since signal speed will differ for each axon depending on the amount of demyelination.

Recovery of function. A fundamental research question is the extent to which demyelinated axons are capable of sustaining an action potential. It appears that, at first,

there may be complete signal conduction block. Since the demyelinated areas are now low resistance and high capacitance, too much of the electrical current is lost during passive spread to initiate another depolarization at the next high density sodium channel area. Over time, however, there is at least partial return of functioning (Waxman, 1982). Remyelination can occur, but is slow and incomplete in the CNS and is not likely sufficient to restore functioning (Prineas & Connell, 1979). The presence of new sodium and potassium channels in previously myelinated areas of the axon suggests that the channels are redistributed to allow signal propagation by continuous conduction. It is not known whether new channels are formed along the internodal membrane, or whether there is a migration of the existing channels from the nodes of Ranvier.

Pathogenesis of MS

Two theories have gained most interest. The viral theory suggests a slow virus, either with a long latency period or incubation period calculated from epidemiological migration studies to be between 10 and 20 years. Since most MS patients have high levels of antibodies to measles, a measles variant has been a favorite candidate. However, non-MS siblings have high measles antibodies as well, and MS patients have high levels of antibodies to many other viruses. To date, there have been only negative results from attempts to isolate a virus from MS brain tissue.

A variant of the viral theory is the critical window theory. The theory suggests that a viral infection occurring during a critical period in normal immune system development causes a secondary abnormal immune response. The response slowly develops into a full blown autoimmune process. Physiological findings from CNS studies documenting systemic immune system abnormalities are consistent with this hypothesis (Haffler & Weiner, 1989). The genetic disposition suggested by familial risk studies (Ebers et al., 1986) may be a tendency to produce high levels of antibodies. The theory accords well with findings from epidemiological and migration studies. For example, measures of measles antibody titers are arranged in a pattern similar to the at-risk

distribution, ranging from highest to lowest in MS females, MS males, non-MS siblings, age and sex matched childhood friends, and random controls (Paty, Dossetor, Stiller, et al., 1977).

One important aspect of the pathogenesis of MS is the demonstration by means of enhanced CT and MRI (Poser, 1980) of an alteration in the permeability of the blood-brain barrier. In the periphery, CNS myelin is identified as a foreign substance and is destroyed by the immune system. Changes in the integrity of the blood-brain barrier might result in immune-mediated demyelination wherever these breakdowns occur. This theory accords well with the abundance of demyelinating lesions in the periventricular regions and around small blood vessels in the deep white matter.

Diagnostic Tests

Diagnosis of MS is difficult because a) the symptoms are transient, lasting sometimes not more than hours or minutes, b) although many signs, symptoms, and laboratory findings are characteristic of MS, none are specific to the disease, and c) many of the symptoms are often of the type associated with psychogenic conversion reactions. The diagnostic dilemma increases when symptom onset closely follows a stressful event. While the diagnosis of MS is primarily made on the basis of clinical information, several laboratory tests have been useful as diagnostic aids.

Computerized tomography (CT). Brain imaging techniques have become an important tool, particularly in demonstrating the pattern of multiple and spatially disseminated lesions characteristic of MS. The CT scan is an image produced by computerized reconstruction of the degree to which different tissues absorb transmitted X-rays (Oldendorf, 1980). In order to compute such an image, a narrow X-ray beam is transmitted through the head, and the X-ray photons on the other side are detected and counted. The reduction in the number of photons emerging relative to the number of photons emitted is the attenuation value. Multiple projections (a row or strip of attenuation values) are obtained at different angles through the head. The mathematical

calculation of the attenuation values for tissue deep within the brain is complex, but essentially consists of the addition of projections to create a 2 dimensional matrix. The reconstructed image reflects the fact that different tissues absorb X-rays to differing degrees. Bone and calcifications within the brain have very high attenuation values and appear white on the image, whereas soft tissues yield intermediate values appearing grey; CSF and fluid is much less attenuating, thereby appearing very dark on the image.

A routine CT scan of an MS patient substantially underestimates the number of lesions, as is evident from post mortem studies. Administering intravenous radiopaque contrast material will increase the number of lesions visible on the scan. Enhancement is usually done by scanning one hour after the injection of a high dose of iodine contrast material. The delayed scan permits the contrast material to penetrate the blood-brain barrier in areas where the permeability has been altered to only a minor degree. Enhanced lesions are associated with disease activity and may be clinically active lesions. For example, Ebers, Paty, and Sears (1984) reported one or more enhanced lesions in 56% of patients experiencing acute exacerbation, in 45% of patients with some worsening in the last 3 months, but in only 9% of patients with no recent physical changes. Thus one in ten patients with inactive MS had enhanced lesions on CT scan that were asymptomatic. Enhanced lesions have been shown to disappear with the administration of adrenocorticotrophic hormone (ACTH) or other corticosteroid treatments (Goodkin, Ransohoff, & Rudick, 1992). Paty (1990) suggests that routine scans identify areas of demyelination, while enhanced lesions are likely areas of active inflammation and demyelination. Enhanced scans may obscure lesions visible on routine CT, highlighting the need for both types of scans.

Magnetic resonance imaging (MRI). MRI is of particular diagnostic value because of its greater resolution than CT scanning. A structural tomographic image of the brain is generated when the distribution of hydrogen nuclei in brain tissue is measured (Jernigan, 1990). When atomic nuclei with uneven numbers of protons are placed in a

strong magnetic field, the protons will orient parallel to the force of the field and precess, or spin in an elliptical orbit around the longitudinal axis of the magnetic field. The proton has a characteristic frequency of precession that depends on the field strength of the magnet. A radio signal tuned to this characteristic frequency will displace the protons by causing them to absorb energy and thus precess through a wider circle. Once the signal is discontinued, the protons give off a predictable amount of energy as they return to their low energy state. The strength of the energy signal they emit can be measured, and reflects the concentration of protons in the tissue. The rate at which they return to their low energy state can also be measured (relaxation time), either as the exponential time to return to the longitudinal plane (T1) or to the transverse plane (T2). These parameters are influenced differently by tissue characteristics such as temperature, viscosity, and protein content. Relaxation measures provide much of the anatomical detail and sensitivity to tissue abnormalities.

Since tissue types differ in water content and other characteristics, a structural image of the brain is produced by spatially encoding the signals. On T1 weighted images (inversion recovery) white matter is light contrasting with dark areas indicating grey or abnormal white matter. T2 weighted images (spin echo) yield a homogeneous grey image where luminescences indicate abnormal white matter. The optimal sequence for visualizing demyelination in MS is a multislice, multiecho, spin echo (T2) scan, including a sequence where CSF is "not white", so that lesions can be differentiated from the CSF around the ventricles (Paty, 1990; Ebers, Paty, & Sears, 1984).

MRI is positive in over 90% of MS patients (Hashimoto & Paty, 1986). With a resolution of approximately 3 mm, however, small lesions are not seen. MRI is ten times more sensitive than unenhanced CT, particularly in identifying brain stem and cerebellar lesions. Because of its resolution, MRI has been valuable in evaluating the distribution of lesions in MS. In a recent study of 62 patients (Baumhefner et al., 1990), the MRI was abnormal and consistent with the diagnosis of MS in 60 patients. Of these 60 patients,

75% had abnormality in the upper cervical cord, 35% had cerebellar lesions, 42% had brain stem lesions, and 100% had lesions located in the cerebrum. There were, on average, approximately 100 cortical lesions for every one lesion in the brain stem or the cerebellum.

Apart from increasing overall sensitivity to the presence of lesions, MRI has been useful in assessing disease activity. In studies obtaining a series of MRI for each patient, asymptomatic new lesions were frequent in both relapsing-remitting and chronic-progressive patients, indicating that MS is a more active process than is indicated by clinical evaluation. Individual lesions can be seen to evolve and resolve independent of one another (Thompson et al., 1992). MRI can be used as an indicator of disease activity over time, and statistical guidelines have been developed by several investigators that take into account measurement error so that erroneous inferences regarding disease activity versus measurement artifact are not made (Goodkin, Ross, Medendorp, Konecsni, & Rudick, 1992).

An MRI obtained with gadolinium infusion is similar to contrast-enhanced CT in highlighting areas where there is breakdown of the blood-brain barrier (Grossman, Braffman, Brorson, Goldberg, Silberberg, & Gonzalez-Scarano, 1988). Although routine MRI cannot distinguish inflammatory lesions from demyelinated or gliotic regions, gadolinium-diethylene penta-acetic acid (Ga-dTPA) injected will show not only areas of blood-brain barrier breakdown, but also improves detection of new lesions, particularly in the subcortical areas. When used with series of MRIs, it is useful in demonstrating reactivated chronic lesions. Enhancement of old lesions or new lesions have been shown to correlate with clinical relapse in relapsing-remitting MS patients, with new abnormalities occurring seven times more frequently than clinical events (Thompson et al., 1992). On the basis of the evidence from series studies of enhanced and unenhanced MRI, Paty (1990) has suggested that new lesions are probably areas of inflammation that become demyelinated only after several episodes of inflammation have repeatedly

damaged a particular area of white matter. The evidence suggests that the disease process is between five and seven times more active than assessed by clinical evaluation.

Evoked potentials. The hallmark of demyelination in studies of the physiology of single fibers is slowed signal conduction (Waxman, 1982). It is this slowed conduction that allows the use of cortical evoked potentials (EP) in the diagnosis of MS. EP is a measure of the time between a stimulus presentation and an agreed upon part of the resultant neuronal signal. In MS, EPs typically show a longer latency but near normal wave form, implying the slowed conduction characteristic of demyelinated fibers. EPs are useful for detecting lesions along the auditory, optic, and somatosensory pathways.

CSF abnormalities. A pattern of multiple monoclonal globulins (IgG), referred to as oligoclonal banding, is evident in the CSF of over 90% of patients with MS (Ebers, 1984; Ebers & Paty, 1979). In contrast, only 8% of other neurological patients show such banding. Half of these non-MS patients have a history of infectious or inflammatory conditions (encephalitis, polyneuritis, meningitis) which would be expected to arouse an immune response restricted to the CNS. The banding found in MS indicates an immune response in the CNS sometime in the past. Interestingly, the banding pattern seen in MS is variable from one patient to another, but remains the same once developed. The observation has given weight to an autoimmune theory of MS where the CNS immune response, once developed, is perpetuated. Banding is found in 40% of suspected MS cases, 14% of which will develop into clinically definite MS within 2 years, in contrast to 7% of suspected MS cases without banding who will develop clinically definite MS within two years (Hashimoto & Paty, 1986). While banding is a useful diagnostic test in early suspected MS, the absence of banding does not exclude MS. However, positive banding and a positive MRI together are the best predictors of future development of clinically definite MS.

Diagnostic Criteria

Diagnosis is made only when evidence indicates recurrent or chronic disease affecting multiple areas of the CNS; hence the diagnostic criteria of evidence supporting the dissemination of lesions in both time and space (Poser, Paty, McDonald, Scheinberg, & Ebers, 1984). The criteria allow MS to be distinguished from single white matter lesions, and from lesions that are not chronic or progressive. The average time from first symptoms to diagnosis is usually reported in studies as between 5 and 10 years (Klonoff et al., 1992).

The Schumacher et al. (1965) criteria. The most widely used diagnostic scheme until recent years was that of Schumacher et al. (1965). The criteria include 1) objective abnormality on neurologic examination attributable to CNS dysfunction; 2) evidence of involvement of two or more separate parts of the CNS; 3) objective neurologic evidence that reflects predominantly white matter involvement; 4) involvement that occurs temporally as either two or more episodes of worsening separated by a period of 1 month or more, or a slow or stepwise progression of signs and symptoms over a period of at least 6 months; 5) the age of the patient at onset falls within the range of 10 to 50 years; and 6) the condition cannot be explained better by some other disease process.

The Poser et al. (1983) criteria. Because of the development of ancillary clinical and laboratory procedures that assist in diagnosis of MS, a new set of diagnostic criteria was developed by Poser et al. (1983). Not only are the types of acceptable evidence expanded and detailed, but the definition of terminology and other aspects of diagnosis that require subjective input from the clinician are made clear. *Episode* refers to the occurrence of symptoms with or without objective confirmation on neurological examination lasting more than 24 hours. *Remission* is an improvement of signs or symptoms lasting more than 24 hours, while remission lasting more than 1 month is considered "significant". The types of evidence used in these criteria include *clinical* evidence (objective abnormal signs on neurological examination), *paraclinical* (Evoked

Potentials or MRI/CT lesions that are subclinical or asymptomatic), and *laboratory supported* evidence (positive findings of oligoclonal banding, increased IgG levels, evoked potentials, MRI, or CT). As with the Schumacher criteria, the new guidelines require evidence of multiple lesions disseminated in both time and space. The categories for diagnosis are outlined below.

Clinically Definite: Two episodes, separated by 1 month, with clinical evidence of two separate lesion sites; or, two episodes separated by 1 month with clinical evidence of one lesion and paraclinical evidence of another.

Laboratory Supported Definite: Two episodes, with clinical or paraclinical evidence of one lesion plus oligoclonal banding; or, one episode with clinical evidence of two lesions plus oligoclonal banding; or, one episode with clinical evidence of one lesion, paraclinical evidence of another, together with banding.

Clinically Probable: Two episodes with clinical evidence of one lesion; or, one episode with either clinical evidence of two lesions or clinical evidence of one lesion with paraclinical evidence of another.

Laboratory Supported Probable: Two episodes and oligoclonal banding.

Disability Assessment

Kurtzke (1955) devised the Disability Status Scale (DSS) to be used to assess treatment outcome in drug studies of MS. The scale, with 10 grades ranging from "0 = normal" to "10 = death from MS", was intended to measure the maximal functioning of each patient as limited by neurologic deficits. The scale considers ambulation, work and daily activities, and assistance requirements. In higher (more impaired) grades, the scale focuses on restrictions of movement, the inability to care for oneself, and difficulty in communication. Only objectively verifiable defects due to MS (i.e., as evident on neurological exam) are included in the scale. Thus the scale does not include symptoms. Kurtzke also provides a rating of individual Functional Systems (FS), including pyramidal (P), cerebellar (CII), brain stem (BS), sensory (S), bowel and bladder (BB), visual (V),

cerebral or mental (Cb), and other (O). While the DSS gives an overall picture of functioning of the patient, the FS scales are independent anatomically and not additive (for example, as P worsens, CII will improve because as plegia increases ataxia will decrease).

Kurtzke later revised the scale (Kurtzke, 1983) because clinicians and researchers wished to note smaller differences in clinical status. The Extended Disability Status Scale (EDSS) was developed by dividing each of the 10 categories into two. These categories are used extensively now and are described in more detail in Appendix A. The FS scales were also modified, and are used as an index of neurological impairment or abnormality in each domain. The EDSS is used as a scale of general disability due to neurological impairment, but is not a handicap scale. Thus, a concert pianist with an EDSS of 3 or 4 will be severely handicapped at work, while for other patients, this level of disability will interfere minimally with work or daily activities.

Chapter 3

Neuropsychological Functioning in MS

Two recent reviews (Peyser & Poser, 1986; Rao, 1986) summarizing the neuropsychological functioning of MS patients highlight a triad of impairment in learning and memory, problem solving and conceptualization, and information processing efficiency. Visual-spatial skills are often affected, while prior knowledge, skills, and language functions remain intact. Emotional changes include depression, euphoria, and lability. While these conclusions are the product of more than 40 years of neuropsychological research, it is sobering to consider that Charcot, in his 1877 lectures, gave a remarkably similar description of MS on the basis of clinical observation of a few patients at the Salpêtrière. In a widely quoted passage he remarked that, for most patients, "There is marked enfeeblement of memory; conceptualizations are formed slowly; the intellectual and emotional faculties are blunted in this totality. The dominant feeling appears to be a sort of almost stupid indifference in reference to all things. It is not rare to see the patient give way to foolish laughter or, on the contrary, melt into tears without reasons" (quoted in Peyser & Poser, 1986). The harshness of Charcot's description is likely due to the severity of the cases he observed. Nevertheless, while research methods have changed, clearly our basic conception of the psychological functioning of MS patients has remained relatively intact over the last 100 years. In every era, MS continues to be characterized by enigmas, and research seems to generate more questions than answers (Namerow & Thompson, 1969). The present chapter reviews the extant literature on cognitive functioning in MS.

Early Studies of Intellectual and Neuropsychological Functioning

Probably the first systematic attempt to assess the intellectual functioning of MS patients was carried out in France by Ombredane in 1929 (described in Peyser & Poser,

1986). Using techniques that were forerunners of current neuropsychological testing methods, Ombredane administered tests of attention, memory, manipulation of spatial and temporal relationships, comprehension, and calculation to a random sample of 50 MS patients. Of this group, 72% displayed varying degrees of intellectual difficulty, and 12% of these patients he considered to be globally demented. In general conversation, Ombredane found that most of the patients appeared perfectly intact, but once the patient began to carry out intellectual exercises, the deficits became apparent. He concluded that intellectual impairment was an integral component of MS.

A different conclusion was drawn in North America. Until well into the 1940s, researchers judged intellectual functioning solely on the basis of observations made during clinical interviews (Bramwell, 1905; Moxon, 1875). One very influential study by Cottrell and Wilson (1926) reported that, of 100 patients who were extensively interviewed, only 2 showed intellectual impairments. More recent epidemiological surveys employing a brief mental-status examination administered by neurologists have supported these findings (Kurtzke, Beebe, Nagler, Auth, Kurland, & Nefzger, 1972). Outcomes such as these have encouraged the opinion among clinicians that intellectual functioning is not an important aspect of MS (for example, see McKahn, 1982).

The development of individually administered intelligence tests in the 1950s and 1960s created a resurgence of interest in the intellectual functioning of MS patients (Canter, 1951; Fink & Houser, 1966). Results on tests such as the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) were inconsistent. For example, Reitan, Reed, and Dyken (1971) found that MS patients, compared to controls matched on age and education, were significantly lower on every WAIS subtest except Information, Comprehension, and Arithmetic. On these three, MS performance was also lower, but not significantly. In contrast, Jambor (1969) found no differences between MS patients and normal controls (again matched on age and education level) on Verbal IQ, Performance IQ, Similarities, Block Design, or Digit Span. MS patients did no worse on

cognitive measures than other brain-damaged groups (Goldstein & Shelley, 1974; Ivnik, 1978; Jambor, 1969; Matthews, Cleeland, & Hopper, 1970), physically disabled patients (Jambor, 1969), or psychiatric patients (Goldstein & Shelly, 1974; Jambor, 1969). In each study, group differences occurred, but none consistently. Vowels (1979) explained the lack of group differences by noting that an intelligence test such as the WAIS is heavily influenced by educational experience, and suggested that MS may disrupt more dynamic problem-solving abilities, leaving overlearned knowledge and skills relatively intact. Vowels' explanation accords well with the observation made by Rao (1986) that among the WAIS and WAIS-Revised (Wechsler, 1981) subtest scores, Digit Span is consistently the lowest on average for MS patients, followed closely by Arithmetic, two tasks requiring efficient mental manipulation of information.

A more consistent picture is revealed by the neuropsychological tests included in these early studies. Clearly, MS patients exhibited substantial cognitive impairment on a variety of tests that could not be explained by impairment in motor functioning. For example, Reitan et al. (1971) found the MS group to be impaired on tests from the Halstead-Reitan Neuropsychological Battery (Reitan & Davison, 1974) that do not rely on motor speed and coordination, including the memory and location scores from the Tactual Performance Test, and Categories, a test of inferential rule-learning. MS groups were also impaired compared to other groups with neurological conditions causing motor dysfunction such as muscular dystrophy (Ivnik, 1978; Jambor, 1969; SurrIDGE, 1969). The most consistent finding from these early studies was difficulty in learning and memory, including tests of multiple-trial list learning (Beatty & Gange, 1977), sentence learning (Jambor, 1969) and paragraph recall, both immediate and delayed (Beatty & Gange, 1977; Staples & Lincoln, 1979).

The inconsistencies in many of these early studies are difficult to explain, since the studies do not adequately describe their subject samples and inclusion criteria. Factors such as diagnostic criteria, the percentage of patients with relapsing-remitting versus

chronic-progressive course, current medications, and the percentage of patients currently experiencing relapse, may have a major impact on the outcome. For example, symptom exacerbations causing motor incoordination, sensory deficits, and general fatigue have a large impact on test performance. Inclusion of patients currently in relapse might change the group mean sufficiently to indicate deficits that would not otherwise be apparent.

Diagnostic procedures alone may account for substantial differences in these studies. Compare, for example, Jambor (1969), who found no impairment on the WAIS, with Reitan and his colleagues (1971), who found impairment on virtually every test given, including 8 of 11 subtests of the WAIS. Both studies recruited subjects on the basis of a prior diagnosis of MS reported in hospital records. However, Reitan discarded half of his sample on the basis of clinical information contained in hospital records, so that the remaining 133 patients (of whom 30 were randomly chosen and contacted) were "unequivocal" MS. In contrast, Jambor contacted by letter an unreported number of patients diagnosed with MS, and tested the first 105 patients who agreed to co-operate. Reitan's sample was older (mean 36.43 years, sd 9.83) than Jambor's sample (mean 32.3 years, sd not reported, but with a criterion cutoff of age 40). Finally, Reitan included all subject scores on every test, while Jambor excluded subjects from each test if sensory and motor impairment were judged to hamper their performance. Taken together, it is reasonable to assume that these differences in procedure resulted in a more homogeneous sample being tested by Reitan, a sample that may have included more late-stage and functionally disabled MS patients.

Thus, while early studies warranted the conclusion that cognitive impairment of some type occurs in at least some patients with MS, it is difficult to draw conclusions about the nature of the impairment.

Characterization of the Impairment: Studies from 1980 to the Present

More recent studies have applied clearer guidelines for diagnosis (Poser et al., 1983) and have been more thorough in reporting sample characteristics such as disease

course, age of onset of symptoms, years since diagnosis, current level of disability, and number of subjects experiencing relapse (Peysner, Rao, LaRocca, & Kaplan, 1990). The emphasis has moved from the question of whether or not cognitive impairment occurs to understanding the nature of the impairment and its relationship to other aspects of the disease process. A large number of recent studies have focused on identifying the components of a cognitive function that are affected by MS. By far the most extensively researched area has been aspects of learning and memory, but has also included abstract reasoning and conceptualization, visual-spatial functioning, and information processing efficiency.

Memory and learning. As with the early studies, the most robust finding in the literature is a consistent impairment in learning and memory for both verbal and visual novel information. The deficit is more likely to be evident on delayed tests of free or cued recall rather than recognition (Carroll et al., 1984; Rao et al., 1984). When presented with verbal materials such as word lists, paired associate lists, or short stories, MS patients acquire information incrementally over trials, but at a slower rate (Carroll et al., 1984; Grant et al., 1984; Rao et al., 1984; Rao, Leo, & St. Aubin-Faubert, 1989). MS patients have particular difficulty in acquiring novel associations between unrelated pairs of words (Klonoff et al., 1991; Minden, Moes, Orav, Kaplan, & Reich, 1990), and in organizing words into semantically logical groups that facilitate recall (Carroll et al., 1984). In contrast, on tasks requiring immediate recall of short spans of information such as Forward Digit Span, MS group performance is similar to controls (Grant et al., 1984; Heaton et al., 1985; Rao, Leo, & St. Aubin-Faubert, 1989).

Several researchers have investigated whether the memory impairment in MS could be accounted for by a more rapid rate of forgetting. There have been conflicting reports as to whether MS patients are more susceptible to interference on the Brown-Peterson trigram paradigm, a test designed to measure rate of forgetting (Peterson & Peterson, 1959). Rao, Leo, and St. Aubin-Faubert (1989) found that although there was a

trend to recall fewer trigrams, the MS group showed the same rate of forgetting as controls after retention intervals of 3, 6, 9, and 18 seconds filled with an interference task. In contrast, Grant, McDonald, and Trimble (1989) found a clear effect of rapid forgetting with an interference task during the intervals. One should not assume, however, that poorer performance on the Brown-Peterson task indicates a change to the memory system per se. The Grant et al. (1989) study was conducted with MS patients, about half of whom were experiencing exacerbations at the time of testing, whereas all but 2 of the patients in Rao, Leo, and St. Aubin-Faubert (1989) were in remission at testing. As Muter (1980) has pointed out, the Brown-Peterson task is as much a measure of distractibility as it is of forgetting rate, and patients in an active phase of the disease may differ on such a measure. The best indication that rapid forgetting is not associated with MS comes from several studies that have shown that, once learned, information is retained over delays similarly in MS and control groups, providing one takes into account the original amount of information learned (Minden et al., 1990; Rao, Leo, & St. Aubin-Faubert, 1989).

The finding that recognition tests are less likely to be impaired than tests of free recall has led some researchers such as Rao (1986) to suggest that the memory deficit stems from difficulty with retrieval rather than encoding or rapid forgetting. However, Rao et al. (1984) found recognition to be impaired in chronic-progressive patients. As well, Minden et al. (1990) did not find any differences between MS patients and controls in the pattern of recall and recognition memory performance. They found that performance for both groups was improved on recognition testing, but the MS group remained significantly impaired in comparison to controls. The average increment in the MS group's memory performance on recognition was no larger than it was for the controls. Indeed, Minden et al. (1990) found that memory impaired MS patients' performance benefitted less by the presentation of retrieval cues for novel paired associates, a finding that cannot be explained easily by a retrieval deficit.

The finding that MS patients have more difficulty with novel associative learning and do not benefit from semantic cueing might suggest that MS patients have a semantic encoding deficit. Beatty, Goodkin, Beatty, and Monson (1989) examined this hypothesis using Wicken's (1970) release from proactive interference (PI) paradigm. Frontal lobe lesion patients who also exhibit memory deficits fail to show the normal release from PI after a categorical shift, suggesting that memory impairment associated with frontal dysfunction arises from an inability to adequately encode the semantic aspects of the materials (Freedman & Cermak, 1986). Beatty et al. (1989) found that even those MS patients with clear impairment in memory and other "frontal lobe" functions showed normal release from PI. In another study, Grafman, Rao, Bernardin, and Leo (1991) showed that MS patients encode incidental properties of the stimuli, such as the modality of presentation or the frequency of presentation. Although MS subjects were impaired in recall and cued recall for the materials, they were able to estimate the frequency of the prior presentations of the word with the same accuracy as controls. Taken together, these results suggest that MS patients are not impaired in the encoding and representation of either semantic or incidental aspects of the materials, but rather in the use of strategic aspects of memory. Decreased use of strategy as an explanation for MS memory impairment is consistent with Carroll et al. (1984) who found that MS patients were less likely to spontaneously employ a semantic strategy as an aid to accurate performance on a verbal recognition task.

Conceptual and abstract reasoning. Conceptualization or problem solving ability has been most often tested with the Category Test (CAT) from the Halstead-Reitan Battery or the Wisconsin Card Sorting Test (WCST). Most studies since 1980 have not found impairment on the CAT when MS patients with a relapsing-remitting course were tested (Heaton et al., 1985; Jennekens-Schinkel et al., 1989; Klonoff et al., 1991). Chronic-progressive MS groups, however, have been found to be impaired on the CAT, the WCST (Heaton et al., 1985), and Levine's (1966) Concept Formation Test (Rao et al.,

1984). For example, Heaton et al. (1985) found that chronic-progressive patients performed worse on both CAT and WCST compared to a relapsing-remitting group, and both MS groups made more perseverations on the WCST than the control group. In contrast, Jennekins-Schinkel et al. (1989) found that chronic-progressive and relapsing-remitting groups performed virtually identically to one another and compared to normal controls on all measures of the CAT and the WCST. The only significant finding was that scores for the MS group as a whole were more variable than controls. Finally, while Peyser et al. (1980) found that 54.7% of an MS group were above the normative cutoff for classifying brain damage on the CAT (50 errors; Reitan, 1986), Jennekins-Schinkel et al. (1989) point out that using such a cutoff in their study would have misclassified 54% of the MS patients *and* 58% of control subjects as having organic brain dysfunction.

Increased perseverative responding has been frequently reported in MS patients, either regardless of disease course (Heaton et al., 1985) or only in patients with chronic-progressive MS (Rao & Hammeke, 1984). Beatty et al. (1990) found that a group of chronic-progressive MS patients differed from controls on the WCST only in the number of perseverative responses; number of categories achieved, and failures to maintain set were similar, suggesting that MS patients have difficulty abandoning a formerly correct hypothesis. Jennekins-Schinkel et al. (1989) also found that their MS group tended to have difficulty in using the "if correct, then shift" strategy, but this difference did not reach statistical significance.

While the evidence suggests that difficulties in conceptual reasoning are more likely to occur for chronic-progressive than relapsing-remitting MS patients, patients in the former group tend to be older, have more severe disability, and are in effect experiencing an exacerbation at the time of testing. Beatty et al. (1990) found that when disease variables (such as duration of symptoms and age at onset) and demographic variables (such as age and education) were controlled for, course type contributed nothing to the prediction of performance on a number of cognitive tasks, including the WCST.

Negative results, both with relapsing-remitting (Klonoff et al., 1991) and chronic-progressive (Jennekens-Schinkel et al., 1989) groups indicate that it is not necessarily the case that MS results in impaired conceptual ability. The most consistent finding appears to be increased variability in performance, suggesting that only a subgroup of MS patients are impaired on these measures.

Visual-spatial ability. When assessing the performance of MS patients on tests of visual-spatial and constructional abilities, a major difficulty arises. Most of the tests are either pencil and paper copying tests, or are heavily reliant in other ways on motor coordination, speed of responding, and visual acuity. Thus, although MS groups are likely to be impaired on tests such as Object Assembly and Block Design (Heaton et al., 1985; Klonoff et al., 1991; Reitan et al., 1971), it is unclear whether their poor performance is attributable to impairment in visual-spatial functioning. For example, Franklin et al. (1988) reported that 52% of MS patients were impaired on a figure copying test. Jennekens-Schinkel, Lanser, van der Velde, and Sanders (1990), employing a similar figure copying test, also showed that MS patients made more errors. The errors, however, were due to difficulty controlling pencil stroke, rather than structural details, suggesting a motor and coordination problem rather than a visual-perceptual deficit. Similar negative results have been found on the Hooper Visual Organization Test, an identification task for cut-up pictures that requires no motor response (Minden et al., 1990; Rao et al., 1991). However, Rao et al. (1991) found significant impairment on other subtle visual-perceptual tasks such as judging line orientation, matching faces shown at different angles, and choosing identical complex designs from an array that differed only in small details. Poor performance on these tasks was not attributable to decreased visual acuity. Rao concluded that visual-spatial impairment was common among MS patients.

Language functioning and classic focal symptoms. Classic aphasic syndromes associated with focal brain lesions are rarely reported in the MS literature. However, several cases have been described (Olmos-Lau, Ginsberg, & Geller, 1977). For example, a

recent case report (Achiron et al., 1992) described two patients with relapsing-remitting MS having acute onset of aphasic symptoms. Interestingly, both patients were severely nonfluent aphasic, that is, they could express only a few abnormal syllables with preserved language comprehension and markedly impaired writing ability. In both cases, language functioning improved over several weeks. MRI indicated large plaques in the left frontal region in one patient, and in the left centrum semiovale in the other, neither of which were evident on MRI several months previously.

Both Rao (1986) and Peyser and Poser (1986), in their reviews of the literature, are cautious in their conclusions that language dysfunction is rare in MS, since few studies have administered language testing to groups of MS patients. Jennekins-Schinkel et al. (1990), Jambor (1969), and Heaton et al. (1985) did not find group differences on tasks such as naming common objects, repetition of words and sentences, or verbal comprehension. It would appear that, although isolated cases of frank aphasia occur, language functioning is unlikely to be impaired in MS.

Processing efficiency. The concept of processing efficiency is complex and fraught with difficulty. Shallice (1988) describes this ability as the application of a schema, or task-specific organization, that places a particular pattern of demands on a set of specific functional subsystems necessary to attain a goal. The efficient application of a schema is multifaceted, and includes (at least) mental processing speed, sustained attention, a good repertoire of and ability to choose among strategies, parallel tracking of multiple sets of information, execution of plan sequences, flexibility in the face of feedback, and the suppression of automated responses. Generally, one can say that "efficiency" is the ability to execute a complex task successfully with a minimal amount of effort. Clearly, then, efficient processing is likely to affect every test in every cognitive domain.

In the neuropsychological literature, efficiency is considered to be most directly assessed by tests such as Backward Digit Span, Trails B, Word Fluency, Mental

Arithmetic, the Stroop Color Naming Task, and aspects of the WCST such as perseverations and set losses (Lezak, 1983; McCarthy & Warrington, 1990; Shallice, 1988). A key element in all of these tasks is the production of rule-guided responses in conjunction with the suppression of highly automated, but inappropriate, responses (Norman & Shallice, 1986).

In recent years, the subject of information processing has garnered considerable attention in the MS literature. Results to date suggest that MS patients may have particular difficulties in this area. For example, tests of verbal fluency using letters, animals, and occupations as cues for retrieval have all shown MS patients to be uniformly and severely impaired compared with normal control groups, regardless of the disease course (Heaton et al., 1985; Klonoff et al., 1991; Rao, St. Aubin-Faubert, & Leo, 1989; van den Burg et al., 1987). Interestingly, in contrast to most other tests where MS groups show increased variability, the variance of the MS group on fluency tasks is either the same or lower than the control group, suggesting a consistent impairment across most individuals. Van den Burg and colleagues (1987) found that MS patients were also substantially more susceptible to interference from more salient aspects of stimuli, as measured by the Stroop Color Naming test.

A recent study (Rao, St. Aubin-Faubert, & Leo, 1989) measured MS patients' mental processing time using the Sternberg (1969) paradigm. On this task, subjects hold in memory a digit set (either 1, 2 or 4 digits), and are asked to respond "yes" or "no" as quickly as possible to whether a target presented on the computer screen belongs to the digit set. Sternberg showed that, as set size increases, there is a linear increase in reaction time. The slope of the line can be considered a pure measure of memory scanning speed independent of basic reaction time. Rao, St. Aubin-Faubert, and Leo (1989) found that, while total number of errors did not differ between the groups, the MS group had a mean slope of 100 msec per digit, which was 47% slower than the control group, with a mean slope of 68 msec per digit.

Taken together, the results of these studies suggest that MS may result in difficulty in several aspects of information processing efficiency that may translate on complex tasks into difficulty with general organization and execution of plans or schemata. The results accord well with the findings discussed earlier of difficulties with mental arithmetic, poor use of strategy on problem solving and memory tasks, perseverative responding, and difficulty with consistent retrieval of previously learned information. The contribution of these types of impairments to other complex tasks clearly warrants further investigation.

In 1977, Beatty and Gange reported the intriguing finding of a significant correlation between scores on various memory tests and scores on motor tests such as Finger Tapping and Static Steadiness from the Halstead-Reitan Battery. This finding was replicated by Rao et al. (1984) who showed that memory impairment among chronic-progressive MS patients was related to decreased upper motor extremity coordination and gait ataxia, despite the fact that the memory measures did not rely on motor responses. Beatty and Gange (1977) suggested that the neuropathology of MS affects a unitary substrate mediating both these cognitive functions. It is tempting to speculate that disruption of the temporal organization of neuronal signals responsible for fine motor coordination may have a similar effect on complex cognitive tasks by disrupting the efficient and coordinated processing of information.

Prevalence of Cognitive Impairment

In groups of MS patients with heterogeneous length of illness and disease course, likely half of the sample will show evidence of some cognitive impairment. For example, Heaton et al. (1985) found that on cognitive tests with no motor component, 46% of remitting-relapsing and 72% of chronic-progressive MS patients were within the impaired range on a global measure of cognitive functioning. These estimates are similar to earlier studies that did not consider disease course (e.g., Ombredane, 1926, 70%; SurrIDGE, 1969, 61%; Peyser et al., 1980, 55%). Rao's group (Rao et al., 1991) has recently reported a careful study of prevalence using a sample of 100 MS subjects (39 relapsing-remitting, 19

chronic-progressive, 42 chronic-stable), and 100 age-, education-, and gender-matched controls. Employing criteria that excluded 95% of the normative sample, Rao reported that 48% of the MS subjects were cognitively impaired. Considering that 5% of these subjects would likely have occurred by normal variation in ability, he puts the final figure for incidence of impairment at 43%. In specific areas of functioning, 21% of the MS patients were impaired on the WAIS-R Verbal IQ, 22 to 31% on tests of learning and memory, 13 to 19% on abstract reasoning tasks, 11 to 25% on processing efficiency measures, and 13 to 19% on visual-spatial tasks. These are likely conservative estimates since the study did not include subjects with severe motor or visual impairment, subjects residing in a nursing home, or subjects who had previously undergone neuropsychological evaluation at their centre.

While the prevalence estimates of cognitive impairment are surprisingly high, there has been a tendency to characterize the MS deficit as mild (Beatty & Gange, 1977; Goldstein & Shelley, 1974; Peyser & Poser, 1986). SurrIDGE (1969) categorized intellectual deterioration in comparison to premorbid functioning. Of the patients studied, 40.7% showed evidence of mild deterioration, 13.9% moderate, and 6.5% severe deterioration. Other studies (e.g., Rao et al., 1984; Vowels & Gates, 1984) found considerably higher rates of severe and incapacitating deficits.

Correlates of Cognitive Impairment

Although depression has been suggested as the cause of poor cognitive performance in patients with MS (Goldstein & Shelley, 1974; Weingartner & Silberman, 1982), this hypothesis is not borne out by studies directly addressing the question. Jambor (1969) found that MS patients who were clinically depressed did no worse, and actually did better on some measures, than nondepressed MS patients. No correlation has been found between depression on the Minnesota Multiphasic Personality Inventory and abstract reasoning tasks (Peyser et al., 1980). Even in a group of relapsing-remitting MS

patients with mild neurologic involvement and minimal functional disability, cognitive impairment is not associated with depression (Good et al., 1992).

Impairment is not confined to late stages of the disease, but is evident in a substantial number of patients in relatively early or mild stages. Indeed, for some patients, difficulty in memory and concentration may be the earliest and most prominent complaint (Young et al., 1976). Borberg and Zahle (1946) reported that of 330 patients, 41.6% showed signs of euphoria and dementia within the first 3 years of the disease. In samples of patients with little functional disability, no current exacerbation of symptoms, and in whom no cognitive impairment is evident on neurological examination, the incidence of cognitive impairment on neuropsychological testing ranges from 30% to 50% (Grant et al., 1989; Ivnik, 1978; Klonoff et al., 1991), figures not particularly lower than the general prevalence rates described earlier. Ivnik (1978) tested 3 groups varying in years since the onset of symptoms (1 to 5 years, 6 to 10 years, and greater than 10 years) and found no differences between the groups on various cognitive tests, even tests sensitive to motor impairment. Others (Heaton et al., 1985; Rao & Hammeke, 1984) have failed to find a correlation between length of disease and impairment on conceptual reasoning tasks.

Counterintuitively, the severity of impairment correlates poorly, if at all, with measures assumed to reflect severity of pathology, including degree of disability or number of relapses (Baumhefner et al., 1990; Huber et al., 1987; Rao et al., 1985). Franklin, Nelson, Filley, and Heaton (1989) described 12 cases where cognitive impairment far outweighed neurologic disability, sufficient to severely incapacitate these individuals in their daily functioning at work and at home. Beatty et al. (1990) found that education and gender were the best predictors of performance, while disease variables such as course type, duration, and age at onset, contributed little to prediction of performance on a number of tasks that are sensitive to MS group impairments. A slight effect of level of disability was found for those tests that put a premium on speeded responses, visual acuity, or required rapid complex informational processing. Beatty

emphasizes, however, that although statistically significant, level of disability was not an accurate enough predictor of test performance to be of any practical importance.

It would appear that chronic-progressive disease course is more likely to be associated with cognitive impairment (Beatty et al., 1989), and the impairments have been shown to be consistently more severe than in relapsing-remitting groups in the areas of information processing speed (Litvan, Grafman, Vendrell, & Martinez, 1988), learning and memory (Jambor, 1969; Rao et al., 1984), and problem solving (Peyser et al., 1980). For example, memory performance in chronic-progressive patients is more severely impaired than in relapsing-remitting patients, to the extent that they learn less (Heaton et al., 1985), show less incremental learning over multiple trials, and are more likely to be impaired on both recognition and recall (Rao et al., 1984). However, Beatty et al. (1990) employed multiple regression to show that disease course did not predict performance on cognitive tests independent of other factors. Rather, chronic-progressive course was highly predictive of increased disability that influenced some, but not all, cognitive measures.

Patterns of Cognitive Impairment

The preponderance of periventricular and frontal lobe plaques have led researchers to consider whether the cognitive impairments found in MS are similar to those found in other diseases with striatal and frontal damage, such as Huntington's disease or Parkinson's disease. The pattern of cognitive functioning characteristic of such "subcortical" groups includes slow and inefficient information processing, impaired memory retrieval, difficulty in problem solving and abstract conceptualization, with an absence of aphasia or apraxia (Cummings & Benson, 1984). Rao (1990) has highlighted the similarity of this pattern to the impairments found in MS groups. He and others (Beatty, 1992; Vowels & Gates, 1984) have postulated that many, if not all, of the mood disturbances and cognitive deficits that occur in MS may be accounted for by frontal lobe dysfunction.

The description of a characteristic pattern of deficits implies that the pattern should be evident in most, if not all, MS patients who are experiencing cognitive difficulties. The hypothesis that a diffuse disease results in a prototypical pattern of deficits has been borne out in the past, particularly in the case of dementia of the Alzheimer's type. The course and pattern of cognitive impairment are the major sources of diagnostic information for Alzheimer's dementia, and are 89% correct on post-mortem examination (Wade, Mirsen, Hachinski, Fisman, Lau, & Mersky, 1987).

Whether or not MS patients show a typical subcortical pattern of cognitive impairment is unclear. Only two papers to date have addressed this question. Rao et al. (1991) calculated the percentage of MS patients who were impaired in a range of cognitive functions. While these authors conclude that the overall pattern of cognitive impairment is compatible with a "subcortical dementia" classification, they also point out that impairment is not uniform in MS. They found that, for example, half of the 31 patients impaired on one memory measure were normal on another. Sustained attention and visual-spatial perception were as likely to be impaired as memory functioning. Importantly, as many or more MS subjects were impaired on verbal measures such as Vocabulary as on measures of abstract reasoning, and as many subjects were impaired on confrontational naming as on measures of information processing, findings that are not consistent with Cummings and Benson's (1984) description of subcortical dementia. Unfortunately, Rao et al. (1991) did not report the frequency with which various combinations of areas of cognitive impairment occurred. The results do, however, argue for a substantial amount of heterogeneity in the types of impairment experienced by an individual with MS.

Beatty (1992) has pointed out that the results of current research give strong support to the hypothesis of a subcortical or frontal dysfunction. As a group, MS patients display all the characteristics associated with this subtype of dementia. However, on inspecting the data for individuals, Beatty et al. (1989) found that only 12% of the MS

patients they tested exhibited the expected pattern of impairment in memory *and* problem solving *and* information processing speed. While the majority of patients were within normal limits on all tests, the remaining patients exhibited relatively isolated deficits in one or another area of functioning. In general, measures of various "frontal" tasks, including perseverative responses on the WCST, verbal fluency, and recognition memory, were independent of one another.

Beatty (1992) argues that the heterogeneity of cognitive impairment in MS may be a powerful tool for understanding the cognitive processes underlying complex informational tasks. For example, Beatty and Monson (1991) identified a group of MS patients who were impaired on the WCST, another group impaired on recognition memory, and a third group who were impaired on both the WCST and recognition memory. Only the group impaired on both tasks had difficulty with metamemory; that is, they overestimated their recall on memory testing by more than 50%. In contrast, the patients who were impaired on one or the other test, but not both, were able to predict their recall performance as accurately as normal controls (Beatty & Monson, 1991).

Conclusion

In reviewing the literature, it is clear that many questions still remain unanswered regarding the cognitive impairment associated with MS. Early clinical observations, followed by more systematic psychometric testing of intellectual functioning, established that cognitive impairment is an important aspect of the disease. While many of the early studies suffered from methodological problems, more recent studies have replicated and extended their findings with samples that are well described (see Peyser et al., 1990). The trend in MS research (and, indeed, in neuropsychological research in general) is moving toward more indepth study of a single area of functioning (e.g., Jennekens-Schinkel et al., 1989; Rao, Leo, & St. Aubin-Faubert, 1989), rather than administering a broad range of clinical tests. While this approach may add more detailed knowledge of a particular area of functioning in MS, it may also muddy the waters. There is the risk that, by

focussing on each area individually, we prematurely assume that the characterization of cognitive impairment associated with MS is complete. We know that, on average, groups of MS patients will be impaired on a variety of tests, particularly those that require learning of new materials, abstraction and conceptualization, mental processing efficiency, and, perhaps, visual-spatial ability. What is lacking, however, is an understanding of how these findings generalize to the individual MS patient. Beatty's work (1992; Beatty & Monson, 1991) would suggest that substantial heterogeneity exists within this group. Without first identifying the nature of this heterogeneity, group studies will continue to be hampered by averaging artifacts that may obscure a wealth of information. At issue is how best to combine information about group performance with adequate assessment of the individual, a dilemma for many domains of psychology.

Chapter 4

Neuropathologic Correlates of Cognitive Impairment

The advent of in vivo structural brain imaging techniques such as CT, and more recently, MRI, has allowed an investigation of the association between cognitive impairment and neuropathology of the individual MS patient. The increased resolution of MRI has quickly made it the imaging method of choice for these studies (see Chapter 2). More recently, several studies have employed positron emission tomography (PET) and single photon emission tomography (SPECT) in order to determine the metabolic or functional integrity of brain regions.

Emotional Functioning

One important purpose for studies was to establish that cognitive impairment, even in early stages of the disease, was due to neuropathology and not to other confounding factors such as depression and psychological distress. The body of existing literature suggests that measures of cognitive functioning show a moderate relationship to the global measures of neuropathology, even in early or mild MS. In contrast, no relationship has been found between neuropathology and level of depression. For example, Clark et al. (1992) found no correlation between ventricular size and depression, although significant correlations were found with cognitive performance. Others (Reischies, Baum, Brau, Hedde, & Schwindt, 1988) have failed to find a correlation between the number of lesions on MRI and emotional disturbance including depression, irritability, or euphoria. However, patients with severe emotional lability had a greater number of total lesions compared to MS groups with other emotional disturbances.

Disease Variables

Few studies have found associations between measures of neuropathology and illness variables. In one study, total area of abnormal signal on MRI in the cerebrum,

cerebellum, or brain stem did not correlate with age of onset, illness duration, or number of exacerbations (Baumhefner et al., 1990). Only the brain stem lesion measure was moderately correlated with functional disability as measured by the Kurtzke (1983) EDSS ($r = -.35$). No correlation has been found between ventricular size on CT and length or severity of illness (Rao et al., 1985), and between number of MRI lesions and the EDSS (Franklin et al., 1988).

Cognitive Impairment

The majority of the studies in this area have investigated the relationship between a global measure of neuropathology (such as total number of lesions or total area of lesions) and a global measure of cognitive impairment (such as a clinical rating of severity). This approach has yielded conflicting results. In one study, Huber and his colleagues (1987) classified MS subjects as minimally, moderately, or severely impaired on a neuropsychological test battery. MRI scans were coded on a 5 point scale for cerebral atrophy relative to age, atrophy of the corpus callosum (CC), and severity of periventricular lesions. The only significant difference between the groups on these measures was that atrophy of the CC was greater for the severely impaired group; general atrophy or periventricular lesions did not differ. In contrast, Franklin et al. (1988) correlated the total number of lesions weighted by size on MRI with performance on individual neuropsychological tests. Correlations with tests of learning and memory ranged from .31 to .36, while tests with a motor component correlated somewhat higher (e.g., Trails A, $r = .47$). The total lesion score correlated .35 with a cognitive summary score derived from the test battery. These authors accounted for the positive finding with the larger number of subjects (60 vs 32 in Huber's study), the more extensive test battery, and the choice of chronic-progressive patients in whom impairment was more likely to be found. Other researchers have also found a relationship between number of cerebral lesion and "grades" of overall cognitive ability (Callanan, Logsdail, Ron, & Warrington, 1989).

Rating scales of impairment and number of lesions may restrict the range of values denoting the extent of neuropathology, thereby artificially restricting the strength of the obtained correlations. In light of this, several studies have employed total lesion area as their measure of pathology. Studies that calculate the actual area of each lesion present on MRI slices have, indeed, shown somewhat larger correlations with cognitive measures. Baumhefner et al. (1990) found that the total area of cerebral abnormal signal intensity on MRI correlated $-.5$ with performance on the Symbol-Digit Modalities test, a test that is sensitive to generalized cognitive impairment. Rao, Leo, et al. (1989), also using total lesion area on MRI, found consistent correlations with tests from various areas of cognitive functioning, in particular, with tests of memory and abstract reasoning. For example, after partialling out the effects of age and education, they obtained a correlation of $-.49$ with number of categories completed on the WCST, and correlations in the order of $-.31$ to $-.48$ with delayed memory measures.

Ventricular enlargement, either on CT (Rao et al., 1985), or on MRI (Clark et al., 1992) is associated with cognitive impairment on a variety of tests. Ventricular enlargement is presumed to reflect the preponderance of demyelinating lesions within the white matter surrounding the ventricles. For example, Rao et al. (1985) found that a linear measurement, the maximum width of the third ventricle, predicted performance on tests of learning, memory, and conceptual reasoning. Somewhat surprisingly, a subjective global rating of ventricular enlargement was better than any linear measurement in classifying patients with impairment on multiple cognitive tests. As mentioned earlier, no ventricle measure correlated with length of illness or with the EDSS.

Clark et al. (1992) measured ventricle size on MRI for 123 relapsing-remitting MS patients. An important feature of this study was the inclusion of a well-matched control group ($n = 60$). Ventricular enlargement and periventricular white matter lesions occur with normal ageing. Memory functions and speed of information processing also decline with age. Hence, without a control group, one cannot be assured that an association

between ventricle size and various cognitive tasks is not a normal phenomenon of aging. Clark et al. (1992) calculated the correlation matrix for 9 linear and area ventricular measures and 12 neuropsychological tests. For the MS group, 29 of the possible 108 correlations were significant, while none of the correlations for the normal controls were significant. Of note was the finding that the tests with the highest demand on tactile and motor functions, such as the Tactual Performance Test, had fewer significant correlations than measures of memory, supporting the hypothesis that motor dysfunction does not account for cognitive impairment.

While studies of ventricular size have obtained a consistent association with cognitive performance, the magnitude of the relationship is modest, usually with correlations in the order of .2 to .4. These are several possible reasons for this. As Clark et al. (1992) point out, ventricular enlargement is a secondary measure of disease burden, since it may reflect pathology only in the periventricular region, and may not include demyelination distal to the ventricles. Number of lesions or total lesion area throughout the brain may be better estimates of the extent of global pathology. The correlations obtained with these measures, however, are not much larger. Instead, the difficulty may be in the very notion that the extent of pathology should correlate equally well with tests of memory, abstract reasoning, visual-spatial ability, and so on. In classic neurology, cognitive functions are assumed to some degree to be localized in specific grey matter regions. To date, there is no comparable theory for the effects of white matter lesions on cognition. Since one well-placed spinal or cerebellar lesion can render a patient incapable of walking, it is not inconceivable that the same is true for white matter lesions and cognitive functions. Given the idiosyncratic nature of MS neuropathology, whether or not a particular cognitive function is affected in an individual may depend on such factors as the localization, size, and distribution of their lesions. For this reason, one should not expect a strong fit between cognitive measures (particularly individual test scores) and global measures of neuropathology. Global indicators of neuropathology give no clue as

to the relationship between affected area and cognitive dysfunction, and one is sobered by the finding that the strongest relationships found are accounting for at best 20 to 22% of the variance on tests.

Lesion Placement and the Role of the Corpus Callosum

Several recent papers that focus on demyelination within the corpus callosum (CC). Huber et al. (1987) found that a rating of atrophy of the CC was associated with more severe cognitive impairment. To investigate this further, Rao and his colleagues (Rao, Leo, et al., 1989) found that the total area of the CC (presumably measuring amount of atrophy due to demyelination) predicted performance on processing efficiency measures such as memory scanning speed, sustained attention, and rapid problem solving. In contrast, total number of cortical lesions was the best predictor of recent memory, abstract reasoning, language ability, and visual-spatial problem solving, areas of cognition most closely associated with classic "cortical" dementia. Unfortunately, CC atrophy correlated equally well with tests of verbal skill and reasoning that should be "cortical" in nature, such as the Vocabulary and Comprehension subtests of the WAIS-R.

Pozzilli et al. (1991) based their hypotheses on neuropsychological and animal literature suggesting that the anterior CC (the genu) is specifically involved in cognitive functions, while the posterior CC (the splenium) is involved in sensory integration. They used multiple regression analysis using area of the genu, splenium (both corrected for brain size), periventricular lesion area, and subcortical lesion area (lesions separate from the ventricles) to predict performance on various cognitive and visual-spatial tasks. They found a specific and independent association between anterior CC size and Verbal Fluency, independent of the periventricular and subcortical lesions. However, no independent relationship of the anterior CC was found with other cognitive tasks including problem solving and memory performance. No independent relationship was found for the posterior CC to any of the cognitive measures, including visual-spatial and constructional tasks. Thus, while CC atrophy is clearly associated with cognitive impairment, it remains

to be seen whether CC atrophy is related to specific functions or is simply another marker of the extent of total cerebral demyelination, in the same way as ventricular enlargement.

Several papers have classified lesions according to brain regions. Swirsky-Sacchetti et al. (1992) calculated total lesion area on MRI in the frontal, temporal, and parieto-occipital regions unilaterally. Multiple regression analyses indicated that left frontal lobe involvement best predicted performance on problem solving, verbal recall, and word fluency tasks. Left parieto-occipital involvement best predicted deficits in verbal learning and visual integrative skills such as the Hooper Visual Organization test. In contrast, Huber, Bornstein, Rammohan, Christy, Chakeres, and McGhee (1992) did not find any function-specific association with area of MRI lesion in the left and right hemispheres, or in left and right frontal, temporal, parietal, and occipital lobes. Total lesion area, regardless of distribution, correlated best with the vast majority of neuropsychological tests, ranging from $r = .31$ for a problem solving test (Category Test) to $r = .82$ for an alternate sequencing task (Trails B). Most correlations were in the order of .5 to .6, substantially larger than those obtained in similar studies, a particularly surprising outcome given that the study only included 35 patients. The correlations were consistent across all areas of lesion placement. As with the CC studies, it remains unclear as to whether white matter lesions show functional specificity similar to those seen with grey matter lesions.

Other Imaging Techniques

Perhaps all of the measures, including ventricular enlargement, number of lesions, lesion area, and CC atrophy, reflect diffuse processes that are not adequately captured by the structural abnormalities evident on MRI. Functional studies have identified some interesting reasons to believe that this is the case. Feinstein, Kartsounis, Miller, Youl, and Ron (1992) have shown that T1 relaxation time values on MRI taken from samples of normal-appearing frontal lobe tissue correlated as highly with cognitive ability as did total lesion area, including naming ability (Pearson's $r = -.43$), problem solving (Spearman's $r =$

-.43) and visual memory (Spearman's $r = -.50$). Only frontal lobe samples were obtained, so it is not clear whether this phenomenon is specific to frontal lobe functioning or whether it would apply to other areas as well. A similar intriguing association between T1 parameters and severity of cognitive decline has been reported in the Alzheimer's literature (Besson, Crawford, & Parker, 1989). Increased T1 relaxation times reflect the presence of microscopic abnormalities including perivascular inflammation, myelin breakdown, and astrocyte hyperplasia in normal-looking white matter (Allen, Glover, & Andersen, 1981).

Evidence for decreased blood-flow of the frontal lobes and the left temporal lobe has been found using single proton emission computerised tomography (SPECT) in a group of 17 MS patients with impaired verbal fluency and memory performance compared to a well-matched control group (Pozzilli, Passafiume, et al., 1991). Blood-flow was measured by uptake of Tc99m HMPAO, a radio-pharmaceutical that passes the blood-brain barrier and is trapped within functioning cells. In spite of the metabolic asymmetry of the left hemisphere in the MS patients, no lateralized differences appeared on MRI. In a second study measuring cerebral metabolic rates for glucose uptake using positron emission tomography (PET) with the analog tracer deoxyglucose, Pozzilli et al. (1992) found metabolic asymmetry only in those MS patients who had extensive CC atrophy on MRI compared with controls or with other MS patients without CC atrophy. Left frontal, temporal, and parietal association cortices showed significantly lower metabolic levels on the left than on the right for this group. Again, no asymmetry was found in the distribution of lesions on MRI for any group. The asymmetry of metabolic functioning is consistent with evidence from animal studies showing that normal metabolic interactions between the hemispheres are disrupted with callosotomy in the rat (Soncrant, Horwitz, Sato, Holloway, & Rapoport, 1986).

Investigations of the relationship between cognition and functional measures of the brain are in their infancy, and thus it is difficult to understand the implications of these findings. The importance of these studies, however, is that they highlight changes to the

functional status of brain regions that may be distal to structural abnormalities evident on MRI. The findings of frontal lobe dysfunction and left temporal lobe dysfunction are of particular interest because of their association with cognitive impairments found in MS patients, including abstract reasoning, verbal fluency, perseverative responding, and learning and memory.

Summary and Future Directions

The relationship between cognition and neuropathology in MS is sufficiently established to rule out alternative explanations for the impairment such as depressed mood or motor dysfunction, even in samples of early and mildly affected MS patients. While some studies have obtained surprisingly high correlations, (e.g., Huber et al., 1992), most researchers have found that, at best, global measures of neuropathology account for approximately 20% of the test variance. The result, replicated often, that increased neuropathology is associated with increased cognitive impairment has not broadened our understanding of the role of myelin in cognitive functioning. Evidence thus far supporting the hypothesis of more specific relationships between lesion site and cognitive functions (as would be predicted by models of grey matter lesions) is contradictory. The question is how to best to proceed with future research in this complex area.

As with the cognitive literature, a major problem concerns the heterogeneity of the MS subjects. With the exception of Clark et al. (1992), who included 123 MS subjects, no study described earlier included more than 64 MS subjects, and some, as few as 17 (Pozzilli, Bastianello, et al., 1991). The average number of subjects was 36. Considering Rao et al.'s (1991) estimate of the prevalence of cognitive impairment (43%), the typical study included 15 subjects with cognitive impairment. However, since cognitive impairment is not consistent across all areas, far fewer subjects would be impaired on any one test. Correlations, multiple regression, or statistical tests of area-specific associations, particularly using individual test scores, will suffer from a lack of power due to the preponderance of unimpaired subjects.

A second difficulty with the research to date is its reliance on clinical neuropsychological tests. One can fail a complex task such as the WCST for many reasons, and expecting that one specific lesion site will be associated with its impairment is an oversimplification. (Indeed, this is one good reason why global measures of neuropathology correlate moderately with virtually every neuropsychological test, since they are multifaceted and draw on numerous abilities.) The work of Beatty (1992; Beatty & Monson, 1991) exemplifies this. He found that subgroups of MS patients with memory impairment differ qualitatively from MS patients with problem solving *and* memory impairment. Both groups are impaired in their ability to recognize previously learned materials, but their underlying deficits may differ. Analysis of the quality of impairment on neuropsychological tests may be essential prior to identifying associations with anatomical brain regions.

The techniques of neuropsychology employed to identify the behavioural sequelae of focal cortical or grey matter damage may prove fruitful in this regard. By carefully selecting groups of MS patients (or even several patients) who are differentially impaired in two cognitive areas, double dissociations between impairment and lesion sites can be identified (Shallice, 1988; Teuber, 1955). In this way, hypotheses may be generated as to the function(s) of particular white matter tracts and replicated with similarly impaired MS patients.

Several developments in MRI scanning and analysis may be of particular interest in MS research. For example, lesions in MS occur within axonal tracts that often project to distal and diffuse areas of the brain. Two lesions occurring, for example, even a few millimeters apart within the internal capsule will affect very different areas of the brain, and may have different behavioural consequences. In subgroups of MS patients whose cognitive impairment is well documented, careful morphometric analysis of lesions, with registration to a standardized atlas, may be particularly useful in identifying anatomical commonalities. The technique reconstructs three dimensional images of a "typical" or

averaged brain (Jernigan, Archibald, Berhow, Sowell, Foster, & Hesselink, 1992). As well, the use of gadolinium-dTPA enhanced scans will be of particular interest in the future in providing information about the various stages of a lesion (Paty, 1990). A lesion in its early stages of demyelination may have very different effects on cognition than a gliotic scar, and MRI cannot disentangle these two on routine scan.

An equally intriguing issue for research in MS is the information about brain functioning that the structural images of MRI alone cannot provide. Functional images and metabolic measures of brain functioning, such as PET and SPECT have already given indications that MS pathology may result in important brain changes that are diffuse, distal to, and perhaps independent of, the site of lesions (for example, the work of Pozzilli et al., 1992 and Feinstein et al., 1992). An important caveat to the use of measures such as PET and SPECT is that they assume a constant baserate for uptake in all areas of the brain. In a disease such as MS, where the blood-brain barrier is compromised, the basic assumptions of the model may be violated, leading to erroneous inferences regarding area-specific changes in metabolic functioning. The techniques for assessing in vivo brain changes need to become better understood before inferences can be made about the information they provide.

One final caveat: There has been an explosion of papers in this area in recent years. Unfortunately, the quality of the research has been extremely variable. Reminiscent of the early neuropsychological literature in MS, researchers are inconsistent in their descriptions of sample characteristics, with no mention, for example, of how many patients are experiencing exacerbations, current medications, or recruitment procedures. In several studies, MRIs were administered up to six months prior to the date of neuropsychological testing. In one study (Mariani et al., 1991), scans were completed using a range of repetition times and echo times. The method section states that four images were "usually" obtained on the axial plane, and coronal slices were "frequently" obtained. No mention was made of how many slices were used for each subject to obtain the numerical

estimates of lesion area. Further, although this was designed as a longitudinal study with 24 months intervening between the two test sessions, no attempt was made to precisely reposition the head for scanning, or even to use the same scan protocol on the two sessions. Thus, changes in lesion area from one session to the other may have had little to do with actual changes in neuropathology.

Another study (Izquierdo, Campoy, Mir, Gonzalez, & Martinez-Parra, 1991) assessed MS patients using the WAIS (a test that was revised in 1981) and an obscure memory battery that is not described in detail, with no control group, and using unspecified normative data to assess impairment. The authors then correlated the memory measures with lesion area in the periventricular region, the brain stem, the corona radiata, the centrum semiovale, and the basal ganglia. Based on the finding that only periventricular lesions correlated (.34 to .44) with 4 of the 11 memory measures, they concluded that verbal learning and memory disturbances are specifically due to periventricular lesions. With only 17 subjects, it is highly likely that the number of patients with lesions in an area such as the basal ganglia was close to zero, but the authors fail to report the actual incidence of lesions within each area.

Clearly, there is a need for researchers in this area to provide detailed information regarding both the imaging techniques employed and the methods for neuropsychological assessment. Without such information, the outcomes of studies remain uninterpretable.

Chapter 5

Methods

Subjects and Test Procedures

The MS patients were volunteers from the University of British Columbia MS Clinic who met the following criteria: 1) age less than fifty; 2) a diagnosis of clinically definite MS with relapsing/remitting course; 3) in remission at the time of the assessment; 4) diagnosis made before the age of forty; 5) functionally independent as assessed using the Kurtzke Clinical Rating Scales and the Expanded Disability Status Scale (Kurtzke, 1955; 1983); 6) no medication or excessive non-prescribed drug usage (e.g., alcohol abuse, cocaine use); 7) no other complicating medical condition; and 8) no history of psychiatric illness predating the diagnosis of MS. These criteria ensured a relatively homogeneous sample that was free from many of the possible confounding factors discussed in the literature (Klonoff et al., 1991; Peyser et al., 1990).

Where possible, the MS subjects were asked to find a same sex, unrelated control subject of similar background and interests. Once potential control subjects were identified, they were interviewed by phone to ensure that they met the same criteria where appropriate as the MS group, including age, medical complications, psychiatric history, and drug usage.

Medical history and most recent neurological examination results were obtained for the MS subjects through the MS Clinic records. On the test day, all subjects were interviewed in order to obtain demographic information, and several psychological and personality tests were administered. A neuropsychological test battery was then administered in random order. The battery took approximately 3 hours to complete, and subjects were given appropriate rests during the examination period. The MRI was administered during the afternoon on the same day. The present study included 177 MS

patients and 89 matched controls with complete neuropsychological and historical data. Of this group, scans were available for data analysis for 150 MS patients and 66 controls.

The procedures in the present study were approved by the University of British Columbia Clinical Screening Committee, and informed consent was obtained from all subjects.

Cognitive Test Battery and Analyses

Thirteen tests were selected for analysis in the present study. These tests were administered as part of a larger neuropsychological battery (described in Klonoff et al., 1991). The tests were selected because they cover a range of cognitive functions that have been assessed previously in MS, including five areas of interest: verbal skills, learning and memory, abstract conceptualization, information processing efficiency, and constructional abilities. The tests included the Information, Vocabulary, Digit Span, Arithmetic, Similarities, Picture Completion, and Block Design subtests from the Wechsler Adult Intelligence Scale-Revised; the Benton Visual Retention Test; Word Fluency (FAS); Trails A & B, and Categories from the Halstead Reitan Neuropsychological Battery; Paired Associates from the Wechsler Memory Scale - Revised; Memory for Objects. A description of each test is provided in Appendix B.

Analyses performed included: 1) descriptive statistics and significance tests comparing MS and controls for each neuropsychological test; 2) an analysis describing the distribution of impairment within the MS group; 3) a cluster analysis that identified patterns of impairment across tests from various cognitive domains; and 4) two independent validations of the cluster solutions.

Descriptive statistics. Mean group performance was analysed with Hotelling's T-square omnibus test to control for Type I error rate, and followed up with univariate t -tests. All significance levels were reported for one-tailed t -tests, since brain damage to the MS group was expected to result in decreased levels of performance compared to matched controls. Group differences in variance were tested using Hartley's F-max ratios.

Incidence of impairment. Since the purpose of the present study was to investigate patterns of impairment in MS, a logical first step was to identify those subjects whose cognitive impairment was unequivocal.

On each test, the scores of all subjects were standardized relative to the control group. That is, z-scores were calculated using the mean and standard deviation of the control group. Scores that reflect number of errors or response times were multiplied by -1, so that negative z-scores consistently reflected poor performance. Impairment on a single test was operationally defined as a z-score of -1.64 or greater, which is consistent with the significance level chosen for the one-tailed *t*-tests described earlier, and indicated a level of performance worse than 95% of the normative sample. The percentage of MS subjects who were impaired on each of the 13 tests was calculated.

In order to classify subjects as "impaired" or "unimpaired", the number of tests out of 13 that met this criterion were counted for each subject. The number of impaired tests required to classify a subject as cognitively impaired was derived by examining the distribution of impaired tests for the control group, and choosing the number that excluded at least 95% of the control group. Such a stringent criterion likely underestimates the prevalence of significant cognitive impairment among the MS patients as some subjects may decline from a high level of premorbid functioning to performance levels that would still be considered within the average range.

For the purposes of the cluster analyses, two groups were formed. The impaired group included MS and control subjects (i.e., 5%) who fell below the cutoff described above. The unimpaired group included MS and control subjects (95%) who were not classified as impaired.

Cluster analysis. Cluster analysis was employed in order to identify patterns of impairment. Cluster analysis is a non-inferential statistical technique that can be used on multivariate data in order to create classifications by forming relatively homogeneous groups of subjects with similar profiles of scores across multiple variables. Cluster

analysis is thus a descriptive technique that is particularly useful when the structural aspects of multivariate data are of interest and a large number of subjects are included in a study (Kaufman & Rousseeuw, 1990).

The most widely used and best investigated method of clustering is the hierarchical agglomerative method (Ward, 1963). Ward's minimum variance method, used in the present study, considers all possible combinations of profiles. The method computes a distance measure (squared Euclidean distance) between profiles and combines the pair with the smallest sum of the-squared differences to form the first "cluster". Subsequently, it combines profiles that minimize the increase to the within-group sum of squared variance. The technique parcels the total sum of squares into "within-group" and "between-group" variability, thus yielding a measure of the percentage of variability accounted for by the clustering solution. In an ideal cluster solution, group members would obtain very similar profiles of scores, thus yielding a minimal within-group error term. As well, an ideal solution would yield group profiles that are clearly distinguishable from one another. Thus, the majority of the variability should be accounted for by the between-group term.

Ward's (1963) method is not as sensitive to small outlier groups as are other types of cluster techniques (Milligan, 1980), but has been shown empirically to yield more accurate clusters than three other techniques, namely single linkage, complete linkage, and average linkage. The method is biased toward finding severity groups or spherical clusters (Blashfield, 1976). Golden and Meehl (1980) showed that Ward's method yielded equally high or higher values of coefficient kappa compared with other techniques. Coefficient kappa indicates the improvement in classification over random assignment. However, no matter which technique is employed, the stability of the cluster solution is determined by the reliability of the measures being clustered. The more unreliable the test variables, the less susceptible the clusters will be to replication (Kaufman & Rousseeuw, 1990).

Morris, Blashfield, and Satz (1981) point out that cluster methods using different types of distance measures and combination criteria will yield different cluster solutions for the same data set. They further point out that, even with randomly generated profiles, cluster analysis will yield a solution. Thus, the empirical assessment of internal consistency in the obtained cluster solution using other statistical methods such as discriminant function analysis is critical. Validity of the cluster profiles may be assessed by determining their ability to predict performance on an independent set of measures.

Cluster solution. In the present study, cluster analyses were carried out separately for the impaired and unimpaired groups. Solutions were obtained separately for the two groups in order to determine: 1) whether patterns arose that were specific to the impaired group or occurred naturally in the unimpaired group; and 2) whether profiles occurred within the unimpaired group with an overrepresentation of MS subjects that might signal early or less severely impaired profiles. Clustering was carried out on three of the 13 tests using Ward's (1963) hierarchical method. Tests from the three areas of cognition that showed evidence of impairment in the present study were included, namely, learning and memory (Paired Associates), information processing efficiency (Word Fluency), and constructional ability (Benton Visual Retention). The tests have no fine motor coordination component, and have the widest range of scores of the tests within each cognitive area.

The cluster solutions were chosen when 85% of the variability was between-group. Since Ward's method tends to keep groups separate with similar profiles that show an overall severity difference, the resultant group profiles were examined visually and any similar profiles were combined, provided that they were also combined as the next steps in the clustering solution. Discriminant function analyses were performed using the cluster groups as criteria and the 3 clustering variables as predictor variables, both before and after groups were combined because of visual similarity. This procedure ensured that the resultant groups were consistent and that group discriminability was maintained.

Cluster validation. One of the major assumptions in neuropsychological research is that impairment of function resulting from brain damage is constant (Shallice, 1988). Thus, the clusters should predict the profile of performance on a new set of tests that tap cognitive operations similar to those necessary for the three clustering tests. In order to validate the cluster profiles, different tests were chosen from the test battery that emphasize the same three cognitive functions, namely, memory, processing efficiency, and constructional ability. The tests are compared briefly below.

Word Fluency versus Similarities. Both of these tests require that the subject retrieve appropriate information in response to a rule, while suppressing other information that comes to mind, perhaps more readily, that does not fit the rule. Word Fluency requires subjects to access words on the basis of similar first letters while suppressing other more fluent responses, such as words that are semantically associated with the previous word. Similarities requires the subject to identify the feature that two items have most in common. The word or aspect of the two items that is correct will be the higher-order category; for example, "apple and banana" are both fruits; "table and chair" are both furniture. Subjects must suppress other aspects that come to mind, such as that "table and chair" are made of wood, have legs, etc. There are obvious differences between the tasks; Word Fluency is a timed test, requiring subjects to make continual responses over a one-minute period, while Similarities requires a single, untimed, response. However, both are considered tests that require efficient selection and retrieval of verbal information, and both have been associated with frontal lobe dysfunction.

Benton Visual Retention versus Block Design. Both tests require copying of a geometric design, one using pencil and paper and the other by actually placing blocks in a similar configuration. Performance on the Benton may be impaired because the subject has difficulty remembering the visual array for short intervals, since the test was administered with a ten second interval from presentation to

copy. Memory is not a necessary component of Block Design since the design to be copied is visible to the subject at all times. However, both these tests are sensitive to constructional and visual-spatial difficulties, and the Benton has been shown consistently to be more closely related to performance on other copying tasks than memory tasks.

Paired Associates versus Memory for Objects. The tests require the subject to recall a list of words after a short delay. While Memory for Objects presents study items in a visual array (subjects see the actual objects arranged on a table), all the objects are easily encoded verbally, and hence the test likely reflects verbal memory more than visual memory. Paired Associates also requires the subject to recall items, but in response to an associative cue that was presented with the item at the time of study. As well, Paired Associates are presented over three trials, whereas Memory for Objects entails one-trial learning. These two tests may be most similar on the first trial of Paired Associates. Despite these differences, if subjects are impaired in the areas of learning and/or retrieving verbal information, they would likely have difficulty on both of these tests. Memory for Objects is likely a less sensitive measure of memory ability; this conjecture is supported by the finding that most control subjects perform the test without error.

Cluster validation analyses. A discriminant function analysis was performed using the validation tests as predictors and the original cluster groups as criterion groups. This provided an overall correct classification rate for each cluster group. Chi-square statistics were calculated in order to assess the improvement in classification over chance assignment. Analyses were carried out separately for the unimpaired and impaired groups.

A second approach was to consider the pattern of differences between the impaired clusters on the three tests, and to determine whether the profile pattern was also found with the replication tests. For each of the three clustering tests, differences between the cluster groups were assessed with a one-way Analysis of Variance (ANOVA) and

Tukey pairwise followup procedures. A single hypothesis was generated describing the group differences expected with the validation test. For example, if only one cluster group obtained significantly better performance than all other groups on the clustering test, then this pattern should obtain on the validation test as well. Groups with similar performance were combined so that each hypothesis was tested using a t -test.

Magnetic Resonance Imaging (MRI) and Cognitive Deficits

This section describes the methods and analyses used to determine the relationship between cognitive impairment profiles to findings on the MRI. Subjects included in the analyses were 150 MS subjects and 66 control subjects who underwent an MRI scan on the day of their neuropsychological testing.

MRI protocol. All subjects were scanned on a Picker International Cryogenic MR 2000 machine, with a magnet strength of .28 Tesla operating at .15 Tesla. Images were obtained using a simultaneous multiple 12-slice (1 cm) spin echo sequence with a repetition time of 2000 msec and two echo times, 60 msec on the transverse plane and 120 msec on the sagittal plane. Scans were read and coded by a radiologist, Dr. David Li, for presence of a lesion in fifty predetermined brain sites.

MRI analyses. The main purpose for including an MRI component to the study was to determine the association between lesion site and cognitive impairment. Several statistical problems arise, however, because of the large number of lesion sites and because of the small number of subjects in several of the impaired cluster groups.

First, due to the large number of lesion sites, the analyses only addressed a single lesion model, that is, the hypothesis being tested was whether a single lesion site is associated with a particular cognitive profile. Equally plausible, however, is the scenario where a lesion in two or more adjacent sites cause a deficit to occur, or alternatively, a lesion occurring in either one site or another may lead to a deficit. Entertaining all the possible combinations of lesion sites would lead to an unreasonable number of statistical

tests. However, a single lesion analysis will likely rule out the majority of lesion sites, thus allowing further analyses that may include multiple sites.

Even considering only a single-lesion model, 50 lesion sites makes Type I error a problem. One way to decrease error was to pare down the number of sites considered for analysis by including only those sites with reasonable baserates of lesion occurrence. Although lesions were found in all 50 of the sites in the MS group, the extremely low or high frequency of lesions in some sites precluded their usefulness in differentiating the impaired groups. For example, Clark et al. (1992) found that over 80% of MS patients had lesions in the periventricular occipital horns, while several other sites had lesion baserates as low as 3%. Since the smallest cognitive cluster group constituted 5% of the MS sample ($n = 8$), sites with lesion frequencies below 5% were excluded. Sites with lesion frequencies over 45% were also excluded. Brain stem sites were not included since this area would not be considered important for complex cognitive functioning. On the basis of these exclusion criteria, 24 of 50 sites were chosen for analysis. They included the left and right hemisphere 1) frontal, frontal/parietal, and parietal supraventricular regions, 2) temporal horn of the periventricular region, 3) frontal horn and parietal body of the deep white matter, 4) internal capsule, 5) frontal, parietal, and temporal grey/white junctions, 6) insula of the deep grey matter, and 7) the splenium and genu of the corpus callosum.

For each site, a frequency table was constructed indicating the lesion occurrence for each of the impaired cluster groups and the combined unimpaired MS group. The best outcome for the lesion data would be so obvious that no statistics would be needed; that is, if all the lesions in a given site fell within one of the cluster groups and none of them occurred within other groups. Less obvious outcomes were assessed statistically using the chi-square statistic. However, the low lesion baserates in some sites and the small number of subjects in several of the clusters pose a problem. For example, a frequency table (see Table 1) was constructed using a hypothetical lesion site with a baserate of 10%. On the

basis of the actual n's obtained from the cluster solution, the table indicates the number of lesions in each cluster that would be expected to occur by chance alone. In this example, the expected frequency (EF) of lesion presence is less than 5 in 42% of the cells (5 of 12).

Insert Table 1 here

When the EFs are low or if any cell has an EF of 1 or less, the obtained statistic no longer approximates the chi-square distribution. Siegel and Castellan (1988) suggest that no more than 20% of the EFs be less than 5, with no EF equal to or less than 1. They point out that as the number of rows and columns of the frequency table increase, and as the total number of subjects increases, the chi-square statistic approximates the distribution more closely. However, no guidelines are available in the literature as to when the approximation is acceptable. This does not prohibit the analysis of the low baserate sites. It should, however, make one cautious about interpretation of the frequency table on the basis of the chi-square statistic, particularly when the results are not clear cut. Using the present number of cluster groups and subjects, a lesion baserate of 20% yields 4 of 12 of cells (33%) with EFs less than 5. The EFs are acceptable when the lesion baserate is 30%, yielding 2 of 12 cells (17%) less than 5. Whatever the outcome, the result will be more interpretable if the result is consistent with the extant literature on a particular cognitive function. A brief review of the literature on neuropathological correlates of the three cognitive functions being clustered is contained in Appendix C.

In view of these difficulties, chi-square values and alpha levels were obtained from a Monte Carlo series of frequency tables where lesion baserates and outcomes were systematically varied. The value for alpha was then chosen a priori to be conservative enough to adequately control chance error, but to include outcomes that were theoretically meaningful. Table 2 lists the resultant chi-squared statistics and alpha values

for artificially constructed frequency tables at three lesion baserates, 15%, 20%, and 30%. The percentage of lesion occurrence was systematically varied within the smallest group ($n = 8$) with the remainder of the lesions spread equally (in terms of EF's) throughout the other 5 groups. The smallest group was chosen for the analysis because, statistically, a meaningful result within the smallest group will be most difficult to obtain.

Insert Table 2 here

As is evident from Table 2, alpha increases as the percentage of lesions present in the group increases, but dramatically decreases as the lesion baserate increases. The chi-square statistic, used with the present group n's, is extremely conservative. At a baserate of 35%, even with lesions occurring in 100% of the smallest group, the chi-square statistic is not significant. Thus an alpha of .01 is adequate to be applied to all the analyses. While this value excludes findings for the smallest group for lesion sites with baserates over 25%, the value is less conservative than the Bonferroni adjusted rate of .05 with 24 tests ($p=.002$). When the same percentage criteria are applied to the next largest group ($n=11$), all alpha values exceed the Bonferroni adjustment. Bonferroni adjustments to large numbers of tests are found, in Monte Carlo studies, to be overly conservative (Hays, 1973).

Even with some highly significant findings, the usefulness of the information is likely theoretical and not diagnostic. For example, with a 20% lesion baserate, if lesions occur in 85% of the group with the smallest number of subjects, the diagnostic specificity and sensitivity are good, .84 and .82, respectively, yielding percentage correct classifications of 84%, with a false positive rate of 15%. The false positive rate increases as the baserate increases, so that at 40% lesion baserate and 85% of the group with a

lesion present, the false positive rate will rise to 36%, even though the sensitivity remains at .82.

Chapter 6

Results

Demographics

The demographic information contained in Table 3 indicates that the MS and control groups were well matched on age, education, and female to male ratio. The distribution of highest occupational status achieved was similar. The only aspect that differed between the two groups was in the area of current employment status. Fewer MS subjects were working full time than controls (39.5% vs 66.3%, respectively). MS subjects were more likely to be unemployed (21.4% vs 2.2% for the controls) or working part time (21.5% vs 14.6% for the controls).

Insert Table 3 here

The neurological data for the MS patients are presented in Table 4. The MS sample, on average, began to experience first symptoms at age 27, with an average of 5 years from symptom onset to diagnosis. The Kurtzke Functional Scales and EDSS indicate minimal physical dysfunction on neurological examination. In particular, the minimal score on the Mentation subscale is noteworthy, indicating that cognitive impairment was not evident in virtually all subjects in the sample on standard neurological testing. The EDSS indicated that the sample was ambulatory and able to function without assistance for a full day.

Insert Table 4 here

Neuropsychological Battery Descriptive Statistics

The comparison of the MS group and the controls yielded a significant multivariate Hotelling's T-square ($T(264) = 4.23, p < .0001$), with 9 of the 13 followup contrasts significant. Variance for the MS group was larger on 5 tests, as indicated by F-max statistics, including one test (Digit Span) where the groups means did not differ. Means, standard deviations, t -test and F-max statistics for 13 neuropsychological tests are presented in Table 5. All significance levels reported for the t -tests are one-tailed.

Insert Table 5 here

Incidence of Impairment

Using the control group mean and standard deviation to calculate z-scores, impairment on a test was operationally defined as a z-score of -1.64 or less. This cutoff corresponds to the 5th percentile of the normal sample. Table 6 indicates the percentage of MS subjects with scores below the 5th percentile. On ten of the thirteen tests, 10% or more of the MS group were impaired. These include the nine tests with significant group mean differences, and Digit Span, for which the group variances differed. Nearly a quarter of the MS group were impaired on the Benton Visual Retention Test, Paired Associates, and Trails B-A.

Insert Table 6 here

The distribution of impaired tests for the two groups is presented in Table 7. The mean number of impaired scores for the MS group (mean = 1.76, sd = 1.91) was larger than for the control group (mean = .73, sd = 1.08), as indicated by a t -test ($t(264) = 4.72$, $p < .001$, two-tailed). Of the total subject sample, 80% of the control group had zero or one impaired test score, while only 55% of the MS group had zero or one impaired test score. Five control subjects (5%) performed in the impaired range on 3 or more tests, compared to 58 MS subjects (33%). No control subject was impaired on more than 4 tests, whereas 14 of the MS patients (8%) were impaired on 5 or more tests. Two MS subjects were impaired on 9 of the 13 tests. On examining individual profiles for the MS subjects with 5 or more impaired tests, 8 subjects scored near or substantially below the cutoff on virtually every test administered, suggesting global cognitive decline. Considering the results, any subject with 3 or more z-scores of -1.64 or lower (i.e., below the 5th percentile of the control group) was classified as "impaired" for the purposes of further analyses. Thus, the impaired group consisted of 58 MS and 5 controls. The unimpaired group included the remaining subjects, 119 MS and 84 controls.

Insert Table 7 here

Cluster Analysis Results

Cluster analyses were performed separately for the impaired and unimpaired subjects using Ward's (1963) hierarchical method. The clustering variables were the

standardized scores on the Benton Visual Retention Test, Paired Associates, and Verbal Fluency.

The clustering solution for the impaired group with 85% between-group variability resulted in 10 groups. The profiles of the 10 groups were graphed, and any groups with profiles that appeared to be similar in shape but with a severity difference were collapsed. Collapsing visually similar profiles yielded 6 final groups. The combinations corresponded to the next combinations in the cluster analysis, resulting in 63% between-group variability. Discriminant function analysis using the 3 clustering variables as predictors and the original 10 impaired clusters as criterion groups correctly classified 96.83% of the subjects. After collapsing the profiles to 6 on the basis of visual similarity, the correct classification rate dropped only slightly to 95.24%. Three of the 6 groups were 100% correctly classified, while the other three groups each had one subject misclassified. The profiles of the ten original impaired clusters and the resulting six groups are presented in Figure 1.

Insert Figure 1 here

For the unimpaired subjects, the cluster solution with 85% between-group variability yielded 14 groups. These resolved into 10 groups when similar profiles with severity differences were combined. The visually collapsed groups corresponded to the next statistical combinations in the cluster analysis, and resulted in 72% between-group variability. Discriminant function analysis performed on the 14 original unimpaired clusters yielded a correct classification rate of 91.63%. When collapsed to form 10 groups, 89.0% were correctly classified, ranging from 100% correct for 3 of the groups to 75% for 1 group. As with the unimpaired groups, the discriminant function analyses

indicated that the unimpaired groups were clearly distinguishable by three scores, and that a minimal amount of discriminability was lost by collapsing the groups on the basis of visual similarity. The profiles of the fourteen original clusters and the ten resulting unimpaired groups are presented in Figure 2.

Insert Figure 2 here

Description of the Clusters

Impaired cluster groups. Of the six obtained clusters, two showed a decline in functioning across all three cognitive functions, including memory, processing efficiency, and visual-spatial ability. The two clusters differed in severity, and thus are labeled as the Moderate group ($n = 20$), with the three tests near 1 standard deviation below the mean, and the Severe group ($n = 12$), with the three tests near 2 standard deviations below the mean. Three of the clusters indicated more specific impairment on one or two of the tests. For one group, impairment was confined to the Benton Visual Retention (labelled BVR, $n = 9$), while for the other two groups impairment was found on the Benton and Paired Associates (labelled BVR/PA, $n = 9$), or Word Fluency and Paired Associates (labelled WF/PA, $n = 11$). The BVR group likely includes subjects with a specific deficit in visual-spatial ability. The other two groups (WF/PA and BVR/PA) are both impaired in their ability to learn novel verbal associations, but one combines with a verbal fluency impairment, and the other with a visual-spatial deficit. It is possible that the BVR/PA group may be impaired in the acquisition of both verbal and visual novel material, since the Benton Visual Retention was administered with a 10 second delay, and errors may arise from an inability to recall the figure, rather than from a perceptual deficit.

The final group could not be considered a profile associated with MS, since the group contained one MS patient and one control subject. Examining the data for these

two subjects indicated that they both had consistently low scores on the WAIS-R subtests (between -1 and -1.5 standard deviations below the mean). In contrast, their scores on the three clustering tests were near average. The profiles of their scores are not consistent with an acquired cognitive impairment, but likely reflect normal variation in cognitive ability. The group was therefore excluded from further group analyses.

The impaired clusters (excluding the control subjects) are described on other variables in Table 8. The MS patients in these groups did not differ in terms of age, education, age at onset of symptoms, or EDSS scores as assessed by ANOVA (all $p > .05$). While it appeared that fewer female subjects were included in the WF/PA group, the chi-square did not approach significance (chi-square (df 4) = 2.9, $p > .05$). However, the percentage of subjects who were unemployed at the time of testing differed substantially among the groups (chi-square (df 4) = 13.38, $p < .01$). Of the groups, 53% of the Moderate group were unemployed, while 82% of the Severe group (9 of 11 subjects) were unemployed. In contrast, the groups with specific impairments obtained unemployment rates ranging from 10% to 25%.

Insert Table 8 here

Unimpaired cluster groups. Most of the unimpaired groups likely reflect normal variation in test score patterns. Several groups, however, were of interest because of the over-representation of MS subjects in the group, and because of the similarity of their profiles to impaired group clusters. The ratio of controls to MS in the entire sample was .71, and a ratio close to this figure would be expected to occur in each of the unimpaired cluster groups. The obtained ratios of MS to control subjects in each group are presented

in Table 9. A chi-square indicated that the obtained frequencies differed significantly from expected values (chi-square (df 9) = 26.62, $p < .01$).

Insert Table 9 here

Most of the unimpaired clusters obtained ratios similar to the expected values, while two groups (Clusters 3 and 7) included more control subjects than expected. One group (Cluster 1) included 3 MS subjects only, and was identifiable by their isolated impairment on Paired Associates. Two other groups (Clusters 6 and 8), with ratios of .38 and .31, respectively, indicated an over-representation of MS subjects. These two groups had profiles that are visually similar to the BVR/PA group and the WF/PA group, and may include MS patients with less severe cognitive impairment. In Figure 3, the three groups are graphed using the mean scores for the MS subjects only, and are contrasted with the similar profiles from the impaired clusters.

Insert Figure 3 here

Validation of Cluster Patterns

The clustering tests and the validation tests are graphed for the impaired groups in Figure 4. Figure 5 presents the graphs for the unimpaired groups. For the impaired groups, the profiles were visually similar. The one exception is the BVR/PA group; the mean for Block Design is a full standard deviation higher than Memory for Objects, whereas the Benton and Paired Associates are similarly impaired. This is consistent with the hypothesis that this group may have a general deficit in learning both verbal and visual

novel information, rather than a combination of verbal memory impairment and visual-spatial difficulties. In this case, impairment on Block Design would not be expected, since the test relies minimally on memory. A discriminant function analysis using the validation tests as predictors and the original clusters as criterion groups yielded an overall correct classification rate of 46%, where chance classification was 20% given 5 groups, a significant difference as assessed by chi-square (chi-square (df 4) = 33.8, $p < .001$).

Insert Figure 4 here

In contrast, there is less visual correspondence between the patterns for the clustering variables and the validation tests in the unimpaired groups. A discriminant function analysis yielded an overall correct classification rate of 14%, which did not differ from chance classification (10%) (chi-square (df 9) = 1.84).

Insert Figure 5 here

Validating the clusters using three other tests highlights a difference between the impaired and unimpaired groups; that is, tests that are normally unrelated become more closely related due to an impairment of function necessary for the completion of both tasks (see Shallice, 1988). This increased correspondence between the clustering and validation tests in the impaired group was evident in the inter-test correlations. The differences in the magnitude of the correlations between the impaired and unimpaired groups were assessed with a Fisher z test. In all three cases, the correlations increased significantly for

the impaired group (see Table 10). One must ensure that the correlations did not change due to increased variability or range of scores in the impaired group (Clark & Ryan, 1993). However, F ratios comparing the impaired and unimpaired group variances on all the tests indicated that only the variance on Memory for Objects was significantly higher for the impaired group ($F=1.79, p<.01$). No other value approached significance. This would suggest that the increase in inter-test correlations indicated an increased correspondence among test scores for the impaired group.

Insert Table 10 here

Alternative Validation Approach

For each of the three clustering tests, differences between the 5 impaired cluster groups were assessed with a one-way ANOVA and Tukey pairwise followup procedures. On the basis of the results, a single hypothesis was generated describing the group differences. An a priori t -test on the replication test was then performed in order to determine whether the same pattern held for the replication test. All alpha levels for t -tests were one-tailed, since in each case the direction of the difference was hypothesized in advance. Cluster group means in standardized form for the cluster tests and validation tests are presented in Table 11.

Insert Table 11 here

Word Fluency versus Similarities. On Word Fluency, the Moderate, Severe, and WF/PA groups were similar to one another, performing worse than the BVR/PA and BVR groups. ANOVA confirmed this pattern, indicating a main effect of group ($F(4,56) = 22.18, p < .0001$). Tukey's pairwise comparisons were significant at $p < .05$ for BVR/PA versus Moderate, Severe and WF/PA, and for BVR versus Moderate, Severe and WF/PA. A similar result was obtained on Similarities. BVR/PA and BVR combined (mean = -0.32, sd = .73) had higher mean performance than Moderate, Severe, and WF/PA combined (mean = -1.15, sd = .93) as indicated by a t -test ($t(59) = 3.69, p < .0005$).

Paired Associates versus Memory for Objects. The analyses indicated that the BVR group performed better on Paired Associates than all other groups, with the Moderate group intermediate between BVR and the Severe, WF/PA, and BVR/PA groups combined. An ANOVA indicated a main effect of group ($F(4,56) = 16.07, p < .0001$), with Tukey pairwise comparisons indicating mean differences at $p < .05$ for Moderate versus Severe, WF/PA and BVR/PA, and for BVR versus all other groups. Thus, the hypothesis tested on Memory for Objects was that the Severe, WF/PA, and BVR/PA groups combined (mean = -1.17, sd = 1.49) would obtain poorer performance than the Moderate and BVR groups combined (mean = -.79, sd = 1.11). The t -test failed to reach significance ($t(59) = 1.11, p = .13$). The difference appeared to be due to the Severe group, where the mean on memory for objects was substantially higher than Paired Associates performance (see Table 11). When this group was excluded, the Moderate and BVR groups combined (mean = -.79, sd = 1.11) versus the WF/PA and BVR/PA groups combined (mean = -1.52, sd = 1.59) differed significantly ($t(47) = 1.88, p < .02$).

Benton Visual Retention versus Block Design. An ANOVA indicated a group difference on the Benton ($F(4,56) = 43.91, p < .0001$), with Tukey pairwise comparisons significant at $p < .05$ for WF/PA versus all other groups, and for the Moderate group versus Severe, BVR/PA, and BVR groups. Thus, on Block Design, the Severe, BVR/PA,

and BVR groups combined were expected to perform poorly in comparison to the Moderate and WF/PA groups. However, a second possibility, discussed earlier, was that the BVR/PA group may not be impaired on Block Design, since their poor performance on the Benton may be due to memory problems, rather than constructional difficulties. Testing the first hypothesis, with Moderate and WF/PA groups combined (mean = -1.09, sd = .94) vs Severe, BVR/PA, and BVR groups combined (mean = -1.57, sd = .86), the t -statistic was significant ($t(59) = 2.02, p < .025$). When the groups were recombined so that BVR/PA was included with the Moderate and WF/PA groups (mean = -1.08, sd = .96), and compared to the Severe and BVR groups (mean = -1.80, sd = .67), the p value increased to $p < .001, t(59) = 3.06$.

MRI Results

MS subjects who had undergone MRI on the day of their testing and whose scans were coded were included in these analyses. MRI data were available from a total of 150 MS patients and 66 normal controls. Lesion frequency for the MS and Control groups is presented in Table 12. For the MS patients, lesions occurred in all 50 sites. For the control group, lesions occurred in 14 of the 50 sites. Both groups had the most lesions in the periventricular regions and in the body of the CC. The incidence of small white matter lesions occurring in normals has been well documented (Jernigan et al., 1991). The lesion sites included in the present analyses excluded those areas with a large number of control subjects. Six sites included in the analyses each had one control subject with a lesion, while one site had two control subjects with a lesion. The sites included the right and left temporal horns, the right frontal horn of the deep white matter, the genu and splenium of the CC, the midline of the brain stem, and the right cerebellum.

Insert Table 12 here

Groupings of MS subjects. Six groups of MS subjects were included in the MRI analysis. The groups were formed on the basis of the results of the cluster analysis, with the assumption that the MS patients who fell within three of the "unimpaired" clusters (presented in Figure 3) were experiencing impairment in specific areas, although not sufficiently severe to have been classified as globally impaired according to the present criterion. Thus, the first two groups were formed from subjects in the Moderate group (n=18) and the Severe group (n=8). The third group (n=28) included 8 subjects from the impaired WF/PA group and 20 MS subjects from the unimpaired WF/PA cluster. The fourth group (n=11) included 8 subjects from the BVR/PA impaired cluster together with the 3 unimpaired PA cluster subjects. The fifth group (n=19) included 8 subjects from the impaired BVR cluster and 11 MS subjects from the corresponding unimpaired BVR cluster. Finally, the control group included all other unimpaired MS patients (n=68) who did not show a pattern suggestive of cognitive impairment.

The cluster groups differed marginally in the total number of lesions evident on MRI (see Table 13). There was a trend ($F(5,144) = 1.83, p = .10$) for the Moderate and Severe groups to have more lesions than the other groups.

Insert Table 13 here

Cluster by lesion site analysis. Two sites yielded chi-square values significant at the chosen alpha of $p < .01$. These sites were the deep white of the left parietal region (chi-square ($df=5$) = 14.01; $p < .01$) and the genu of the CC (chi-square ($df=5$) = 13.84; $p < .01$). The expected frequency and the obtained percentages of the groups with a lesion these sites are presented in Table 14.

Insert Table 14 here

The highest percentage of patients with lesions in both sites were within the Severe group. For both sites, the unimpaired MS group had less lesions than the expected frequency. Of interest is the pattern of the groups with frequencies above the expected value. For the genu of the CC, lesions occur most frequently for the Severe and BVR groups. These two groups have the most consistently low scores on the BVR, suggesting that the genu may be associated with visual-spatial ability. A higher lesion frequency would not be expected in the BVR/PA group, since the validation analyses suggested similarity to other memory impaired groups rather than visual-spatial impaired groups. In contrast, the deep white left parietal region showed an increase in frequency of lesions for all of the groups with poor scores on Paired Associates, ranging from 64% in the BVR/PA group to 75% in the Severe group.

Thus, the analyses suggested that two sites, the genu and the deep white left parietal region, may be differentially associated with two cognitive functions, visual-spatial and memory, respectively. In order to further investigate the hypothesis, groups were reformed including subjects whose only impairment was on the Benton, on Paired Associates, or on Word Fluency. A control group was also formed who were most likely unimpaired on these three tests.

A subject was included in a group only if their score fell at or below the impairment cutoff of -1.64 standard deviations on one of three tests, but *above* -0.64 on the other two tests. For example, the MS patients included in the BVR group all obtained scores of -1.64 or greater on the Benton, and scored at least one standard deviation higher on Paired Associates and Word Fluency; 21 subjects met these criteria. Similar groups

were formed for Paired Associates (PA; $n = 15$) and for Word Fluency (WF; $n = 9$). MS subjects were included in the control group only if their performance on all three tests was above -0.64 standard deviations, thus decreasing the likelihood that they were experiencing difficulty in these cognitive domains. Frequency tables for the genu and the left parietal deep white region were constructed for the groups, and are presented in Table 15.

Insert Table 15 here

The results indicated that, for the genu, 67% of the patients in the BVR group had a lesion in the genu of the CC, in contrast with less than 40% of the patients in each of the other groups (χ^2 (df=3) = 7.9, $p < .05$). In the left parietal deep white region, lesions were present in 80% of the PA group, while less than 35% of the other groups had a lesion in this site (χ^2 (df=3) = 8.1, $p < .05$). Thus, the lesion sites are specifically associated with two different cognitive functions.

No association was found between lesion site and impairment on Word Fluency. However, the WF group had fewer lesions present on MRI, regardless of site. On average, 72% of the BVR group had more than ten lesions, while 90% of the PA group had more than ten lesions. In contrast, 22% of the WF group (2 subjects) had more than 10 lesions. The remainder (78%) had between 3 and 7 lesions, suggesting that Word Fluency impairment may be a very early manifestation of cognitive impairment, even in patients with relatively little white matter disease evident on MRI.

Chapter 7

Discussion

The results of the present study indicate that MS results in cognitive impairment across a wide variety of neuropsychological tests, despite minimal physical disability and no cognitive decline evident on neurologic examination. This finding replicates others in the literature (Ivnik, 1978; Grant et al., 1989). Cognitive impairment is not, however, ubiquitous among MS patients. For the majority of the MS patients, cognitive difficulties were not apparent on any neuropsychological test; 35% of the MS group were above the 5th percentile of the normative sample on every test. However, using the 5th percentile as a standard for impairment, 33% of the MS group (58 of 177 individuals) were impaired on three or more tests, compared with 5% of the control group. Eight of the MS patients (5%) scored near or substantially below the impaired cutoff on the majority of the 13 tests in the battery. Thus, in a small percentage of early stage MS patients, there is evidence for global cognitive decline that would be considered severe by clinical standards.

Importantly, the results suggest that there is no single pattern of cognitive impairment characteristic of MS. Rather, the MS patients classified as impaired resemble a heterogeneous group of brain damaged patients. Two of the clusters suggested moderate and severe decline across all three areas of verbal fluency, memory, and visual-spatial ability. Three other clusters were obtained with specific deficits in one or two of these areas, highlighting the relative independence of these functions. While the groups did not differ in severity of physical disability, the MS patients with global decline in functioning, particularly those with severe impairment in all three areas, had a high rate of unemployment. This would suggest that, for MS patients with mild physical disability, cognitive impairment may be sufficiently severe to adversely affect daily functioning.

In a clinical setting, neuropsychological assessment judges an individual's performance in each functional area compared to not only normative data, but also to estimates of the individual's premorbid functioning. As well, dissociations between areas of functioning in a given individual may signal impairment, whether or not scores are "impaired" by normative standards. However, this sort of clinical judgement is extremely difficult to apply in a systematic way in research. By using a stringent criterion for classification, the present study ensured that only those subjects with unequivocal cognitive impairment were identified. However, the use of such a criterion also likely underestimated the occurrence of cognitive impairment. This hypothesis is supported by the results of the cluster analysis performed with the unimpaired group, which showed an over-representation of MS patients within several of the unimpaired clusters with similar profiles to the impaired clusters. Using pattern analysis to identify MS patient with less severe decline may be most useful in longitudinal studies investigating the natural history and evolution of cognitive impairment in MS. Taking this into account, the actual incidence of cognitive impairment in MS may be underestimated.

The results of the cluster analyses are important on both a clinical and theoretical level. Clinically, the information gives a better picture of what deficits are likely to occur in MS patients, and with what frequency. The results suggest that the only way to identify the pattern of cognitive impairment in an individual with MS is to administer neuropsychological tests that range across cognitive functions. The present study concentrated on patterns arising from three areas of cognitive functioning, and it is unclear whether other patterns, perhaps unique ones, may arise in individuals when other cognitive functions are considered.

Theoretically, the results suggests that demyelination does not result, as some researchers have suggested (e.g., Rao, 1986), in a general deficit in information processing efficiency, or in a "subcortical dementia" that is applicable to all MS patients. Rather, the present study gives credence to the suggestion that the disseminated lesions result in more

idiosyncratic patterns of deficits, possibly dependent on the site or distribution of lesions. As Beatty (1992) has pointed out, very different conclusions are reached when one considers the results of group studies (the vast majority of the extant literature) and studies that focus on the individual with MS (for example, Beatty & Monson, 1991). Group studies in MS likely hide a wealth of information because of averaging artifacts, and much of the inconsistency from one study to the next can be explained by the random combinations of subgroups of differentially impaired patients. The present study is a good indication of this phenomenon; group data indicated that the MS group was significantly impaired on a large number of measures. However, the mean differences between MS and control groups were minimal, and one might conclude that MS results in mild deficits across multiple areas of cognitive functioning. In contrast, the cluster analysis identifies subgroups of MS patients who are severely impaired in particular areas, with other cognitive functions intact.

Only two lesion sites from the MRI analyses were associated with cognitive impairment. First, a lesion in the genu was associated with impairment on the Benton Visual Retention test. While the genu itself has not been implicated in visual-spatial impairment, Le Doux, Wilson, and Gazzaniga (1978) have noted that spatial impairments occur in patients with complete commissurotomy. These researchers emphasize the particular importance of the posterior section of the CC (the splenium) in visual-spatial functioning, connecting the left and right posterior areas of the parietal and occipital lobes. Lesions in the genu in the present study may be indicative of generally more demyelination within the CC which then compromises the connections between the two hemispheres. This hypothesis is supported by the finding that, of the 21 patients who were impaired only on the Benton, 11 (or 52%) of the patients had lesions in all three areas of the CC, while only 16% of the unimpaired MS, and 20% of those impaired only on Paired Associates, had lesions in all three areas.

If the genu is associated with visual-spatial functioning, then it is a sufficient but not necessary lesion site for expression of the impairment. A third of the MS patients with specific impairment on the Benton (i.e., those in the BVR group) did not have a lesion in the genu, and the mean performance for patients who did or did not have this lesion were virtually identical. Two possibilities exist; first, patients with and without the critical lesion may be failing the tests for different reasons. The Benton is adversely affected by constructional deficits, visual perceptual impairment, unilateral attentional neglect, and visual memory impairment. The integrity of the CC may differentially affect only one aspect of performance. Secondly, lesions in multiple sites may result in a similar impairment. For example, lesions in tracts disconnecting the occipital and parietal hemispheres may have a similar impact on visual-spatial skills as a lesion at the grey-white junction of the right parietal-occipital association areas. These types of questions are best answered in studies of a single subgroup of patients emphasizing a detailed analysis of the quality of impairment and the relationship to neuropathology.

The second outcome of interest from the MRI analyses was the association between lesions in the left parietal deep white matter region and impairment on Paired Associates. In patients with grey matter lesions, memory impairment on verbal tasks such as list learning and Paired Associates has been associated with left temporal lobe and hippocampal pathology (Milner, 1966; Squire & Slater, 1978). Research into the memory deficits in Korsakoff's psychosis has also implicated the area around the third ventricle, including the mamillary bodies, the dorsomedial nuclei of the thalamus, and the internal capsule (Graff-Radford, Eslinger, Demasio, & Yamada, 1984). The qualitative differences in memory performance arising from damage to these two areas has led to the proposal of two types of amnesia, one hippocampal which may affect storage of information and the other diencephalic which may affect encoding or acquisition (for review, see Meudel & Mayes, 1982).

White matter tract lesions may also impair memory performance. Zaidel and Sperry (1974), examining commissurotomy patients on standard tests of memory including paired associate learning, concluded that co-operation between the hemispheres is necessary for optimal encoding and retrieval of material.

The deep white left parietal lesion in the present study may be disrupting the connections between areas necessary for optimal encoding of novel verbal associations. The arcuate longitudinal fasciculus sweeps in a large bundle through this region, connecting the superior and middle frontal gyri to extensive sections of the temporal lobe. Patients with frontal lesions perform particularly poorly on a test such as Paired Associates that requires mental operations to be carried out on the materials, that is, creating new associations between novel pairings of objects (Schacter, 1987). In argument against this hypothesis, Beatty et al. (1989) did not find similar characteristics between the performance of MS patients who were impaired on memory testing and frontal lobe memory impaired patients in their ability to semantically encode information. Beatty hypothesizes that MS patients, although capable under optimal circumstances, do not employ semantic encoding spontaneously or with normal efficiency. The difference may be more one of severity rather than of quality. The answer to this question requires a direct comparison of MS patients and frontal lobe patients.

Rao and his colleagues (Rao, 1990; Rao, Leo, & St. Aubin-Faubert, 1989) have argued that the memory impairment in MS is similar to diencephalic amnesia due to periventricular lesions disconnecting the thalamo-frontal radiations, and resulting in a retrieval deficit (see Chapter 3). The present finding would suggest that the impairment arises due to damage to frontal and temporal structures, and would therefore result primarily in problems of encoding and the representation of novel material. Both these hypotheses may ultimately be correct. To date, the studies of memory functioning in MS patients have considered only group data; no attempt has been made to discern groups of patients with different patterns of memory impairment. Thus it is unclear whether a test

other than Paired Associates would have identified a different group of patients as being memory impaired, and once identified, whether association to other lesions sites might arise.

It is of note that no area on MRI was associated with Word Fluency. Indeed, the group with a deficit only in Word Fluency had fewer total lesions than patients with a single impairment on Paired Associates or on the Benton Visual Retention test. Word Fluency impairment may be a very early occurrence in MS, and may represent the general decline in efficient processing that is associated with disruption of the normal temporal ordering of signals that occurs with demyelination in white matter tracts. The fact that Word Fluency is one test in the literature that does not result in increased variability in MS patients compared to controls supports the notion that inefficient processing is a ubiquitous feature of MS, even for those patients with minimal neuropathology evident on MRI. MS patients may experience a combination of a general deficit in information processing efficiency together with impairment in particular cognitive functions that are associated with localized white matter tract lesions.

The finding that the genu and the left parietal regions are differentially associated with visual-spatial and memory performance in MS does not constitute a true double-dissociation (Teuber, 1955), since the hypotheses were not generated a priori. While it is tempting to suggest functional specificity for these areas, with 24 sites and three tests the possible combinations for finding what appears to be a double dissociation by chance alone is extremely high. Thus, the present study provides only the basis for generating hypotheses to be investigated in future studies. Since minimal research exists at present that identifies the cognitive function of various white matter tracts, the importance of generating such predictions should not be underestimated.

Future directions in MS research.

Future research attempting to characterize the cognitive impairment in MS patients is warranted. The present results apply only to MS patients in relatively early or mild

stages of the disease process; a rather different set of results may obtain when patients have progressed into more physically disabling stages of the disease. Studies that follow a large sample of MS patients longitudinally will be of particular value in understanding the natural history and progression of the cognitive impairments, an area of research that is sorely lacking at present. For example, retesting the patients in the current study after a period of 2 to 3 years would give a rich data base from which to address questions regarding the rate of decline and the stability of both the severity and of the patterns of impairment over time. The relationship of longitudinal changes in cognition to changes on MRI is of interest as well. Most crucial, from a clinical standpoint, such a data base would be helpful in understanding the implications of cognitive decline for a patient's ability to function adequately in daily life.

A more fruitful approach in answering questions regarding cognitive impairment and its relationship to neuropathology will be to identify small subgroups of patients who are impaired in specific functions, and to then study these patients in depth. Once identified, careful characterization of the quality of their impairments should precede attempts to identify dissociations between the groups in terms of the quantity and distribution of neuropathology. The heterogeneity of cognitive impairment resulting from MS cannot be disregarded. Indeed, this heterogeneity makes MS an extremely interesting group to study in order to elucidate the mosaic of functional aspects of cognition through what Geshwind (1965A, 1965B) would refer to as "disconnection syndromes". That said, one must be careful in making a direct comparison between white matter lesions that result in the total destruction of axonal tracts (such as those studied by Geshwind) and demyelinating lesions. Demyelination within a tract may result primarily in the disruption of the temporal organization of signals between cortical areas, rather than the complete disconnection between areas. Thus, the behavioural and cognitive effects of these two types of lesions may differ.

In addressing the question of the association of cognitive impairment to neuropathology, the research to date has relied almost solely upon the structural aspects of lesions as indicated by MRI. Other MRI measures, such as T1 and T2 relax times (for example, Feinstein et al., 1992) reflect significant neuropathological changes in normal-appearing white matter in MS. Taking into account other aspects of MS neuropathology, such as active versus stable lesion status (using gadolinium enhanced MRI) and metabolic measures (using PET, SPECT, and functional MRI) may provide an undoubtedly more complex, but more complete, model of brain functioning in MS.

Finally, MS may offer important insights into the role of efficiency in complex cognitive tasks. One of the most striking aspects when testing a person with MS in a clinical setting is the effort that these patients often put forth in completing a task. In spite of the obvious difficulty they experience, they may look average on actual test results. Clinical neuropsychological tests (or experimental cognitive ones, for that matter) are insensitive to subtle changes in effortful processing. One of the challenges for this area of research will be to create experimental paradigms that measure efficiency without relying on reaction time, so that one can parse apart the contributions to a complex task of 'ability' from 'efficient execution of an ability' from 'coordination between abilities' from 'speed'. Such an analysis may be the key to understanding the effects of demyelinating diseases on cognition.

Appendix A

The Extended Disability Status Scale and Functional Systems Scales

Kurtzke (1983)

Functional Systems

Pyramidal Functions (P)

0 (normal) to 6 (quadriplegia).

Cerebellar Functions (CII)

0 (normal) to 5 (unable to perform coordinated movements due to ataxia).

Brain Stem Functions (BS)

0 (normal) to 5 (inability to swallow or speak).

Sensory Functions (S)

0 (normal) to 6 (sensation essentially lost below the head).

Bowel and Bladder Functions (BB)

0 (normal) to 6 (loss of bowel and bladder function).

Visual (or Optic) Functions (V)

0 (normal) to 6 (worse eye with maximal visual acuity less than 20/200; maximal visual acuity of better eye of 20/60 or less).

Cerebral (or Mental) Functions (Cb)

0 (normal).

1 (mood alteration only).

2 (mild decrease in mentation) to 5 (dementia; severe or incompetent).

Other Functions (O)

0 (none) to 1 (any other neurologic findings attributed to MS).

Expanded Disability Status Scale (EDSS)

- 0.0 = Normal neurologic exam, all grade 0 in FS; Cerebral grade 1 acceptable.
- 1.0 = No disability, minimal signs in one FS.
- 1.5 = No disability with minimal signs in more than one FS.
- 2.0 = Minimal disability in one FS (one grade 2, others 0 or 1).
- 2.5 = Minimal disability in two FS (two grade 2, others 0 or 1).
- 3.0 = Moderate disability in one FS (one grade 3, others 0 or 1), or mild disability in three or four FS, though fully ambulatory.
- 3.5 = Fully ambulatory but with moderate disability in one FS together with mild in one or two others.
- 4.0 = Fully ambulatory without aid, self-sufficient, active 12 hours a day despite relatively severe disability of one FS (grade 4), or combinations of lesser grades exceeding previous steps. Able to walk without aid or rest some 500 meters.
- 4.5 = Fully ambulatory without aid, active much of the day, able to work a full day, may require minimal assistance, relatively severe disability (usually one FS grade 4). Able to walk without aid or rest some 300 meters.
- 5.0 = Ambulatory without aid or rest for about 200 meters. Disability severe enough to impair full daily activities or requiring special provisions to work a full day (usually one FS grade 5 or combinations of grade 4's).
- 5.5 = Ambulatory without aid or rest for about 100 meters. Disability severe enough to preclude full daily activities (same FS grades as 5.0).
- 6.0 = Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting.
- 6.5 = Constant bilateral assistance required to walk about 20 meters without resting.
- 7.0 = Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair. Wheels self in standard wheelchair and transfers alone, up and about 12 hours per day.
- 7.5 = Unable to take more than a few steps, restricted to wheelchair, wheels self but may require assistance in transfers. Cannot carry on in standard wheelchair a full day, may require motorized wheelchair.

8.0 = Essentially restricted to bed or wheelchair, but may be out of bed much of the day.
Retains many self-care functions and has generally effective use of arms.

8.5 = Essentially restricted to bed much of the day, has some effective use of arms.
Retains some self-care functions.

9.0 = Helpless bed patient, can communicate and eat.

9.5 = Totally helpless bed patient, unable to communicate effectively or eat/swallow.

10 = Death due to MS.

Appendix B

Description of Neuropsychological Tests

Thirteen neuropsychological tests were employed in the present study. The following table summarizes the ability areas that each test measures, as it is described in the research literature.

Test	Motor Component	Prior Knowledge	Abstract Conceptual	Learning & Memory	Processing Efficiency	Constructional Ability
Information		XX				
Vocabulary		XX				
Digit Span				XX	XX	
Arithmetic		XX			XX	
Picture Completion			XX			XX
Block Design	XX		XX			XX
BVRT				XX		XX
Similarities		XX	XX			
Letter Fluency		XX			XX	
Trails A & B	XX				XX	
Categories			XX			XX
Paired Associates			XX	XX		
Memory for Objects				XX		

WAIS-R Subtests

The following tests are taken from the Wechsler Adult Intelligence Test-Revised (WAIS-R; Wechsler, 1981). All WAIS-R subtests are scored according to the WAIS-R scoring manual and are expressed as age scaled scores using the WAIS-R norms.

Information: The subject is asked 29 questions that reflect the amount of general information that individual has absorbed from the environment. Information tests both breadth of knowledge and verbal skill, since the test requires formulation of complex verbal responses. It correlates with formal education and motivation for academic achievement, and is among the least affected WAIS-R subtest in brain injured populations (Lezak, 1983).

Vocabulary: The subject is asked to define 35 words arranged in order of difficulty. Performance on Vocabulary reflects amount of general knowledge, verbal skill, and the ability to organize and formulate thoughts coherently. It deteriorates very little with age, and is thus a good indicator of general intellectual and premorbid functioning (Lezak, 1983).

Digit Span: Both Forward Span and Backward Span consist of seven pairs of random number sequences that are read aloud at the rate of one digit per second. For Forward Digit Span, the subject is required to repeat back the sequence in the same order they heard them. For Backward Span, the subject must repeat the sequence in the reverse order. Forward Digit Span is considered a measure of working memory capacity, but is also sensitive to attentional efficiency, since span decreases with anxiety (Baddeley, 1986). Backward Digit Span is a complex attentional task that requires the inhibition of more automatic responses and double-tracking in that both the memory for the digits and the reversing operations must proceed simultaneously.

Arithmetic: This subtest contains 14 mathematical problems to which the subject must answer verbally without the aid of paper and pencil. It is considered a sensitive test of efficient mental processing rather than of mathematical skills, since the most difficult

arithmetic computations are only at the 8th grade level (Lezak, 1983). Difficulties in concentration and attention, immediate memory, conceptual manipulation, or mental tracking, will impair performance.

Picture Completion: The subject is shown 20 incomplete pictures and asked to identify the "most important part of the picture that is missing". The test taps the ability to process detail in a visual array, but also requires judgement regarding both practical and conceptual relevancies. Although it does not require the same complex verbal skills as Vocabulary or Information, it assumes a cultural background that allows exposure to such items as a horse and saddle, or snow on a woodpile.

Block Design: Nine designs are presented to the subject printed on cards. The subject must mentally partition the visual design so that it can be replicated using blocks that are on a different scale than the picture. Block Design measures nonverbal reasoning and problem solving, and requires intact visual-spatial organizational ability. The test is timed, so that additional points are given for speed of responding. Thus, test performance is difficult to interpret by speed alone when the subject is motorically impaired.

Similarities: A test of verbal concept formation and retrieval of verbal information, the subject must identify what each of a pair of words has in common. The correct response is a higher-order category, such as "forms of art" for "poem and statue".

Other Neuropsychological Tests:

Benton Visual Retention Test (BVRT): The subject is presented a card with geometric designs for 10 seconds. The card is removed and the subject is asked to reproduce the designs as accurately as possible. Scoring consists of errors in reproduction. The test is sensitive to visual-spatial ability, visual detail and spatial organization, as well as immediate memory for nonverbal information. However, the BVRT has higher correlations with tests of design copying than with memory tests, suggesting that the constructional component far outweighs the memory component

measured by the test (Benton, 1979). The test is not timed, and thus is a good test of constructional ability in patients with difficulty in fine motor coordination.

Word Fluency: The subject is told a letter of the alphabet and asked to produce words beginning with that letter as quickly as possible, without using proper names or places, or repeating a word with different suffixes. Subjects are given one minute to respond to each of three letters (F, A, and S). Scoring is the total number of correct words produced. Fluency tests with letters require the subject to choose optimal strategies for retrieval (such as a grouping of words starting with "st..."). The test also requires subjects to limit responses to those that conform to the rules by suppressing more automatic responses that come to mind, i.e., words that are semantically related. Although fluency may be impaired in some aphasic groups, it is more often impaired due to difficulty monitoring verbal responses, effective strategy use, mental organization, and processing efficiency (McCarthy & Warrington, 1990). The test can be extremely impaired in subjects for whom no other language disturbance is evident.

Trails A and B: In Trails A, the subject joins a series of numbered dots. In Trails B, the subject joins dots according to an alphanumeric sequence (e.g., 1 - A - 2 - B). On both parts of the test, the score is the time in seconds to complete the test. Trails A measures visual scanning speed and motor speed, since the numeric sequence is overlearned or automatic. Trails B, however, requires mental tracking of two sets of information and switching between them. The task is therefore considered a complex attentional task requiring efficient mental tracking and flexibility. Impairment in motor speed will also adversely affect performance. However, one way to control for individual motor speed is to subtract time on Trails A from Trails B. Since the number of dots on both forms are the same, this scoring controls for both motor speed and speed of visual scanning.

Categories Test: Part of the Halstead-Reitan Neuropsychological Assessment Battery (Reitan & Davison, 1974), on this test subjects are presented with a series of slide

sets. Each set is made up of geometric designs with a number concept underlying it. The subject's task is to determine the rule based on feedback as to whether their responses (1 to 4) are correct or incorrect. Scoring is the total number of errors. Pendleton and Heaton (1982) note that the test is an experiment in learning that requires effective learning skills, problem solving, and abstract concept formation. However, the test also requires intact visual-spatial ability.

Paired Associate Learning: Word pairs were taken from the two alternate forms of the Wechsler Memory Scale-Revised (Russell, 1975). Twenty word pairs are read aloud to the subject, half that are semantically associated (e.g., king - queen), the other half without prior semantic association (e.g., cabbage - pen). Memory for the pairs is tested by presenting the first word of the pair and asking subjects to recall the word that made up the pair. There are three learning trials. Scoring is the total number of correct pairs over the three trials, but can also be broken into the number of low and high associate pairs that were learned over three trials. The pairs without semantic association require abstract conceptualization, since the subject must devise some association between novel paired words.

Memory for Objects: Subjects are presented with 15 common objects (e.g., spoon, pen, watch, etc) simultaneously for one minute. They are then asked to recall as many objects as possible. Scoring is the total number of objects correctly recalled. Since all the objects can easily be encoded verbally, Memory for Objects is as much a test of verbal memory as it is a test of visual memory.

Appendix C

The following section is a brief literature review of what is known about brain damage, either to cortical grey matter regions or to white matter tracts, resulting in cognitive impairment in the areas of verbal fluency, memory, and visual-spatial ability.

Lesion Sites and Cognitive Functioning

As discussed in the introduction, the effect of white matter lesions on cognitive processes has only recently begun to be explored. The vast majority of the neuropsychological literature deals with grey matter or cortical lesions, with the exception of some discussion of the effect of damage to the corpus callosum (for example, Sperry's research into "split-brain" patients; see Sperry et al., 1969). Hence, the following section describes the effect of lesions to the cortex, and not to white matter unless explicitly stated. I have tried to emphasize, where possible, studies in the literature that have employed the same, or very similar, tests to the ones used in the present study, or that have implications for white matter disease.

Constructional Impairment. The Benton Visual Retention test and block design are two of many tests that are sensitive to constructional difficulties (Benson & Barton, 1970). While some patients may do poorly on all such tests, others may exhibit very particular deficits, say, in copying designs vs drawing freehand, etc. Lesions to both hemispheres may cause impairment to constructional ability, but tend to differ qualitatively (Walsh, 1987). In general, however, lesions to the right hemisphere are more likely to produce constructional deficits than to the left, and more likely when the lesion is posterior rather than anterior. The most widely discussed area is the junction between the parietal, temporal, and occipital lobes. Lesions confined to the temporal lobes do not result in constructional difficulties, while damage extending into the parietal and/or occipital areas often results in constructional apraxia (Luria, 1973).

Nielsen (1975) put forward a disconnection model of constructional apraxia. He posits that the right posterior cortex contains the basic module for spatial integration,

while the left hemisphere contains the motor control center for the right hand. Unilateral lesions to the right parietal area will result in impairment, as will lesions to the tracts connecting the two hemispheres. In this latter case, an uneven spatial ability between the two hands will be exhibited. This notion was put forward independently by Le Doux et al. (1978) based on their observations of a patient with a complete commissurotomy. By their view, lesions to the corpus callosum may result in spatial difficulties, particularly to right handed individuals. As well, lesions within the tracts of the deep white in the right hemisphere may produce spatial difficulties to the left hand when the lesion disrupts the connections between the posterior cortex and the motor control for the left hand. Le Doux et al. (1978) argue that such a lesion would only produce a constructional deficit if the subject is predominantly left handed.

The third area that has been implicated in constructional impairment is the frontal lobes. From extensive case observations, Luria and Tsvetkova (1964) described two types of constructional apraxias; lesions to the parietal-occipital area produce disturbances in the spatial organization of elements, while lesions to the frontal lobes produce a loss of regulation of sequential behaviour, and an inability to compare the ongoing results of efforts with original intentions. The difference can be seen between the two types of constructional difficulties in that frontal lesion patients improve when given a detailed programme to follow, whereas parietal-occipital lesion patients do not (Walsh, 1987).

Verbal Fluency. The classic lesion study of word fluency is Milner (1964). Milner compared the performance of patients with left frontal, right frontal, or left temporal lobectomy on Thurstone's Word Fluency test. This test requires the patient to write as many words as possible in 5 minutes beginning with the letter S, and then as many four-letter words which begin with C. Milner found that the left frontal cases performed poorly compared to either the right frontal or left temporal groups, indicating the specificity of verbal fluency to the left frontal region, rather than to the language dominant hemisphere in general. Further, she found a double dissociation between the left frontal

and left temporal groups on verbal fluency and verbal recall. Left frontal patients performed poorly on verbal fluency but adequately on paired associates, while the reverse was true of the left temporal patients. Benton (1968) confirmed these findings using the verbal equivalent of Thurstone's task, where subjects say as many words aloud in one minute periods beginning with the letters F, A, and S. (This is the form of the verbal fluency test used in the present study.) Benton found that left frontal and bilateral frontal lesion groups were impaired when compared to a right frontal lesion group. Importantly, Benton found that the impairment was evident in patients whose other verbal abilities, including comprehension, reading, fluent speech, and object naming abilities, were intact. His patients showed similar verbal fluency difficulties in both verbal and written responding. This led him to conclude that verbal fluency is a higher-level language function that is not modality specific.

Memory Impairment. No other area of cognition has been more closely studied in neuropsychology than the impairment of memory due to brain damage. The vast literature can be broadly organized according to various memory phenomena such as short term memory, autobiographical memory, and the acquisition, retention, and retrieval of novel information. For present purposes, the latter area, namely learning and remembering novel information, will be discussed since the tests used for clustering and replication (paired associates and memory for objects) fit into this category.

Most consistently associated with deficits in the acquisition of new material are the temporal lobes. The findings are based predominantly on studies of anterior temporal lobectomy, a surgical treatment for intractable complex partial epilepsy. The resection typically includes the anterior 6 cm (approximately) of the temporal lobe, and includes the underlying structures of the uncus, amygdaloid nucleus, and part of the hippocampus and parahippocampal gyrus. These patients and others with temporal lesions of different origin exhibit difficulty in learning and retention of new material. When damage is bilateral, the resultant memory deficit can be dramatic, as in the case of HM (see

Baddeley, 1990). This line of research has focussed attention on the role of the hippocampus, in particular, in anterograde amnesia.

The left and right temporal lobes have been described as material-specific. The right temporal lobe differentially affects visuospatial and non-verbal pictorial material, while the left temporal lobe results in more severe deficits in learning verbal material. Verbal material deficits occur whether the retention of material is measured by recognition, free recall, or rate of associative learning, as in the case of paired associates (Smith & Milner, 1981). The generality of this material specificity is not conclusive, however. Warrington and Shallice (1969) have shown that patients with temporal or temporal-parietal lesions on the left side have difficulty with verbal memory for all forms of auditory material, but little or no difficulty with the same material presented via the visual modality, suggesting a modality-specific, rather than a material-specific, deficit. The general finding, however, of memory impairment on tests such as list learning and paired associates after left temporal lesion is incontrovertible, and is further supported by unilateral ECT studies (e.g. Squire & Slater, 1978) and by sodium amytal ablation studies (see Milner, 1966).

The specificity of the memory deficit on the basis of lateralization of lesion is not clearcut, and lesions to both temporal lobes can result in verbal memory impairment. That is, the material specificity described above is seen in the comparison of performance between verbal and nonverbal forms of memory tests. For example, a right temporal lesion may result in impairment to verbal memory tests, but will likely have a greater detrimental effect on pictorial information. The most severe memory impairment for both types of materials occur when lesions are bilateral. Zaidel and Sperry (1974), examining commissurotomy patients on standard tests of memory including paired associate learning, concluded that the intact functioning and co-operation between the hemispheres is necessary for optimal encoding and retrieval of material, and hence can be seriously disrupted by dissection of the commissural tracts.

The deficits associated with Korsakoff's psychosis has implicated the area around the third ventricle as important for memory function. This area includes the mamillary bodies, the dorsomedial nuclei of the thalamus, and the internal capsule. While bilateral damage to the thalamic nuclei and surrounding areas can cause profound amnesia, unilateral thalamic damage (usually due to intracerebral haemorrhage) can cause rather severe memory impairment, and this impairment seems to follow the same right/left hemisphere bias for material specificity as is seen in temporal lobe lesions (Graff-Radford et al., 1984). However, these cases usually have abnormalities in other intellectual functions and in personality, and are best described as part of a more global "subcortical" dementia. These distinctions have become important in describing MS patients, as several authors (Rao et al., 1984) have described MS memory deficits as more closely resembling those seen in diencephalic damaged patients rather than those with temporal or hippocampal damage.

The last area that has been implicated in impairment of memory functioning is the frontal lobes. There is debate currently in the literature as to whether or not there is indeed a "frontal" memory disorder, or whether poor performance on memory tasks by frontal patients is a function of other processes that are impaired, such as the integrated execution of behaviour and rule following (see Schacter, 1987). Patients with frontal lesions may perform poorly on a test such as paired associates, which require the person to carry out mental operations on the materials (ie, creating new associations between novel pairings of objects). In contrast, when frontal patients are required to merely repeat the material frequently, they are quite able to retain new information.

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Table 1

Expected frequency values of lesions occurring in 6 groups of MS patients for a hypothetical lesion site with a baserate of 10%. The frequency table uses the actual numbers of subjects obtained from the cluster solutions.

		MS group						
		A	B	C	D	E	F	
No Lesion		61	16	7	26	10	15	135
Lesion		7	2	1	2	1	2	15
		n=68	n=18	n=8	n=28	n=11	n=17	N=150

Table 2

Chi square values and resultant p values for hypothetical group data varying lesion baserate and the percentage of lesions occurring within the smallest cluster group (n = 8).

Lesion baserate	% lesions in cluster n=8	chi square (df=5)	p value
15%	60%	12.74	< .05
"	75%	20.24	< .01
"	85%	39.37	< .001
25%	60%	5.26	> .05
"	75%	9.12	> .05
"	85%	14.05	< .02
"	100%	19.73	< .002
35%	85%	6.79	> .05
"	100%	10.33	> .05

Table 3**Demographic variables.**

	MS		Controls	
Number of subjects	177		89	
Age (years)	36.2 (7.8)		35.2 (7.0)	
Education (years)	13.5 (2.2)		13.9 (2.2)	
Sex (%):				
Female	72.9		70.8	
Male	27.1		29.2	
Highest Occupational Status (%):				
Professional/Managerial	27.1		38.2	
Clerical	28.8		20.2	
Technical	25.5		21.3	
Unskilled	12.4		12.4	
Housewife	1.7		--	
Student		3.4		7.9
No occupation	1.1		--	
Current Employment Status (%):				
Full time	39.5		66.3	
Part time	22.1		14.6	
Unemployed	19.2		4.5	
Housewife	9.6		4.5	
Student	4.5		9.0	
Retired	5.1			1.1

Table 4**Disease variables and neurological data for the MS patients.**

Age of first symptoms	26.6 (7.3)
Age of diagnosis	31.4 (8.0)
Age at assessment	36.6 (7.8)
Number of relapses since Dx	4.7 (2.6)
Duration of disease since Dx	5.2 (3.5)
Relapses per year	0.9 (1.1)
Kurtzke Scales:	
Pyramidal	1.2(0.9)
Cerebellar	0.5 (0.9)
Brain Stem	0.5 (0.8)
Sensory	0.8 (0.9)
Bowel/Bladder	0.5 (0.8)
Visual	0.5 (0.8)
Mentation	0.03 (0.2)
Extended Disability Scale	2.0 (1.2)

Table 5

Means, standard deviations, and statistical tests for MS (n = 177) and Control subjects (n = 89) on the thirteen neuropsychological tests included in the battery.

Test	MS	Controls	t-value	F-max
Information	10.53 (2.52)	10.38 (2.61)	<1	1.07
Vocabulary	11.50 (2.34)	12.08 (2.54)	1.84*	1.17
Digit Span	10.84 (2.86)	11.10 (2.34)	<1	1.49*
Arithmetic	10.77 (2.66)	11.19 (2.71)	1.20	1.04
Similarities	10.46 (2.25)	11.01 (2.23)	1.90*	1.02
Picture Completion	9.32 (2.37)	10.08 (2.19)	2.52**	1.17
Block Design	9.96 (2.58)	11.20 (2.32)	3.82***	1.24
Benton Visual Retention Errors	4.34(2.86)	3.04(2.29)	4.01***	1.56*
Word Fluency	36.99 (11.68)	41.65 (10.27)	3.20***	1.29
Category Errors	21.99 (13.23)	19.91 (11.84)	1.25	1.25
Paired Associates	43.36 (7.13)	47.62 (5.84)	5.21***	1.49*
Trails B-A	36.64 (20.61)	26.99 (14.43)	4.43***	2.04***
Memory for Objects	12.25 (1.75)	12.93 (1.44)	3.40***	1.48*

* p< .05 ** p<.01 *** p<.001

All p values are one-tailed.

Table 6

Percentage of MS patients with scores below the 5th percentile (standard score of -1.64 or less) of the normative sample on the neuropsychological tests.

Test	% MS < 5th percentile
-------------	---------------------------------

WAIS-R Subtests:

Vocabulary	3.38
Information	2.26
Digit Span	10.73
Arithmetic	7.34
Similarities	12.43
Picture Completion	13.56
Block Design	18.08

Neuropsychological Tests:

Benton Visual Retention	24.29
Word Fluency	12.43
Categories	10.73
Paired Associates	22.03
Memory for Objects	15.82
Trails B-A	23.16

Table 7

Frequency of impaired test scores for subjects in the MS and Control groups. Impairment was defined as a score falling below the 5th percentile of the control group.

Impaired Tests	Multiple Sclerosis (n = 177)			Controls (n = 89)		
	Frequency	Percentage	Cumulative	Frequency	Percentage	Cumulative
0	62	35	35	53	60	60
1	36	20	55	18	20	80
2	21	12	67	13	15	95
3	29	16	83	2	2	97
4	15	9	92	3	3	100
5	7	4	96			
6-7	4	2	98			
8-9	3	2	100			

Table 8

Demographic and disease characteristics for the MS subjects in the impaired cluster groups. One control subject was clustered in each of the groups with the exception of the BVR/PA group.

	Moderate	Severe	WF/PA	BVR/PA	BVR
Number of MS subjects	19	11	10	9	8
Mean age (years)	36.1(9.2)	40.3 (5.6)	38.0 (8.5)	37.9 (9.5)	38.0 (6.2)
Education (years)	12.9 (1.7)	12.9 (1.8)	12.1 (2.9)	13.1 (2.1)	13.0 (2.0)
Age at onset (years)	27.4 (6.9)	30.1 (7.6)	24.3 (9.0)	22.6 (5.5)	29.9 (5.7)
Sex (% female)	74 %	82 %	30 %	78 %	88 %
Kurtzke EDSS	2.7 (1.4)	2.5 (1.1)	2.4 (1.2)	2.0 (0.8)	2.8 (1.6)
% unemployed	53 %	82 %	10 %	22 %	25 %

Table 9

Ratio of Control to MS subjects in the 10 unimpaired clusters. The ratio of Controls to MS subjects participating in the study was .71 (chi-square (df = 9) = 26.62, p < .01).

Cluster	n (MS)	n (Controls)	C/MS Ratio
1	3	0	---
2	8	6	.75
3	5	10	2.0
4	4	3	.75
5	23	16	.70
6	13	5	.38
7	17	19	1.12
8	26	8	.31
9	9	8	.89
10	11	9	.82

Table 10

Intertest correlations between the clustering and validation tests computed separately for the impaired and unimpaired subjects. Fisher z statistics indicated significantly larger correlations within the impaired group.

Correlation	Impaired	Unimpaired	Fisher z
Word Fluency/Similarities	.33	.19	2.50*
Benton/Block Design	.46	.37	1.69*
Pairs/Memory for Objects	.32	.21	1.84*

* $p < .05$, one-tailed

Table 11**Mean standardized scores for the impaired groups on the clustering and validation tests.****Word Fluency and Similarities:**

Test	WF/PA	Severe	Moderate	BVR	BVR/PA
Word Fluency	-1.61	-1.58	-1.53	-.32	.52
Similarities	-1.08	-1.14	-1.19	-.20	-.44

Paired Associates and Memory for Objects:

Test	WF/PA	BVR/PA	Severe	Moderate	BVR
Paired Associates	-2.52	-2.43	-1.93	-1.18	-.08
Memory for Objects	-1.35	-1.73	-.59	-.86	-.65

Benton Visual Retention and Block Design:

Test	Severe	BVR	BVR/PA	Moderate	WF/PA
Benton Visual R	-2.54	-2.51	-2.13	-.90	.04
Block Design	-1.80	-1.80	-1.03	-1.43	-.50

Table 12

Percentage of MS (n=150) and Controls (n=66) with a lesion in each of 50 sites:

Slice	% MS	% Controls
Supraventricular:		
Frontal right	20.8	0
Frontal left	21.4	0
Frontal/parietal right	17.5	0
Frontal/parietal left	14.5	0
Parietal right	32.5	0
Parietal left	33.1	0
Periventricular:		
Frontal horn right	84.4	25.8
Frontal horn left	85.7	30.3
Occipital horn right	77.9	21.2
Occipital horn left	79.2	18.2
Temporal horn right	42.2	1.5
Temporal horn left	40.3	0
Parietal body right	83.1	7.5
Parietal body left	83.1	6.1
Deep White:		
Frontal horn right	17.5	1.5
Frontal horn left	14.3	0
Occipital horn right	4.5	0
Occipital horn left	3.9	0
Temporal horn right	3.9	0
Temporal horn left	4.5	0
Parietal body right	43.5	0
Parietal body left	44.2	1.5
Internal Capsule:		
Right	17.5	0
Left	14.9	0
Grey/White Junctions:		
Frontal right	20.8	0
Frontal left	16.9	0
Parietal right	20.1	0
Parietal left	22.1	0
Occipital right	5.8	0
Occipital left	1.9	0
Temporal right	13.6	0
Temporal left	11.7	0

Table 11, continued

Deep Grey:		
Insula right	6.5	0
Insula left	4.5	0
Basal Ganglia right	1.9	0
Basal Ganglia left	0.6	0
Thalamus right	1.3	0
Thalamus left	1.3	0
Corpus Callosum:		
Body	74.0	22.7
Genu	37.0	1.5
Splenium	42.2	1.5
Brain Stem:		
Midline	20.8	1.5
Cerebellum right	24.0	3.0
Cerebellum left	11.0	0
Pons right	24.7	0
Pons left	20.1	0
Mid Brain right	14.9	0
Mid Brain left	14.9	0
Medulla right	11.7	0
Medulla left	10.4	0

Table 13**Mean number of total lesions for the impaired cluster groups.**

Group	N	Mean number of total lesions
Moderate	18	16.0 (7.1)
Severe	8	16.4 (6.1)
WF/PA	8	13.5 (6.0)
BVR/PA	11	15.2 (5.1)
BVR	17	12.5 (6.4)

Table 14

Percentage of subjects in the impaired cluster groups with a lesion present in the genu and the deep white left parietal region.

	Genu of the CC	Deep White Left Parietal
Expected frequency:	37 %	45 %
Unimpaired (n=68)	28 %	29 %
Moderate (n=18)	44 %	50 %
Severe (n=8)	88 %	75 %
WF/PA (n=28)	36 %	71 %
BVR/PA (n=11)	27 %	64 %
BVR (n=17)	53 %	35 %

Table 15

Frequency table for lesions in the genu and deep white left parietal region for the reconstructed MS groups with isolated impairment on one of the three clustering tests, compared to a group of MS patients with normal performance on all three tests.

	Genu of the CC	Deep White Left Parietal
Expected frequency:	37 %	41 %
Unimpaired (n = 37)	22 %	35 %
BVR (n = 21)	67 %	33 %
PA (n = 15)	40 %	80 %
WF (n = 9)	22 %	35 %

Figure 1. Cognitive profiles for the impaired clusters. Graphed are the mean standardized scores on the three clustering tests, Word Fluency (WF), the Benton Visual Retention test (BVR), and Paired Associates (PA). Dotted lines indicate profiles that were collapsed due to visual similarity.

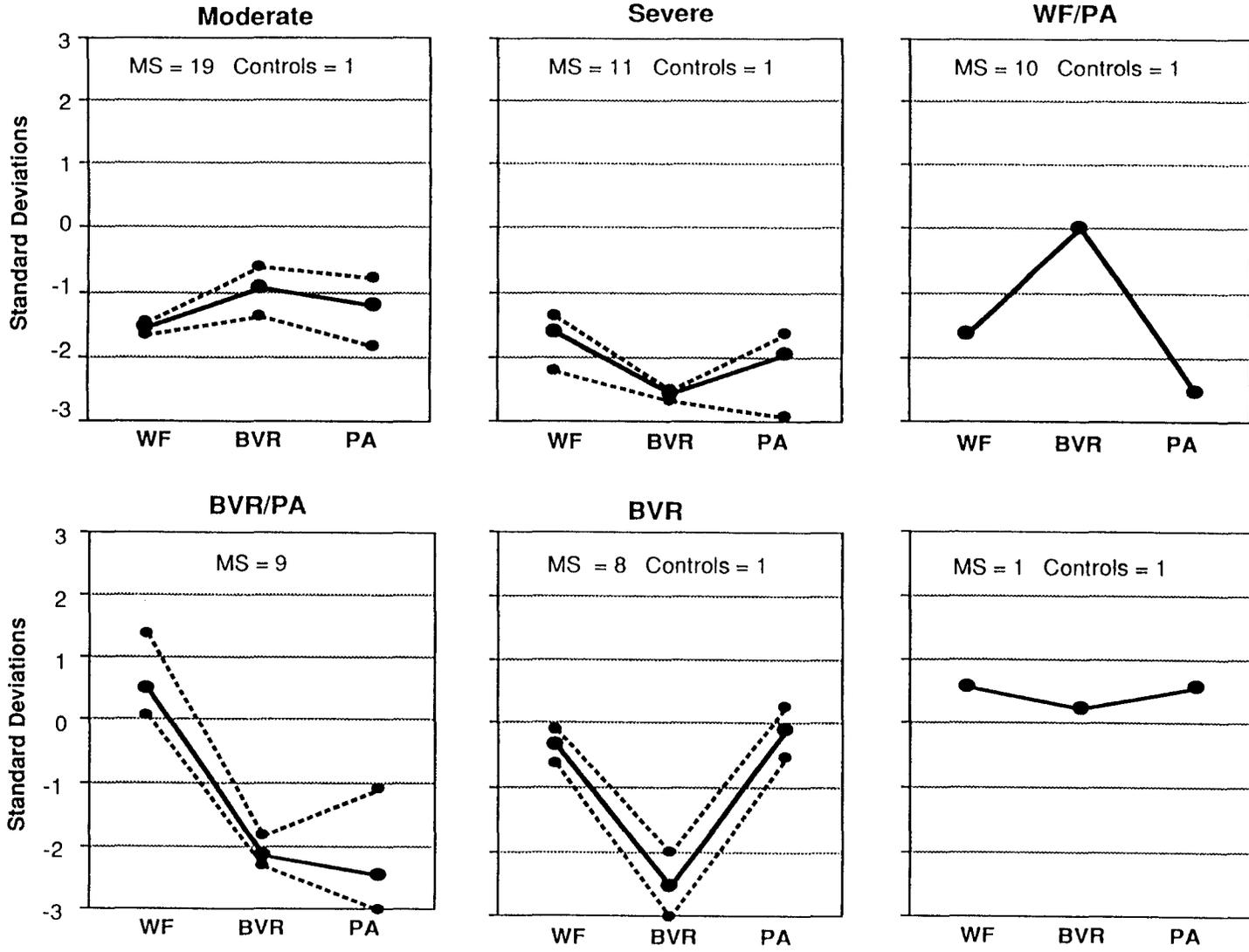


Figure 2. Cognitive profiles for the unimpaired clusters. Graphed are the mean standardized scores on the three clustering tests, Word Fluency (WF), the Benton Visual Retention test (BVR), and Paired Associates (PA). Dotted lines indicate profiles that were collapsed due to visual similarity.

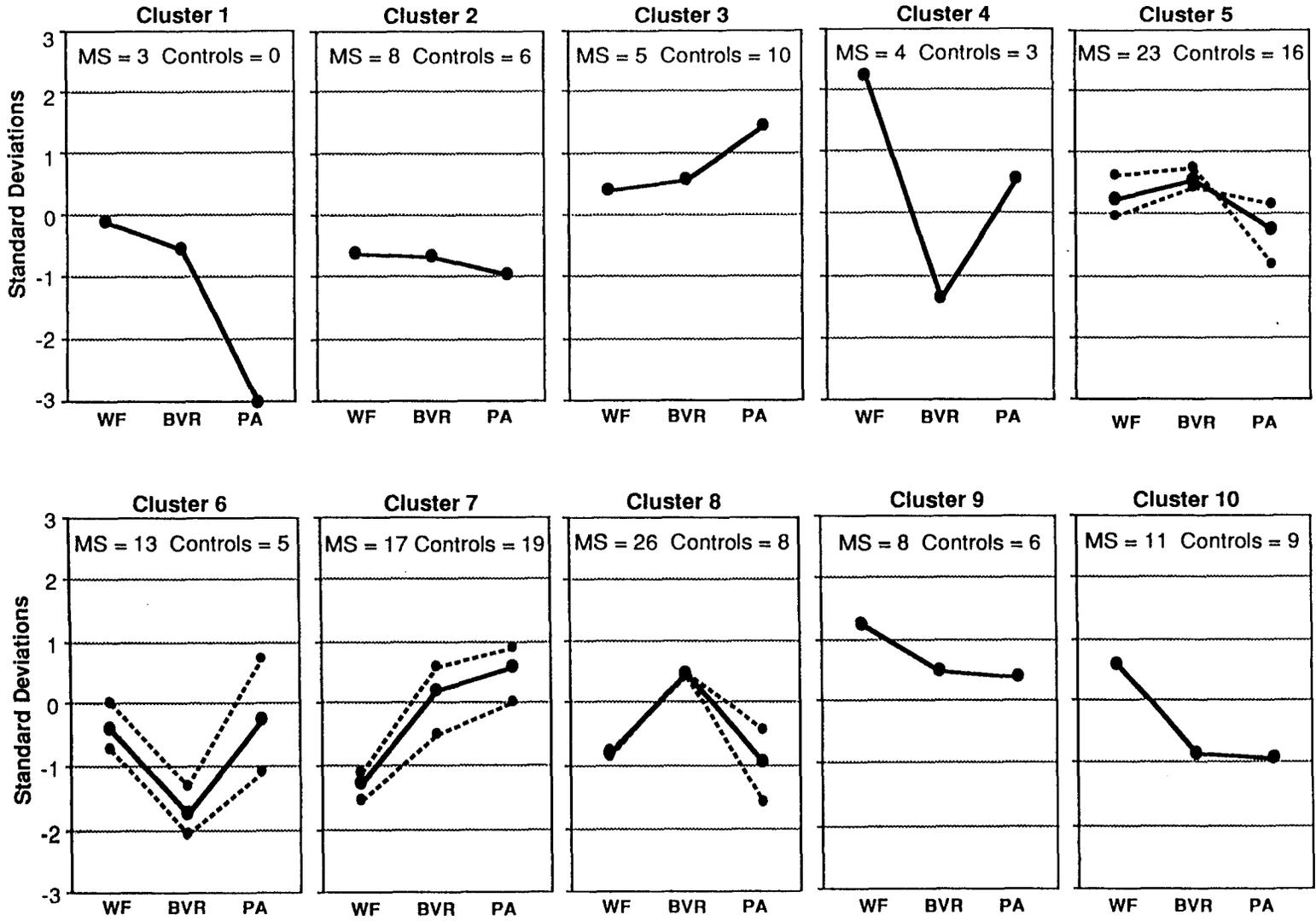


Figure 3. Profiles for MS patients from three unimpaired clusters with an over-representation of MS patients compared to controls (solid lines). The three profiles are presented with similar profiles from the impaired cluster analysis (broken lines).

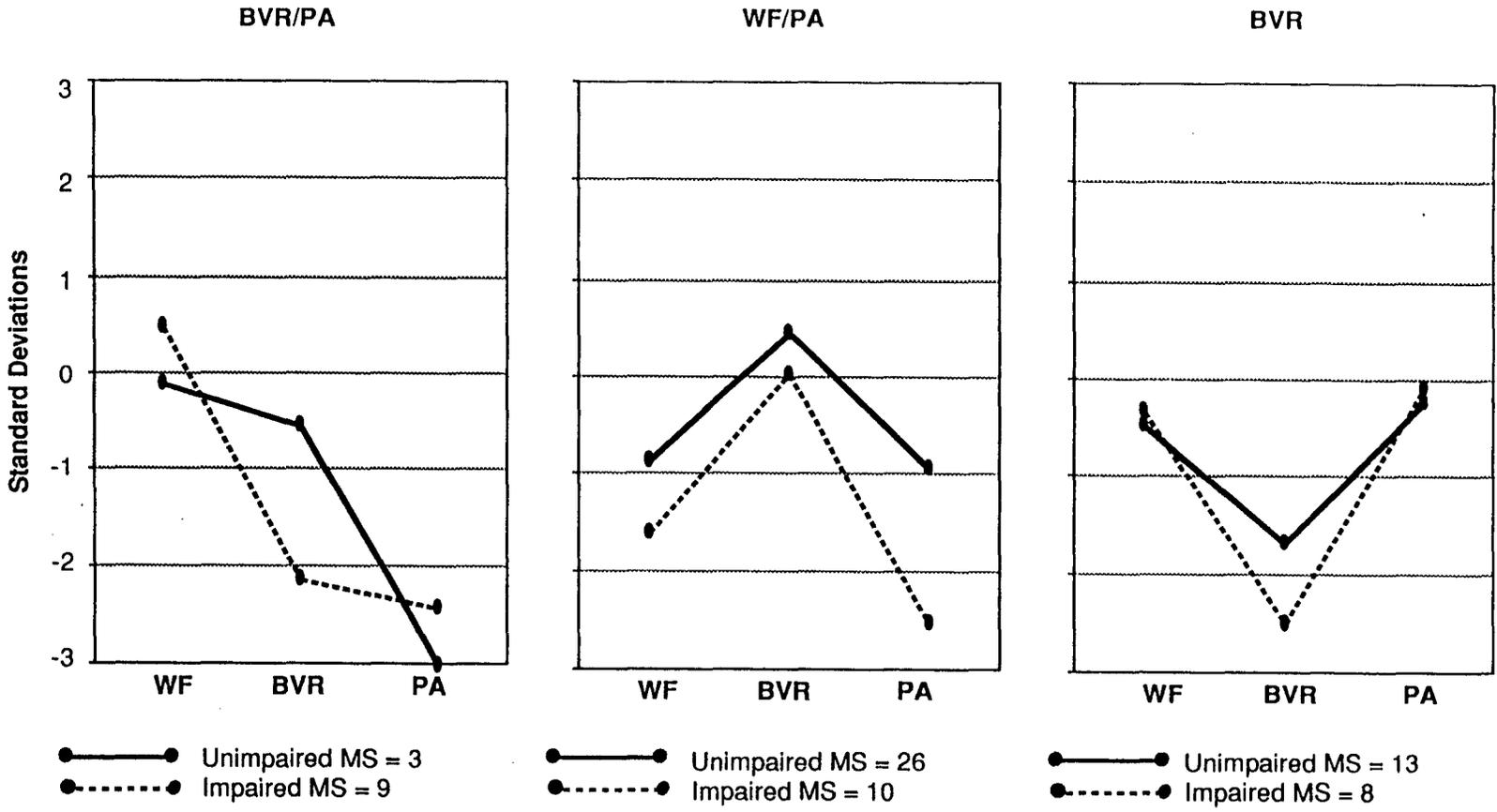


Figure 4. Profiles for the five impaired clusters on the clustering tests, Word Fluency (WF), the Benton Visual Retention test (BVR), and Paired Associates (PA) compared with profiles on the validation tests, Similarities (Sm), Block Design (BD), and Memory for Objects (MO).

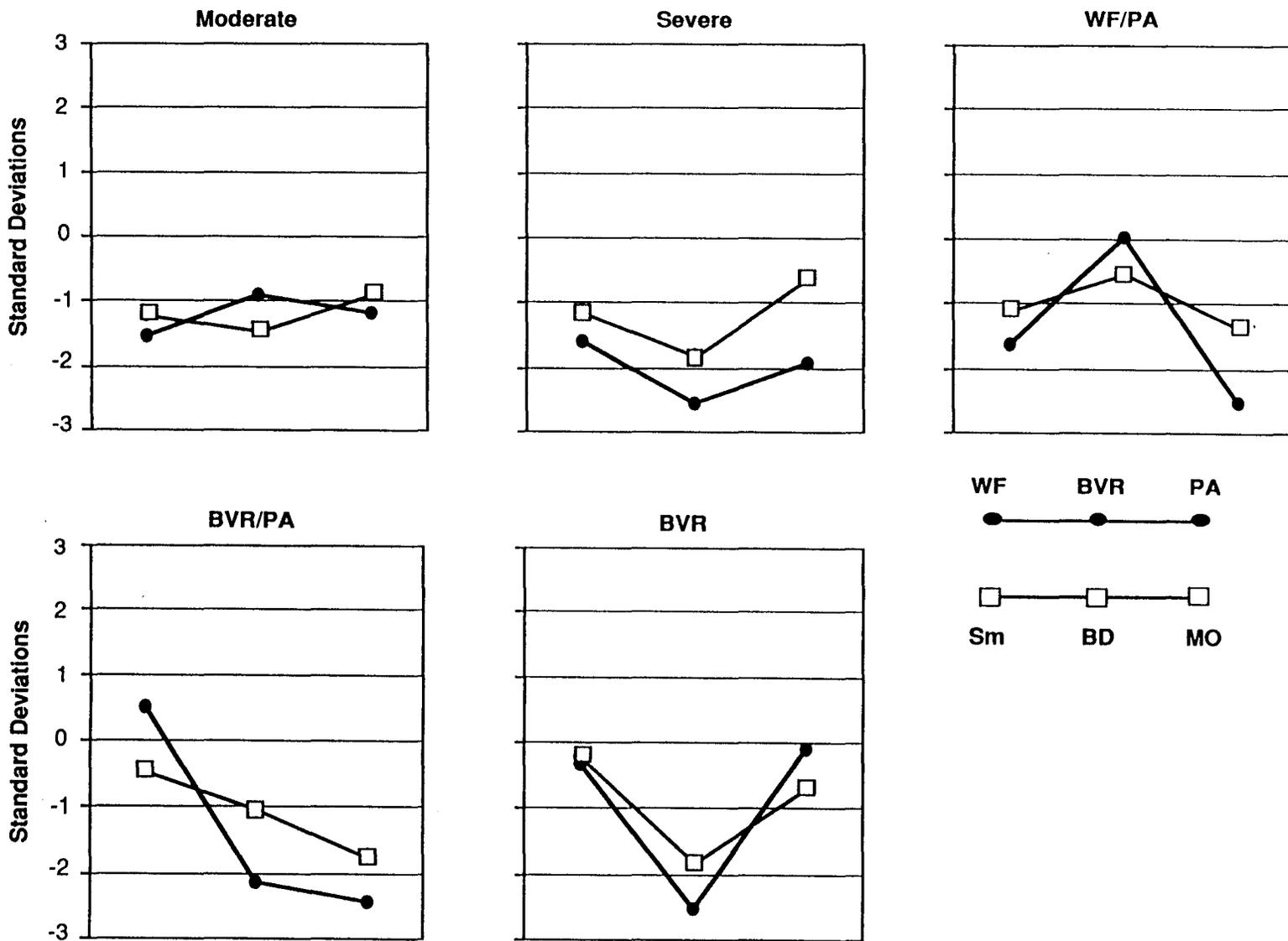


Figure 5. Profiles for the ten unimpaired clusters on the clustering tests, Word Fluency (WF), the Benton Visual Retention test (BVR), and Paired Associates (PA) compared with profiles on the validation tests, Similarities (Sm), Block Design (BD), and Memory for Objects (MO).

