

DISTINCT PSYCHOLOGICAL PROFILES IN MULTIPLE SCLEROSIS:

RELATIONS TO SITE OF LESION  
AND NEUROPSYCHOLOGICAL FUNCTION

by

ELEANOR A. BOYLE

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Department of

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The University of British Columbia  
Vancouver, Canada

Date

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## ABSTRACT

An important question in multiple sclerosis (MS) is whether personality changes result from the neuropathological process or, alternatively, are normal psychological responses to the stress of living with the disease. The purpose of this study was to determine (1) if empirical support could be found for personality profiles described in the literature and (2) if these profiles were related to neuropathology. The subjects for this study were 99 MS patients with mild physical disease, and 56 well-matched normal controls. In addition, a validation study was done on positive results, using 43 MS patients and 20 controls.

A review of the literature suggested four common profiles in MS patients, namely denial, exaggeration of symptoms, 'Depression' (distinct from psychiatrically-defined major depression), and distress concordant with physical disability. These profiles were operationally defined by three variables measuring (i) objective clinical disability (Kurtzke Expanded Disability Status Scale); (ii) the patient's perception of symptoms; and (iii) the patient's level of psychological distress. These three variables were analyzed using Ward's method of cluster analysis, which yielded four groups consistent with the hypothesized profiles. Subsequently, identical results were obtained on the validation study.

To determine if profile membership was related to neuropathological processes, membership in a psychological profile was correlated with lesion site and cognitive function. Site-by-site lesion analyses revealed that 'Depressed' patients had more pathology in one right parietal lobe site than did members of other groups. In the validation study there was a non-significant trend ( $p \leq 0.09$ ) supporting this relation. The remaining sites (26/27) showed no differences, therefore, with the exception of the 'Depressed' group, no support was found for a pathological basis for psychological profiles. Hence, one would infer that in the mild stages of MS, profiles are reactive responses. The profile groups were also compared on number of lesion sites and did not differ, suggesting that profile does not reflect stage of biological disease.

Analyses of neuropsychological test results indicated that only the 'Depressed' group with the right parietal lesion had cognitive impairment in comparison to the other groups. This finding was not replicated on validation.

The current study provided empirical support for distinct psychological responses in MS, but for denial and somatic exaggeration no evidence was found for a pathological basis. These data will be useful to professionals working with MS patients, and may have therapeutic implications.

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## CHAPTER ONE

### INTRODUCTION AND OVERVIEW

#### Purpose of the Study

There is longstanding evidence that multiple sclerosis (MS) patients may exhibit psychological abnormalities, both cognitive and affective. However, the relation between patients' psychological status and the disease process is not clear. Simply, it is not known to what degree behavioural abnormalities result from the organic disease process or, alternatively, are secondary reactive responses in individuals faced with a chronic, debilitating disease. It has been difficult to differentiate between, on the one hand, cognitive and affective changes arising directly from physical disruption to the nervous system and, on the other hand, individual coping or accommodation responses to such disruption. Whereas caution must be exercised in the application of dichotomies such as "organic" vs. "reactive", because there tends to be overlap between categories of human making, the distinction is nevertheless an important one in medicine in general, including in MS. The purpose of this study, then, was to attempt to differentiate between organic and reactive changes, by assessing (1) whether patients show distinct psychological profiles, (2) whether patients with any given profile share common lesion sites

suggesting an organic basis to the profile, and (3) whether patients in a given profile have similar cognitive problems suggesting common lesion patterns.

#### Difficulties Inherent in the Problem: Past and Present

The difficulties in distinguishing between organic and reactive abnormalities in patients with MS exist for several reasons. Firstly, to know whether behaviours are organically-determined, we must have precise information on the anatomical location of lesions and the degree of pathology within an individual brain. Such information has been difficult to obtain and analyse. The distribution of MS lesions is highly variable from patient to patient and the ability to image white matter lesions has been limited until recently. Computerized axial tomographic (CT) imaging has been used, but is limited by poor contrast characteristics (Bydder et al. 1982) and by the potential invasiveness of contrast procedures. High-volume double-dose delayed CT (HVD CT) is more sensitive than other CT methods, and is particularly useful for showing blood brain barrier disruption. However, the recent introduction of magnetic resonance imaging (MRI), which does not necessarily employ contrast material or radiation, has provided more accurate identification of white matter lesions with no known risk to the subjects. MRI has a sensitivity of

perhaps 10 times that of CT in detecting MS lesions (Paty and Li 1988).

Secondly, our understanding of functional neuroanatomy is based on the contribution of gray matter regions to behaviour, and at present there is little theoretical foundation for understanding the effects of white matter pathology on behaviour. Therefore, it has been difficult to draw inferences concerning brain/behaviour relationships based on white matter lesions. Because MS has been considered primarily a somatic disorder, a third difficulty in distinguishing between organic and reactive psychological problems is that patients' mental states have not been systematically documented in the past. Fourthly, MS is a relapsing-remitting disease with a notoriously variable course. Hence, numerous variables may change in unpredictable ways from exacerbation to remission. Finally, there are the ever-present difficulties of correlating any behaviour with a neuroanatomical structure or region, considering the complexity of central nervous system connections. Brain lesions can produce numerous kinds of behavioural abnormality, particularly if the lesions are in higher cortical centers. Such abnormalities can include not only losses, but sudden appearances of simpler behaviours (Jackson 1884, reprinted in Taylor 1958). Kolb and Whishaw (1980) have suggested that brain lesions can have at least three different effects on behaviour: loss of function, release of function, or disorganisation of function.

Because of the brain's complex interconnections, a lesion can have multiple effects - producing loss in one behaviour, for example, and disorganisation in another behaviour.

Psychological Change Has Long Been Reported  
and its Origins Debated

Since before the turn of the century, investigators have reported psychological problems in MS and debated whether the phenomena were primary or secondary to the disease. Charcot first reported psychological abnormalities in patients with what he then termed sclerose en plaques. According to Charcot, patients often displayed intellectual and emotional deficiencies, showed indifference to their physical problems, and frequently laughed or cried without visible cause (Charcot 1877).

During the 20th Century, numerous authors have postulated the existence of an MS personality, namely a constellation of premorbid psychological traits or problems predisposing some individuals to the disorder. Several studies described patients as immature, anxiety-ridden, and otherwise emotionally abnormal (Grinker et al. 1950; Langworthy 1950). Inman (1948) submitted that MS "is a somatic reaction to intolerable mental conflict" (p. 154). Philippopoulos et al. (1958) reported that MS patients had experienced unhappy childhoods and that they displayed emotional problems which may have contributed to the

development of the disease. In the assessment of Grinker et al. (1950), as MS progresses the patient "may neurologically actually become the infant that he has always been psychologically" (p. 459). However, implications that regression necessarily reflects psychological immaturity fail to recognise that both cognitive and physical regression have been noted in other neurological diseases as well as in aging (Lezak 1983). Hughlings Jackson used the term "dissolution" to refer to the result of higher cortical damage in which individuals lose their most sophisticated behaviours and regress to simpler, more-primitive ones (Jackson 1884, reprinted in Taylor 1958).

Recent reviewers (VanderPlate 1984; Peyser and Poser 1986) have commented unflatteringly on some of the early studies in MS psychology, which they said were too often based on biased samples, lack of objective data, and lack of appropriate controls, and which drew conclusions unsupported by the data. In the view of Peyser and Poser (1986), such studies unfairly perpetuated negative descriptions of MS patients. "The existence of a contributory relationship, possibly through the immune system, is an entirely plausible notion, but such a formulation most certainly does not depend on a premorbid hysterical personality style" (p. 383).

Personality studies using the Minnesota Multiphasic Personality Inventory (MMPI) have tended to reinforce the notion that MS patients exhibit neuroses and even

psychopathology. Numerous authors have reported that MS patients score high on the MMPI's Hypochondriasis (Hs), Depression (D) and Hysteria (Hy) scales, the "neurotic triad" (Canter 1951a; Baldwin 1952; Gilberstadt and Farkas 1961). Elevated scores have also been reported on the Schizophrenia (Sc) scale, which is sensitive to bizarre feelings and peculiar body dysfunctions among other problems. Researchers have not always interpreted the elevated scores as indicative of an MS personality. Canter (1951a) suggested instead that the high scores represented a coping style. Nevertheless the data have implicitly seemed to support an "MS personality" hypothesis. One problem is that instruments such as the MMPI were designed for, and validated on, normal and psychiatric population samples. Therefore individuals who genuinely suffer from physical illness may have spuriously elevated scores on scales such as Hypochondriasis, merely because they are endorsing items relating to their physical difficulties. This confound has been pointed out not only for MS but for rheumatoid arthritis (Pincus et al. 1986) in which patients also score high on Hs, D and Hy scales of the MMPI. Prigatano (1987) comments that the MMPI can be misleading if used on individuals with organic brain damage. MS patients' elevation on neurotic scales (Hs, D and Hy) as well as the Sc scale may result primarily from endorsement of items which reflect true physical symptoms and related health concerns. Deletion of MMPI items directly related to MS



symptomatology has been shown to produce profiles much closer to normal (Marsh et al. 1982). These findings underscore the hazards of making inferences about personality in MS patients from standardized tests. Specifically, some of the characteristic signs and symptoms of MS are also signs and symptoms of diagnosable psychiatric disorders. For example, assessments of depression are often based on somatic complaints such as fatigue and physical weakness, two common physical symptoms in MS. Similarly, many signs and symptoms of MS are of the type associated with hysterical conversion reactions. Accordingly, early-stage MS is often initially mistaken for psychiatric illness (Skegg et al. 1988).

Counter to the views of the "MS-personality" theorists is a school of thought which asserts that MS psychological problems are secondary and therefore a response, rather than a contributing factor, to the disease. This approach has prompted questions regarding the origins of such problems, which could broadly be typed as either biological/organic, or situational/reactive. It has been suggested that affective problems can be reactive, such as in MS patients who have spinal cord lesions only (according to clinical assessment) whose depression nevertheless increases with disability (McIvor et al. 1984). However, as noted by Berrios and Quemada (1990), a distinction between cerebral and spinal cases is clinical and not neuropathological; even in spinal cases there may exist brain lesions which are

neurologically but not psychiatrically silent. Nevertheless, it has also been shown that depression exhibited in MS is akin in incidence and severity to that observed in muscular dystrophy, which is also a progressive disease leading to paralysis but not involving the brain (Surridge 1969). Correlational studies have shown that depression is more severe during exacerbations than during remissions (Cleeland et al. 1970) and that depression is related to degree of disability (Baretz and Stephenson 1981); however, such findings could be evidence either for an organic or a reactive cause. For example, if depression increases as the disease produces more and more disability, the increased depression could have resulted either from advancing organic pathology or, alternatively, from accumulated stress. In summary, current reviews of the literature do not vindicate mid-twentieth-century contentions for a typical premorbid MS personality, but suggest rather that psychological abnormalities can arise either directly from the pathological process, or from an interplay of the pathology and the personality of the individual involved.

Though much research on psychological aspects of MS has involved affective changes, cognitive dysfunction in MS is increasingly being documented. For decades, it was believed that such dysfunction might be a mild and relatively inconsequential manifestation of the disease, or might be seen only in its late stages. It was also unclear whether

apparent cognitive difficulties merely reflected patients' motor and sensory problems. However, there is mounting evidence that cognitive changes are a persistent manifestation in MS (Rao et al. 1984; Rao et al. 1989d; Beatty et al. 1988, 1989). Numerous studies illustrate cognitive dysfunction, for example in learning and memory tasks (Beatty and Gange 1977, Beatty et al. 1988; Minden et al. 1990). In cognition as in motor and sensory abilities, dysfunction can be severe but is by no means evident in all patients. There is considerable inter-patient variability even at a given level of clinical disease. Rao et al. (1984) performed a cluster analysis to divide patients into groups differing in memory performance, and commented: "It is also surprising that the three subgroups, which appeared to differ sharply in their performances on measures of motor, cognitive, and personality functions, had equal average Kurtzke disability ratings" (p. 631).

Cognitive difficulties have even been detected in patients with mild symptoms (Peyser et al. 1980b; Van den Burg et al. 1987), including patients with mild MS and in remission at the time of testing (Klonoff et al. 1991). In the view of Rao (1986) and Peyser and Becker (1984), cognitive dysfunction in MS has been underestimated because neurological examinations are not sensitive to subtle or specific problems in cognition.

It is generally believed that, while mood/affective changes may be either organic or reactive, cognitive changes are usually organically-based (Peyser and Poser 1986), emerging directly from lesions. However, interaction can occur between cognitive and affective domains, so that, for example, mood changes can produce cognitive changes - depression can lead to decreased performance on cognitive tests (reviewed in Weingartner and Silberman 1982). As well, the interaction occurs both ways: cognitive changes may influence a patient's mood. For example, memory dysfunction may sufficiently frustrate some patients that they become short-tempered or depressed. To summarize, psychological changes may either have organic foundations or be secondary reactions to the disease. Cognitive changes are generally considered organically-based, though they may be secondary to affective problems; affective changes may be either organic or may be responses to alterations in cognitive or physical state. As well, psychological change, either organic or reactive, may be a feature even of early stages of the disease.

### Psychological Profiles in MS

To examine the basis - reactive vs. organic - of psychological changes in MS, the assumption of this project was that particular changes do not necessarily occur in all patients or in stages reflecting progression of the disease.

As will be outlined, numerous studies have tried to distinguish between reactive and organic psychological changes in MS, often with equivocal results. Generally such studies have assumed that all patients show some degree of abnormality on a specific dimension (e.g., depression). In contrast, the current study takes the view that MS patients may demonstrate psychological change in various ways. Specifically, any two patients, even with similar levels of physical disability, may show quite different psychological profiles. Based on the literature, it was postulated that these profiles may include:

1. Depressive response, when a patient reports psychological problems seemingly out of proportion to his/her level of physical difficulty. Such patients correctly assess their physical status, so that subjective (patient report) and external (neurologist report) assessments of disability/impairment are concordant. Because this response is not assessed on the same basis as depression in the psychiatric Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (though the two definitions of depression have numerous features in common), the response of this study will be referred to as 'Depression'.

2. Denial, when a patient reports few problems either physical or psychological, despite a relatively high score on an external assessment of disability/impairment.

3. Exaggerated Somatic response, when a patient magnifies physical symptoms in comparison to external assessment, yet may claim that such symptoms have no negative repercussions on mood or psychological well-being.

4. Severity-related response, when there is good concordance between a patient's self-reported problems, both mental and physical, and physical disability as assessed by a neurologist. This concordance should hold whether problems are few or many. In particular, it is not unrealistic to expect that a patient with severe physical impairment will be severely distressed.

Any of the profiles may be purely reactive - a secondary effect of the illness, possibly representing an unwillingness or inability of the patient to cope with the diagnosis and/or the physical problems of MS. Alternatively, the profiles, notably 'Depression', Denial or Exaggerated Somatic, may result from an organic process affecting comprehension, mood, judgment, and insight. Therefore, two separate models may explain a reaction such as, for example, denial. In the first model, the response is reactive in a classic psychological sense; clearly some level of denial is frequently used by healthy individuals, and is considered part of normal behaviour (Freedman et al. 1976). In the second model, the response is the result of the underlying organic process. For example, euphoria (associated with denial) and lack of insight have been observed in patients with frontal lobe lesions

(Filskov et al. 1981; Walsh 1987). These two models may both be represented to varying degrees in the patient population, in that some patients who deny their illness are exhibiting purely reactive behaviour, while others who deny are manifesting organic pathology.

### Hypotheses Underlying the Study

This study operated with four working hypotheses.

1. Hypothesis one was that distinctive psychological profiles of accommodation such as 'Depression', Denial, Exaggerated Somatic and Severity-related, do exist, even in patients with similar levels of disease. The method by which profiles were detected, and by which patients were separated into psychological groups, will be described shortly.

2. Hypothesis two, based on support of the foregoing first hypothesis, was that membership in psychological groups was not related to number of sites with lesions. In other words, psychological abnormality or profile is not a function of amount of biological MS. This hypothesis extended the central notion of this study, that psychological problems may not be stages in a disease process or reflective of amount of pathology, but rather may result from specific lesions.

3. Hypothesis three was that membership in groups was related to a different pathological indicator - location of

lesions. For example, patients with virtually no MS disability but severe distress, or patients with extreme physical disability but apparent cheerfulness or even elation, may possess brain lesions which compromise the integrity of the central nervous system, and are in part responsible for their psychological profiles. Membership in certain profile groups, then, may be related to, and a primary result of, lesions detected by MRI. It was suggested that in any particular profile either all members, or a subgroup thereof, may possess characteristic lesions.

4. Hypothesis four was that group membership would be related to performance on cognitive tests. These tests serve as an added measure (along with MRI) of organic pathology. It was suggested that patients' coping styles may be a primary result of diminished cognitive capacity. By relating group membership (reflecting coping style) with both MRI lesion-location and cognitive-function, two tests were performed for a potential organic basis to these profiles.

If neither the third nor the fourth hypothesis was supported, these data would suggest that coping strategies are psychological overlays and reactions to the disease rather than primary results of the neuropathological process.

The purpose of this study, then, was to seek and identify psychological profiles and organic correlates, through the testing of the above four hypotheses.



## General Methodology

To test for the existence of profile groups, it was necessary to assess each patient's (1) actual disability/impairment, (2) self-reported disability/impairment, and (3) psychological well-being with an instrument not confounded by MS signs and symptoms.

Therefore, in the proposed study, two scales were derived:

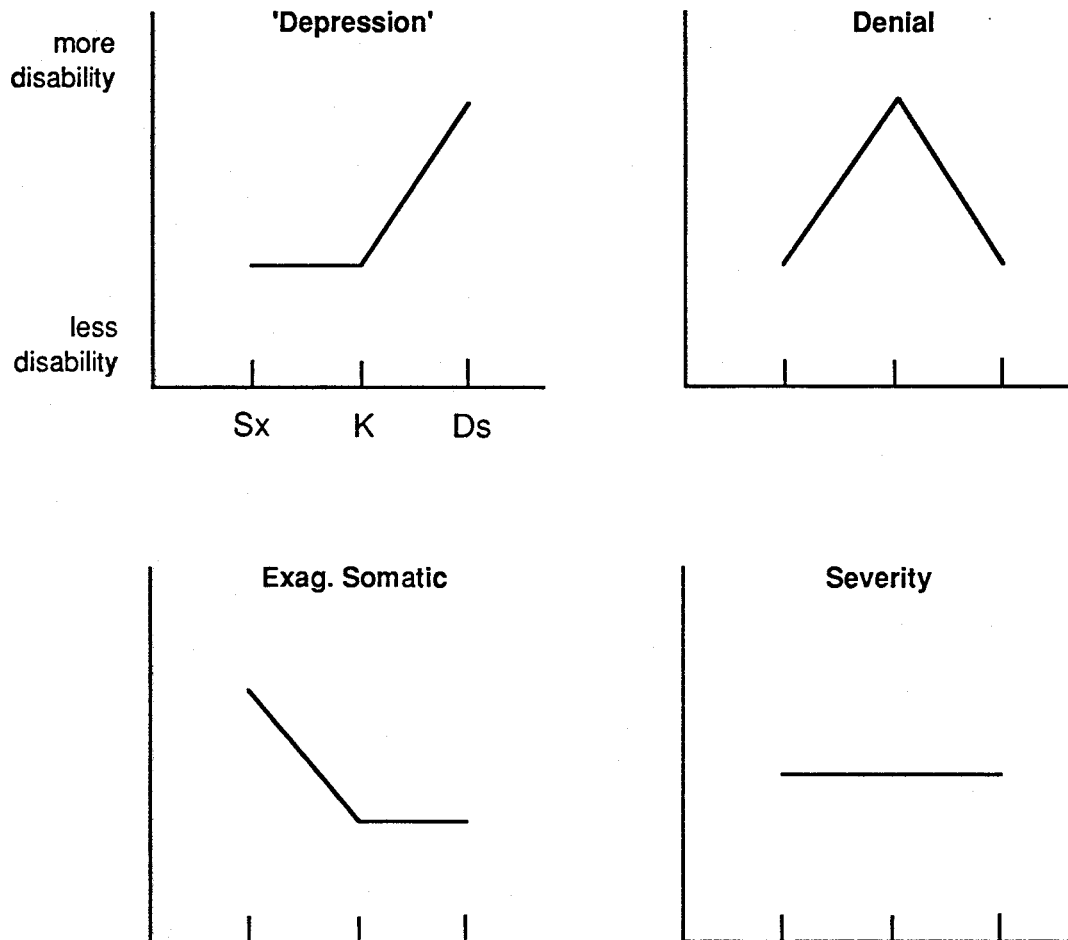
i) Sx: to assess patients' own perceptions of their MS-related signs and symptoms, and ii) Ds: to assess patients' self-reported psychological well-being, or conversely level of distress, independent of Sx. Psychometric evaluation of these scales was done to determine their reliability and, in part, validity. In addition, the Expanded Disability Status Scale (EDSS) (Kurtzke 1983), which will be called the K scale in this study, was used as an objective or external measure of operational disability. The EDSS is a widely-used method of evaluating disability/impairment in MS. A patient's EDSS score can range from 0 to 10, and is based on scores in individual Functional Systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral/mental, and other/miscellaneous.)

MMPI item data from 99 MS patients and 56 matched controls were used to derive the Sx and Ds scales.

The hypothesized profiles, operationally defined on the three variables just described, were then conceptualized as illustrated in figure I. It was then possible to determine

**FIGURE I**  
**Predicted psychological profiles**

Conceptualization of profiles identified from the literature, as operationally defined on three variables: (1) K (EDSS): neurologist's assessment of the patient's level of disability/impairment; (2) Sx: patient's self-report of disability/impairment; (3) Ds: patient's self-report of psychological problems.



whether the hypothesized profiles of accommodation to the disease occur in MS patients. This was accomplished by Ward's method of cluster analysis (Ward 1963) of MS patients (n=99) based on similarity of scores on the three scales (Sx, Ds, and K). The choice of the appropriate mathematical solution (number of clusters) was made using statistical criteria, namely maximization of between-group multivariate variability and minimization of within-group variability for a manageably small number of clusters. The overall accuracy of the solution in terms of group membership was examined to estimate within-group homogeneity. These profiles were then plotted and clusters with similar profiles combined.

Subsequently, MRI data on these profiles were examined to determine whether there was a relation between lesion location, or alternatively the number of sites with lesions, and group membership. The groups were also compared on tests of cognition which were appropriate by their lack of significant motor and sensory components.

As these data were derived from an ongoing research project, the positive results were validated on an additional group of MS subjects (n=43).

### Potential Contributions of the Study

The work just described was designed to support or refute the hypotheses that characteristic and distinct coping responses exist in MS patients and that such responses have correlates in anatomical and/or cognitive abnormalities. The study, and even a refutation of any of its hypotheses, was designed to elicit information for researchers, clinicians, and individuals affected by MS. It may be useful for patients, families, and health care workers to know when psychological changes appear to be a direct result of the disease process. For the scientific community, any knowledge regarding a relation between white matter lesions and psychological responses will add to current understanding of functional neuroanatomy.

This project contributes to the development of white matter models of brain function, through its analysis of the behavioural consequences of disrupted connectivity in the brain. Data from the project also add to the ongoing debate in neuroscience regarding localization of brain function. Despite the acceptance of anatomical localization for some behaviours - few would disagree that body movement is largely mediated in anatomically discrete regions - the localization of some higher functions is still a topic of debate. The current project assumes the existence of functional systems, to the degree that lesions in certain areas can at least influence complex emotional behaviours.

The results from the project are intriguing considering the general lack of knowledge regarding the behaviourally functional role of white matter regions.

## CHAPTER TWO

### BACKGROUND TO THE STUDY

#### Organisation of the Chapter

This chapter presents a deeper foundation for the project, outlined in Chapter One, by tracing the evolving body of knowledge on psychological aspects of MS. Major studies of psychological abnormalities in MS, both cognitive and affective, are reviewed, with the aim of highlighting observations of distinct psychological responses MS patients have shown to their disease. The chapter summarizes historical debates on whether psychological disturbances contribute to or even cause MS ("MS personality" theories) or, alternatively, result from the disease. With respect to this latter position, the evidence for psychological problems as either biological/organic or situational/reactive, will be examined. Past correlational studies which have tested this distinction will then be discussed. As these studies have generally reported weak correlations, it will be argued that these studies do not take into account potential distinct responses (e.g., depression vs. denial). Based on this progression of ideas, the conceptual foundations for the study will be outlined. Finally, methods to be employed will be explained.

For this review of the literature on psychological issues in MS, it should be noted that a distinction between cognitive and affective domains was not made in early work, so that the two were often considered one. Before 1900, a wide range of behavioural functions from memory to mood were subsumed under the general term "mental" (Gowers 1896). In 1922, Wechsler was discussing "mental" and "psychic" changes in MS as roughly analogous to biological and psychological change. Sugar and Nadell (1943) called all changes, both thought and mood, "mental." More recently, Trimble and Grant (1982) use the term "psychiatric" to refer to, for example, personality change, depression, and psychosis, and "neuropsychologic" to refer to cognitive disorders or general dementia. During a historical discussion, then, a sharp distinction between cognitive and affective is not always possible. The current distinctions also have limitations: there is considerable overlap between the constructs of thought, mood, and personality. As always, categorization may clarify complex situations, but can also oversimplify issues, and result in a loss of information.

#### Psychological Aspects of MS: Several Distinct Responses

Multiple sclerosis is a disease involving neuropathological changes and their effects on motor and sensory systems. But since the earliest descriptions of the

disease, references have also been made to its psychological and psychiatric aspects.

One of the best-known of early anecdotal descriptions concerns the case of Augustus d'Este (1794-1848) whose letters and diaries suggest that he suffered from MS for about half of his 55 years. Several of his diary entries have been interpreted as evidence of mental symptoms of MS (Stenager et al. 1989a), and a reading of the text (Firth 1948) reveals at least one stress-related attack.

Inconclusive though the report may be, it hints that psychological factors have always been entwined with MS.

Medical descriptions of MS began to be published in the 19th Century, most notably through the writings and lectures of neurologist Jean Martin Charcot. By the 20th Century, MS was an accepted clinical entity. However, cases of what were probably multiple sclerosis were recorded considerably earlier. For example, the earliest known description compatible with the diagnosis of MS (Hashimoto and Paty 1986) was that of Lidwina of Schiedam (1380-1433) (Medaer 1979).

Nineteenth-century descriptions indicated that psychological problems were part of the disease, though such descriptions are difficult to appraise in twentieth-century terms because of changes in concepts of mental health in the intervening 100 years. For example, Seguin (1878) pronounced one male MS patient psychologically sound partly because he did not masturbate. As pointed out by Aring



(1965), the history of clinical assessments shows that moral judgments have frequently been intrinsic to diagnosis, notably in the zealous application of the diagnosis of hysteria. Seguin (1878) reported that a female patient with weakness and paresis showed inappropriate affect ("at times hysterical laughter and tears"), and "concluded that the patient had a functional palsy of a hysterical nature," only to discover at autopsy that she had numerous sclerotic lesions. Buzzard (1897) also described nine cases of MS which had mistakenly been diagnosed as hysteria. This diagnostic dilemma is more than a historical curiosity. For example, Skegg et al. (1988) reported that 15/91 (16%) of a group of MS patients were given psychiatric diagnoses, including hysterical conversion and hysterical personality, before their MS was diagnosed. The term "hysteria" applies when patients have physical problems, but the cause of which appears to be psychological rather than biological. Examples are the somatoform disorders of DSM-III-R, including conversion disorder in which patients have paralysis, anaesthesia, aphonia or any of a number of other physical manifestations of what is judged to be psychological conflict. However, some observers have commented that the term hysteria has been applied carelessly (Brown and Davis 1922) and as a value judgment of the patient (Aring 1965). Certainly, hysteria has been "an imprecise term" (Trimble and Grant 1982).

Probably the most influential observer of early MS was Charcot (1877), whose graphic account of psychological abnormalities has echoed through the MS literature ever since. Said Charcot, MS patients showed "marked enfeeblement of the memory. . . [and an] almost stupid indifference in reference to all things. . . . It is not rare to see them give way to foolish laughter for no cause and sometimes, on the contrary, melt into tears without reason" (p. 194).

From the turn of the century to the 1920s, MS reports consisted generally of case studies (Dercum 1912; Brown and Davis 1922) noting a variety of mental symptoms. Most such studies were on a small number of pre-selected patients. In the main, studies from this period suffered from a lack of objective psychological measures and overly ambitious generalization from the data. Jelliffe (1921) inferred on the basis of two patients' dreams that MS may have been caused by "illness in the spiritual part" (p.675) of their natures. It is instructive when evaluating such work to recall how much less was known about brain function early in the century, and that pure speculation was much more acceptable in both journals and books than is the case today. It was in this period that the popular Common Sense Medical Adviser (Pierce 1909) informed readers that "excessive intellectual activity" (p. 125) was liable to cause brain damage and serious illness. "The production of

thought wears away the gray matter of the cerebrum" (p. 124).

As can be seen from the above references, early work on the psychology of MS drew attention to the possibility that psychological changes were both frequent and significant in MS. An examination of these early studies also reveals that they recognized another phenomenon: the existence of several distinct abnormalities or responses in MS patients. Early studies reported that some MS patients showed a tendency to fabricate or exaggerate physical problems (Brain 1930), while others showed "euphoria" (Cottrell and Wilson 1926), and yet others showed depression (Brown and Davis 1922). In recent years, the influence of stage-theory in psychology has prompted the suggestion that MS patients may go through a series of emotional stages after diagnosis (Matson and Brooks 1977). However, distinct abnormalities have continued to be observed and reported even as research has become more large-scale and improved measures have been used. As will be seen, the abnormalities found have not correlated well with disease variables, suggesting they are not necessarily a function of degree/amount of disease.

A report based on 1,970 case records, published soon after World War I (Wechsler 1922), concluded that MS was a common disease in the United States, and that it was frequently accompanied by "psychic" symptoms such as irritability, depression and general nervousness, and by "mental" ones such as subtle dementias. Wechsler commented

that numerous psychological problems were distinctive but not characteristic, in that not all patients exhibited them.

One large-scale study of psychological changes in MS was completed by Borberg and Zahle (1946). They summarized data from 330 MS patients, each of whom had been examined by at least five different physicians for psychological abnormality. Borberg and Zahle did not report the criteria used for assessment of abnormality, but did report that 47% overall developed "mental symptoms" of various kinds including euphoria, depression and dementia.

Paradoxically-elevated mood has also been reported in MS patients. Dercum (1912) cites the inappropriate laughter observed in the disease, as had Charcot (1877). Influential in this regard was a 1926 paper by Cottrell and Wilson, based on a list of 48 questions on mood and emotion, administered to 100 patients, in which the authors concluded that emotional change was common and serious in MS. Commenting that every single patient exhibited some mood change, Cottrell and Wilson reported that euphoria, an inappropriate sense of mental well-being, was exhibited by 63% of patients, and that it was associated with denial of illness. Another affective state was an inappropriate sense of physical well-being in the form of a lack of recognition of physical disability. The authors called this state "eutonia" (p.8), and said it was shown by 84% of patients. A separate investigation in the same period (Ombredane 1929) added to this work, suggesting that cognitive problems

existed in some patients as did affective problems in others. In that study, more than 70% of 50 patients had cognitive problems, virtually the same percentage as patients who showed affective problems.

Methodologies varied widely, and at times were not reported, earlier in this century, which contributed to differing prevalence rates from study to study. However, the general conclusions were that (1) psychological changes do accompany MS, and (2) several distinctly different changes can be observed. Some of the disagreements through the years about the prevalence of psychological dysfunction in MS stemmed from the fact that brief mental status examinations were frequently used in neurological studies, while detailed neuropsychological tests were more often used in psychological studies. Generally, studies by psychologists have shown more mental involvement in MS than studies by neurologists (Stenager et al. 1989a; Peyser et al. 1990). For example, Peyser et al. (1980b) found that MS patients who were judged mentally intact on neurological examination frequently showed cognitive dysfunction on more detailed neuropsychological tests. Brief mental status examinations may be inadequate for the detection of subtle abnormalities (Peyser and Becker 1984; Mahler et al. 1989). However, neurological studies have made contributions which large-scale neuropsychological studies have not, including in the elegant descriptions of individual patients' presentations.

The 1940s and 1950s saw the emergence of psychometrics and the development of more objective tests of mental and psychological function. MS was now studied using instruments such as the Minnesota Multiphasic Personality Inventory (MMPI) (Canter 1951a; Baldwin 1952); Wechsler-Bellevue intelligence test (Canter 1951b); and the Halstead battery to assess "biological intelligence" (Halstead 1947) (the forerunner to the Halstead-Reitan test battery used today).

In cognitive function, as in affective function, numerous studies suggested that problems exist, but that not all patients display them. Canter (1951b) was one of the first to establish conclusively that MS can affect cognition; he showed declines in the cognitive test scores of American armed forces veterans who developed MS, over a period of just six months. Canter also pointed out the large standard deviations seen in patients' test scores, reflecting considerable variability, and therefore supporting the notion of distinct responses. A large number of more recent studies have also shown that MS patients can experience cognitive dysfunction. Often cited have been deficits in memory (Jambor 1969; Beatty and Gange 1977; Rao et al. 1984; Beatty et al. 1988; Litvan et al. 1988). Rao et al. (1984) showed that chronic progressive MS patients can experience deficits in both verbal and visual-spatial learning tasks. Numerous studies have also made it clear that cognitive problems are not necessarily late-stage

effects only, but can occur early in the disease (Peyser et al. 1980b; Grant et al. 1984; van den Burg et al. 1987; Klonoff et al. 1991). As Rao (1986) has said in a literature review of the neuropsychology of MS, many such studies show large standard deviations in cognitive test data. "This observation implies that some MS patients may demonstrate little, if any, cognitive dysfunction, while others may exhibit moderate to severe disturbance" (p. 530).

Conceptual and abstract reasoning has also been cited as a problem in MS by numerous investigators of the last several decades (Rao 1986). Tests of abstract reasoning show that MS patients perform worse than non-brain-damaged controls (Peyser et al. 1980b; Rao et al. 1984) and that MS patients' performance is similar to that of brain-damaged controls (Matthews et al. 1970; Goldstein and Shelly 1974).

In the affective domain as well as the cognitive, increasingly detailed reports are being published on the prevalence and severity of dysfunction in MS. Depression is prominent (Baldwin 1952; Whitlock and Siskind 1980; Schiffer et al. 1983; Joffe et al. 1989). Studies of the prevalence of significant depression have reported a range of 27-54% (Pratt 1951; Surridge 1969; Whitlock and Siskind 1980; Schiffer 1983; Joffe et al. 1989). Again, not all patients show the problem.

Euphoria has also long been reported and continues to be so, though there is no consensus on its prevalence, with estimate rates ranging from 0% (Baldwin 1952) to 63%

(Cottrell and Wilson 1926). Differences in observed dysfunction result partly from a continuing lack of reliable and standardized methods for diagnosing euphoria (Minden and Schiffer 1990) but may also result from sampling bias. It may be that only a subgroup of MS patients show euphoria, and that the idiosyncratic selection criteria of different studies result in variable sampling of this subgroup.

### Response Types Identified in the Literature

#### Depression

Depression in MS has been noted repeatedly in the literature (Baldwin 1952; Goodstein and Ferrell 1977; Whitlock and Siskind 1980). While some MS patients are depressed, others are not, so the population is "psychiatrically heterogeneous" (Jambor 1969, p. 767). As well, numerous reports have noted that some MS patients show a depression out of proportion to their apparent physical disability or impairment. Peyser et al. (1980a) did a cluster analysis of 52 MS patients using a variety of physical, cognitive and psychological measures, and showed the existence of a group whose members were acutely distressed despite a relative lack of physical or cognitive problems. Zeldow and Pavlou (1988) also did a cluster analysis of 81 MS patients and identified a group whose members were characterized by unhappiness and distress



regarding their illness, although they were not any more physically impaired than other patients. Other authors have reported depression preceding the onset of more-typical MS symptoms (Young et al. 1976; Goodstein and Ferrell 1977); such depression is therefore also non-concordant with MS signs and symptoms.

### Denial

Peyser et al. (1980a) reported that 13 members (25%) of a cluster-analysed sample showed denial of distress or difficulty. Zeldow and Pavlou (1988) performed a cluster analysis of MS patients using factors from the California Psychological Inventory, and found that a group of 18 (22%) was "unusually concerned with creating a favorable impression and with denying any worries or difficulties" (p.193). Denial among MS patients has also been observed by others (Gilberstadt and Farkas 1961; Surridge 1969). MS patients have also been described who show lack of expected anxiety or a seemingly inappropriate sense of physical well-being. Cottrell and Wilson (1926) cited patients who said they felt physically well when they were in fact disabled. According to this report, such "eutonia" was a common phenomenon and was shown by 84% of the 100 MS patients interviewed. MS patients have also been described who show a lack of expected anxiety. Many of these patients have been called euphoric. Though an imprecise term, euphoria is

related to the phenomenon of denial (Surridge 1969; Weinstein 1970). Many authors have observed euphoria in MS, which Cottrell and Wilson (1926) defined as an inappropriate mood of cheer, happiness and ease despite physical problems which would be expected to elicit tension or anxiety. Recent reports have expressed caution about vague labels which confuse prevalence assessments, but generally agree that euphoria exists (Baretz and Stephenson 1981; Rabins et al. 1986).

It should be noted that the concept of denial can include either or both of: (1) a lack of recognition, or disavowal of, reality; (2) a recognition of reality, but an apparently abnormal lack of anxiety in the face of that reality (Strauss et al. 1990). Denial is sufficiently common, and at times sufficiently maladaptive, that Strauss et al. (1990) have suggested that the next revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association should include a new subtype of adjustment disorder called "maladaptive denial of physical disorder" (p.1168).

### Exaggerated Somatic

Numerous authors have suggested that MS patients sometimes exaggerate problems and create non-existing ones (Brain 1930; Weinstein 1970). "Hysterical symptoms, such as pareses and ataxia, seem to occur more often in association

with disseminated sclerosis than with any other organic disease of the nervous system" (Brain 1930, p. 372).

Though a distinction must be made between hysteria, and exaggeration of somatic complaints, the two have characteristics in common. Hysterical neurological problems are physical realities, for example paralysis or sensory loss, the roots of which are psychological. Exaggeration of somatic complaints involves extreme concern despite a complete or relative absence of physical problems.

The concept of hysteria has been applied in MS since the disease was first described. The label has been loosely used for different groups: (1) patients who are recognized to have physical problems but who are believed to be exaggerating those problems, and (2) patients whose relapsing sensory and motor disabilities are thought to be psychogenic. Skegg et al. (1988) showed that numerous individuals with MS are first given diagnoses of hysteria.

Peyser et al. (1980a) showed some patients' tendency to focus on, or exaggerate, physical problems, by demonstrating the existence of several subgroups of patients with an unusual degree of somatic concern. One such subgroup, constituting 13/52 (25%) of the sample, displayed a concern out of proportion to their moderate impairment. "Such patients will probably be in the physician's office frequently and require as much emotional support and reassurance as medical assistance" (pp. 438-439). Another smaller subgroup, 3/52 (5.8%), showed minimal physical

disability but "hysterical personality style" in the form of elevated MMPI scores on Hysteria and Hypochondriasis. The authors commented that, in the case of such patients, physicians may always have some doubt about the accuracy of the MS diagnosis, and should consider the possibility of conversion reactions occurring alone or during exacerbations (Peyser et al. 1980a).

#### Severity-related

Some studies point out that patients can react in apparent concordance with their physical problems. That is, those with mild disability show mild distress, and those with more disability show more distress. Baretz and Stephenson (1981) report that 4/40 (10%) of MS patients interviewed had a "realistic recognition" (p. 119) of their limitations and physical problems. Peyser et al. (1980a) also defined a cluster of patients whose profound distress matched their severe physical problems.

### Psychological Problems:

#### Cause or Result of the Disease?

Numerous reports through the middle decades of the twentieth century interpreted data in the light of psychodynamic or psychosomatic theories of disease. In effect, such reports suggested that the psychological problems of MS are a cause, rather than a result, of the disease. Inman (1948) reported, based on a small number of patient interviews regarding attitudes toward parents and sexuality, that MS was a somatic response to intolerable mental conflict. Philippopoulos et al. (1958) took an unspecified detailed history of each patient after which the patients' personality configurations were formulated in psychodynamic terms. He reported that MS patients were vulnerable to a specific dynamic process based on emotional and psychosexual immaturity due to early frustrations, which makes them susceptible to "psychosomatic disintegration" (p. 472). Grinker et al. (1950) interviewed 26 MS patients, employing the Rorschach ink blot on a handful, and concluded that MS patients were unusually immature and possess excessive needs which their human relationships could not satisfy. Such studies were interpreted as supporting the notion that MS patients have particular personalities which cause or exacerbate the disease. Subsequent authors (Riklan et al. 1961; Vander Plate 1984; Peyser and Poser 1986) have cautioned against hasty interpretations from such data.

Some authors have said that early investigators too often made "broad generalizations and conclusions" (Riklan et al. 1961) from single tests, or used "anecdotal" evidence (Surridge 1969). A study by Pratt (1951) provided alternative evidence to the controversial MS-personality hypothesis. Pratt assessed 100 MS patients, compared with 100 controls, for similarities in personality by allotting patients to classes after the schemes of Jung (extraversion-introversion) and Sheldon (viscerotonia, somatotonia, cerebrotonia). He found that MS patients did not appear to be of any one personality type, nor did the numbers in each personality class differ significantly between MS and controls. There were also no differences between the two groups in hysterical manifestations, obsessional traits, psychopathy, childhood environment or early separation from parents.

In recent years, support has shifted away from the notion of a typical premorbid MS personality (Vander Plate 1984). However, personality factors may not be completely independent from the disease. There is some evidence that stress may affect MS (Mei-Tal et al. 1970; Grant 1985), and whether a particular event is stressful is partly subjective and personality-based. Nevertheless, many researchers would now say that psychological problems are most likely a result of the MS disease process itself in some way (Vander Plate 1984; Peyser and Poser 1986).

Psychological Problems as a Result of the Disease:  
Reactive or Organic?

If psychological problems result from the disease, the question remains whether the problems result directly from the lesions, or are reactive responses based on the individual personality involved. Such a question applies particularly to behaviours such as depression and denial, which can be normal and which may exist without brain dysfunction. For example, mourning after a loss is expected, and only becomes clinical depression if prolonged.

To the question of whether changes are reactive or organic, support has been marshalled for both sides. On one side, studies including the following have provided support for the notion of a reactive basis to psychological problems. Surridge (1969) showed that depression in MS is similar to that in muscular dystrophy, which is also chronic and disabling but which does not involve the central nervous system. Logsdail et al. (1988) showed that there is a significant correlation between the severity of psychiatric symptoms and patients' degree of social stress, but not between severity of psychiatric symptoms and the presence of MRI abnormalities. Jouvent et al. (1989) showed that recent-onset MS patients are more likely to show depression than are patients with long-standing disease.

On the other side, studies including the following support the notion of an organic basis to psychological

problems. Schiffer et al. (1983) showed that there is more major depression in patients with clinically-inferred cerebral involvement than in patients who do not have such involvement, but rather who have (clinically-inferred) spinal cord and cerebellar lesions. According to Whitlock and Siskind (1980) and Joffe et al. (1989), MS patients sometimes experience serious depressive episodes months or years before physical symptoms appear. Rabins et al. (1986) showed that MS patients with brain involvement (assessed by CT scan) were more likely to be identified as euphoric than were patients with only spinal cord involvement. And Braceland and Giffin (1950), Surridge (1969), and Rabins et al. (1986) showed that euphoria is associated with cognitive deterioration. Then, numerous studies can be interpreted either way. For example, Dalos et al. (1983) showed that MS patients with progressive, non-remitting disease show more depression than patients with relapsing-remitting MS.

Many correlational studies have been done in MS, involving the examination of pairs of phenomena to directly or indirectly address the question of whether psychological abnormalities are reactive or organic. As can be seen from an overview of these studies (Appendix A) data have not converged, and clear conclusions have not been reached. Where correlations have been found, these have often been disappointingly low. Some of the studies have produced seemingly paradoxical results, such as that of Logsdail et al. (1988) which reported that psychiatric problems were



more severe in patients without MRI-imaged lesions than in patients with such lesions. However, those patients with more severe psychiatric problems also scored high on measures of social stress (related to work, finances, housing, and social, marital and family circumstances); therefore, degree of social stress was a better predictor of psychiatric problems than were MRI lesions, emphasizing the complexity of psychological change in MS. The importance of social factors in some cases of affective disorder was recognized by Schiffer (1987), who commented on the heterogeneous nature of depression in MS, and cited four separate categories of the disorder (biological, social, psychological and other).

As can be seen, a reading of the literature reveals apparent contradictions. While individual correlational studies can provide valuable information, lack of consistency in methodology make discrepancies in the literature difficult to analyse (Peyser et al. 1990; Minden and Schiffer 1990). Methodological differences include researchers' choice of (1) subjects' disease course, (2) measure of extent of either clinical or biological disease, (3) measure of mood or cognitive abnormality, and (4) method of assessing and scoring MRI lesions. There are numerous other methodological differences as well. For example, in some studies all variables are continuous, while in other studies one or more variables are categorical or ordinal.

However, even if methodologies were uniform, linear correlational studies may not reveal strong relations between psychological variables and pathological ones, because such studies generally do not take into account the existence of qualitatively different psychological abnormalities.

### The Study: Conceptually

This study relied on a progression of ideas which will be summarized here. MS patients do show psychological responses to their illness. As well, the evidence suggests that several qualitatively distinct responses occur, which will be referred to as psychological profiles. When two patients show different profiles, the difference may be a function of lesion-location or personality-based behavioural tendencies rather than of disease stage. Therefore, identification and separation of patients into different profile-groups allowed for clearer analysis of the aetiology of psychological responses. Profiles identified from the literature have been described earlier. The current study first operationally defined such profiles, and then by means of cluster analysis determined whether such profiles existed in a sample of MS patients. To define such profiles, it was necessary to have measures of objective disability, self-report disability, and mood/distress. Individuals with a 'Depressed' profile would be expected to show significant

distress despite little disability, either objective or self-reported. Those with a Denial profile would have been expected to report few problems, either physical or mood-related, although an objective assessment would have found considerable physical problems. Those with an Exaggerated Somatic profile would have had a much higher level of self-reported physical disability than disability objectively assessed; these individuals would not necessarily have been distressed. Others with a Severity-related profile would have scored similarly on all three measures, either low or high, so that self-reported disability was concordant with objective report of disability, with distress only reflecting amount of disability. Three variables were therefore assessed (amount of distress, level of physical disability, and perceived level of physical disability) which, taken together, defined a profile.

The current study therefore avoided the pitfall of assuming that all MS patients show some level of, e.g., depression, when many patients may not. As well, this study's multivariate approach allowed for separation, not only of distressed patients from non-distressed ones: it went one step beyond, to allow separation of those who are distressed and who have many physical problems, from those who are distressed despite few physical problems.

Cluster analysis was used because it is a statistical technique for determining whether elements of a large group naturally fall into distinct subgroups on given measures.

Cluster analysis has been used in several MS neuropsychology studies (Peyser et al. 1980a; Rao et al. 1984; Rao et al. 1989a; Fischer 1989), and in an MS personality study (Zeldow and Pavlou 1988) but never in the way here proposed. Rao et al. (1984) and Fischer (1989) clustered patients based on memory performance; Rao et al. (1989a) clustered patients into two cognitive groups, one with relatively substantial impairment and one with relatively minimal impairment. Peyser et al. (1980a) grouped patients on a variety of measures, including cognitive and affective, and identified several distinct responses. Zeldow and Pavlou (1988) grouped patients on four personality-related factors of the California Psychological Inventory, and identified distinct groups. Unlike the above studies, however, the current study stated that there may exist certain profiles which could be operationally defined by measures chosen to capture certain domains of interest. The three measures formed the core definition of the profiles.

The study, then, was designed to establish whether MS patients are truly psychologically heterogeneous in response to illness, which would have strong implications for neuropsychological research in MS. It employed a simple but innovative method for separating different profiles one from another, creating the possibility of stronger correlations between such profiles, and lesion data.

The second objective of the study was to determine whether membership in a profile group (e.g., Denial) was

related to the site of MS lesions. MRI data were therefore assessed to see whether members of particular profiles had lesions in common. If such relations were found, one would then have evidence supporting an organic basis to the profile.

An analysis of lesion data was based on the recognition of MRI as the best available technique for visualization of MS lesions disseminated in space (Paty et al. 1988). The MRI image is realized by the emission of electromagnetic radiation from the nuclei of hydrogen atoms after they have been excited by radiofrequency pulses in a constant magnetic field. Because water is a major component of human tissue, and because every water molecule contains two atoms of hydrogen, the MRI image is largely based on water, both on its quantity and on its macromolecular environment. Since different tissues vary in their water content, and edematous and demyelinated regions contain more water than do normally myelinated tissues, MRI can distinguish lesioned areas from non-lesioned ones. The unparalleled tissue contrast of MRI has made it very useful for MS clinicians and researchers.

Several limitations were, however, taken into account in analysis of the MRI data. One was that MRI is not perfect in either sensitivity or specificity. Regarding sensitivity, even in patients with clinically definite MS (CDMS) (Poser et al. 1983) MRI does not always show abnormalities in 100% of such patients. Paty et al. (1988) report abnormal MRI scans in 93% of CDMS patients. One

possible reason is that MRI scans are usually done of the head, not the spinal cord, yet spinal cord lesions may contribute to clinical signs and to a diagnosis of CDMS. Another possible reason is that lesions in the head may impair behavior but be too small to be detected by MRI.

Regarding specificity, MRI sometimes shows abnormalities in subjects with no known MS (Paty et al. 1988). Such abnormalities occur, for example, in individuals with cerebrovascular disease (Ormerod et al. 1984; Gerard and Weisberg 1986). MRI-detected lesions also appear in normal controls (Ormerod et al. 1987; Logsdail et al. 1988; Hunt et al. 1989), particularly with age and in periventricular areas. The specificity of MRI to MS was investigated by Yetkin et al. (1991) who examined scans from 92 MS patients, and 168 other subjects who had hypertension, dementia, or no known illness. Specificity (the proportion of non-MS subjects whose images were correctly classified as non-MS) was 95%-99%, indicating a small risk that periventricular white matter abnormalities can be wrongly interpreted as MS (Yetkin et al. 1991).

Lesions in normal controls have most often, but not exclusively, been reported in subjects over the age of 50. Hunt et al. (1989) reported that 20-30% of 46 normal subjects over the age of 65 had white matter lesions detected by MRI. There have been several reports of abnormalities in apparently normal individuals over 50 (Gerard and Weisberg 1986; Fazekas et al. 1988; Kertesz et

al. 1988) and over 60 (Braffman et al. 1988). Reports of lesions in younger subjects have been few, although Harvey et al. (1990) reported small white matter hyperintensities in 7 out of 36 normal controls under the age of 50. Subjects in the current study are under the age of 50.

Another MRI limitation was that each anatomical site contains many nuclei and tracts. This touches an important issue for any localization study: In what manner should the brain be divided into regions? Theoretically, there are many different ways in which the brain could be divided. It could be divided based on a knowledge of neuroanatomy, so that a functional system constitutes a region. At the other extreme, it could be divided without reference to function, on a grid system. This study took a middle ground: areas were chosen based on previous experience with MS lesions, so that a known high-incidence anatomical area could be viewed as one region. In localization studies there is also the question of number of regions. Considering the complexity of the nervous system, countless regions could be specified. Because analysis of a large number of sites is impractical, how many sites should be delineated for methodological practicality yet recognition of the intricacy of the nervous system? The 50 sites of this study do not amount to fine division of the brain. Nevertheless, considering the lack of knowledge of the biological basis of psychological change in MS, division of the brain into 50 sites was considered a good point of departure.

The third objective of the study was to determine whether membership in a group was related to the number of sites with lesions. If no such relation was found, then a model based on stage of biological disease would not be supported. It is important to note that number of sites with lesions is a measure of biological disease activity rather than severity of clinical signs; there is not a high correlation between clinical and biological MS at least when the latter is measured by the extent of lesion area identified by MRI (Paty et al. 1985). It is also important to note that there is no single measure of extent of biological disease in MS. The measure used in this study (number of sites with lesions) has the advantage of encompassing a component of scatter or dissemination, which measures such as total lesion area do not.

The fourth objective was to determine if specific cognitive abnormalities were associated with group membership. A comparison of groups on neuropsychological test performance was an additional method for determining whether members of any profile had cognitive dysfunction suggestive of an organic basis to their profile. Members of the Denial group, for example, might have been expected to show dysfunction on cognitive tests requiring concept formation and insight, such as the Halstead Category test or the Similarities subtest of the WAIS-R (Lezak 1983). Members of the 'Depression' group may have had problems in tests of new learning and memory (Nott and Fleminger 1975;



Kiloh 1961), such as Sentence Repetition, or Paired Associate Learning (Lezak 1983).

### The Study: Rationale for Methodology

#### Subjects

MS subjects in the study were chosen because they had a clinically mild disease course. Data were therefore not confounded by late-stage deterioration, either physical or psychological, which might have interfered with testing. All patients had a diagnosis of relapsing-remitting MS; this allowed the study to control for the cyclic nature of the disease and search for subtle psychological change by testing only patients in remission. All patients were free of drugs (MS-related or otherwise) which might have had psychological effects, and no patient was included who had a history of psychiatric problems pre-dating the diagnosis of MS: in that way, pre-morbid functioning was controlled. Patients were well-matched with normal controls on sex, age and education, critical parameters of patient characterization which Peyser et al. (1990) note have been inadequately matched in many past studies.

## Measures

Three measures were used for definition of the psychological profiles. The first measure assessed patients' MS signs and symptoms, scored by a neurologist on the Kurtzke Expanded Disability Status (EDSS) scale, the most widely-used rating system for MS physical impairment. The second measure assessed patients' own perceived MS signs and symptoms, self-reported on the Minnesota Multiphasic Personality Inventory (MMPI). A subset of MMPI questions, recognized as reflecting physical problems common in MS, form this measure. The third measure assessed patients' distress or psychological well-being independent of MS signs and symptoms, again self-reported on the MMPI. A subset of MMPI questions reflecting mood form this measure.

The two latter measures were developed as part of this study. For measure (2), it has been noted previously that the MMPI contains items which are symptoms of MS (Baldwin 1952; Marsh et al. 1982). This has been deemed problematic when the MMPI is administered to MS patients without recognition of the inclusion of such items (Marsh et al. 1982); however, their inclusion was usefully employed in the proposed study. For measure (3), the MMPI as a wide-ranging test of emotional status also contains items assessing distress and psychological well-being. Reliability analyses were conducted for each of these two scales, using

Cronbach's alpha (Cronbach 1951) as the internal consistency measure.

### Cluster Analysis

Methodologically, cluster analysis was appropriate for the question of interest. Not only can cluster analysis identify naturally-occurring groups in heterogeneous populations, but it requires no a priori assumption that the underlying variable is normally distributed.

### Lesion Analysis

MRI was used for this study because it is superior to other imaging techniques in showing the demyelinated lesions of MS. As well, because MRI is the imaging method of choice for MS, there is a need for psychological data in relation to MRI. In particular, while there is some literature on the effects of lesion burden in MS (Appendix A), there is less literature on the psychological effects of anatomically-specific lesions.

### Neuropsychological Tests

Because neuropsychological tests can suggest the presence of brain dysfunction (Lezak 1983), such tests can provide a second indicator, along with MRI, of an organic

basis to psychological profiles. Tests were employed which have little or no motor or sensory component. Tables 1 and 2 list relevant characteristics (Lezak 1983) of the tests employed, which are by design relatively simple in terms of cognitive dimension assessed, compared with broad intelligence tests. Table 1 outlines large-scale categories of cognition said to be measured. Some such abilities can be a result either of nature (hereditary potential) or nurture (e.g., schooling), but this potential confound was not a factor in the proposed study considering that patients and controls were closely matched on demographic variables including education. Table 2 gives an overview of gray matter regions which, when damaged, result in decreases in test scores. This overview may serve as a general reference, although it is not known to what degree white matter lesions produce similar dysfunction.

**TABLE 1**

**Neuropsychological tests used:  
dimensions of cognition measured by each test**

**(a) WAIS-R**

Digit Span	attention; immediate memory capacity
Arithmetic	attention; immediate memory; remote recall
Information	verbal; remote memory
Vocabulary	verbal
Comprehension	remote memory; verbal skills; judgement
Block Design	visuo-spatial organisation
Object Assembly	visuo-spatial organisation
Picture Completion	visual acuity; visual organisation
Picture Arrangement	sequential thinking; visual spatial org., social understanding
Similarities	verbal concept formation; abstraction

**(b) non-WAIS-R**

Dichot. Listening	attention; immediate memory capacity; lateral preference
Word Fluency	remote memory; verbal
Speech Perception	verbal recognition; phonetic ability
Halstead Category	abstraction; concept formation; attention; immediate memory
Paired Assoc. Learn.	verbal learning and memory
Trails B-A	speed of visual information-processing
Sentence Repetition	verbal memory; memory span
Benton Visual Memory	visuo-constructive abilities; visual- spatial perception/memory
Memory for Objects	immediate visual memory

TABLE 2

Neuropsychological tests used:  
gray matter lesions thought to be associated

## (a) WAIS-R

	dom. hem.	non-dom hem.	frontal lobe	par. lobe	temp. lobe	occip. lobe
Digit Span	x (?)					
Arithmetic	x			x	x	
Information	x					
Vocabulary	x					
Comprehension	x					
Block Design		x		x	x	x
Object Assembly		x		x	x	x
Pic.Completion	x	x	x	x		x
Pic.Arrangement	x	x	x		x	x
Similarities	x		x		x	

## (b) non-WAIS-R

	dom. hem.	non-dom hem.	frontal lobe	par. lobe	temp. lobe	occip. lobe
Dichot.Listen.	x	x			x	
Word Fluency	x		x			
Speech Percep.	x				x	
Halstead Cat.			x			
Paired A.Learn.	x				x	
Trails B-A	x					x
Sentence Rep.	x					
Benton Vis.Mem.	x	x		x		x
Mem.for Objects	x					x

## CHAPTER THREE

### METHODS

#### Subject Selection and Characteristics

Subjects were drawn from an ongoing study, for which participants were selected as follows. Potential MS-patient volunteers were identified at their annual visit to the UBC MS Clinic, according to certain entry criteria:

- (1) a diagnosis of clinically definite MS (CDMS) as defined by Poser et al.(1983) as follows:
  - a) two attacks and clinical evidence of two separate lesions, or:
  - b) two attacks, clinical evidence of one lesion, and paraclinical evidence of another, separate, lesion.
- (2) relapsing-remitting course and in clinical remission at the time of assessment.
- (3) age less than 50.
- (4) age at onset less than 40.
- (5) ambulatory and functionally independent.
- (6) no other significant medical condition.
- (7) no history of psychiatric illness prior to the diagnosis of MS.
- (8) taking no medications at the time of assessment.
- (9) no prior neuropsychological examination.

Each MS subject was asked to identify a non-related control who was as much like the MS subject as possible on a list of demographic variables: (i) age, (ii) sex, (iii) education, (iv) marital status, (v) occupation when employed.

Controls, like MS subjects, were required in addition to satisfy these criteria: no history of significant medical condition including psychiatric illness; no current drug use, either prescription or non-prescription; and no previous neuropsychological examinations.

Data from 99 MS patients and 56 normal controls were used in the initial study. Data from further subjects, both MS and normal controls, were used in a subsequent validation study.

### Test/Assessment Procedures

Potential subjects, identified at their annual visit to the UBC MS Clinic, received a standard neurological examination, including assessment for physical disability according to Kurtzke Functional Scales and the EDSS (Kurtzke 1983).

Patients who agreed to participate in the study were given an appointment date within one month of their clinic visit. On that test date, subjects were asked whether their physical conditions had changed noticeably in the interim; if so, they were re-assessed neurologically. Demographic data



on patients were collected during formal intake interviews using a structured format. The project was described in detail to patients, who then gave informed consent.

The test procedure, which took place over several hours on one day, included a brain scan by magnetic resonance imaging (MRI). MRI scans were performed on a Picker International Cryogenic 2000 MR scanner at a field strength of 0.15 Tesla. Contiguous slices were obtained at 10 mm intervals in transverse and sagittal planes, using a double-echo spin echo pulse sequence with repetition time of 2,175 msec, and echo delay time of 60 and 120 msec. Scans were read by radiologist Dr. David Li, who recorded any abnormalities greater than 2-3 mm in diameter.

Patients were also given psychological tests, including the MMPI and a neuropsychological battery. A trained psychometrician administered the tests. Because MS patients can fatigue easily, patients were given occasional breaks if that appeared to be needed. So that fatigue did not affect patients' scores on particular tests which might come at the end of the test battery, order of test presentation was random. Test data were entered into a computer file by the psychometrician using an interactive program. There were several double-checks to the data, including that out of bounds values were specified in the computer program. The 439-item MMPI was administered to each subject as part of the test battery; the only difference from standard MMPI administration was that

subjects filled out computer cards. These cards were then copied to disk by means of an optic scanner.

### Development of Scales

#### Signs and Symptoms (Sx)

##### a) Content Domain

For this scale, two raters chose items from the MMPI which were judged to reflect true physical symptoms of MS or related health concerns. Raters were the Ph.D. candidate, Eleanor Boyle, who based selections on readings about MS symptomatology, and Dr. Campbell M. Clark, a psychologist experienced in neuropsychological testing. Only items on which raters agreed were included for subsequent analysis. In addition, items were deleted if missing responses totalled >5%, or if all respondents answered similarly. Statistical analyses were performed using the Statistical Package for the Social Sciences, SPSS (Nie et al. 1983), with the exception of the cluster analysis which was done using UBC:CGROUP (Lai, 1982).

##### b) Item Analysis, Reliability and Validity

An item analysis was done and any item was deleted which correlated with the overall scale with a coefficient  $r < 0.15$ . After deletion of any such items, the scale was analysed for internal consistency, using Cronbach's alpha

(Cronbach 1951). To ensure that this estimate was maximal, the analysis was done over the entire sample, MS and normal subjects (Guttman 1945). As stated, items were initially selected on the basis of agreement between two raters. Subsequently, an analysis was done to determine whether the scales indeed distinguished the MS from the control populations. To answer that question, the two populations' scores on the Sx scale were compared by means of a t-test for difference in means, a Hartley's F-maximum ratio for difference in variance, and a Kolmogorov-Smirnov Z-test (Hays 1988) for a comparison of the two distributions. Classification rates were also determined by means of a discriminant analysis.

#### Distress (Ds)

##### a) Content Domain

MMPI items were chosen in the same manner as for the Sx scale, but to reflect patients' psychological and emotional health separate from MS-related physical symptoms.

##### b) Item Analysis, Reliability and Validity

Item analysis, reliability and validity tests were done as for the Sx scale.

### Kurtzke (K)

The Expanded Disability Status Scale (EDSS) was used as an objective measure of disability. Though in reality recognized as somewhat subjective, and as a measure of impairment (clinical signs) more than disability (limitations to activities) (Willoughby and Paty 1988), the EDSS is the best-known assessment system for MS (Matthews et al. 1985). The EDSS rates patients' overall physical status, based on scores in Functional Systems (FS): pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral/mental, and other/miscellaneous.

Correlations were calculated between each pair of measures: K and Sx, Sx and Ds, and K and Ds.

### Cluster Analysis

A z-score transformation was used to standardize the three scales to the same underlying metric. Hence, each scale had a mean of 0.0 and a standard deviation (SD) of 1.0. This transformation ensured that each scale was equally weighted for variance in the cluster analysis. This mathematical transformation did not change the characteristics of the scales (e.g., ratio for Sx and Ds, ordinal for K) nor the shapes of the distributions, but simply put those scales on a different metric (Bernstein 1988). A cluster analysis was done using Ward's method

(Ward 1963). Cluster analysis was chosen as a desirable technique because it can take several variables simultaneously into account when judging individuals as more or less "alike." Cluster analysis is also designed for ordinal scales (Jain and Dubes 1988) such as the Kurtzke, and for non-normal distributions of data (Morris et al. 1981). Ward's method was employed in this study because it is of the hierarchical agglomerative type most frequently used in scientific research (Morris et al. 1981), and because it has been shown to yield more accurate clusters, in general, than three other cluster analysis techniques: single linkage, complete linkage, and average linkage (Blashfield 1976), or at least to be among superior techniques displaying high values of coefficient kappa, which describes improvement in subject classification through use of the cluster analysis rather than random assignment (Golden and Meehl 1980). Ward's method is not as sensitive to outliers as are other cluster analysis methods (Milligan 1980). This method is also biased in favor of identifying spherical clusters (Cormack 1971; Blashfield 1976), which in this study refers to the Severity groups. It should be noted that the stability of a cluster solution depends on the reliability of the tests on which subjects are being clustered.

In the cluster analysis, the procedure was as follows: scores were compared among the 99 MS subjects on the three scales/variables (Sx, Ds and K). Distances were computed

between each variable for every possible two-subject combination. Subjects with the smallest squared-sum distance between points (therefore the most similarity on the three variables) were clustered into a group. So, for example, if two subjects had scored equally on all three measures, they would have had zero distance between points, that squared sum would have been zero, and the two would have been collapsed into one cluster. By this sequential process 99 clusters became 98, then 98 became 97, until all subjects were clustered into one. Selection of the optimal cluster solution (number of clusters) was based on statistical criteria, namely the minimization of within-group variability and maximization of between-group variability, with the additional goal of as few clusters as possible.

To determine the homogeneity of the clusters, a discriminant analysis was done with scale scores as predictors (dependent variables) and cluster membership as criteria (independent variables). The discriminant analysis showed the efficacy of the cluster solution in its overall correct classification rate of subjects, since that statistic provided an estimate of the degree of overlap or non-overlap among clusters.

The z-scores were graphed, and graphical comparisons were made between empirically-derived clusters, and the hypothesized ideal groupings discussed in Chapter One (figure I). It should be noted, however, that the analysis

operated without reference to any hypothesized profiles, and that scores on the three measures are continuous, so that any of a large number of "shapes" could have resulted from the data.

Similarly-shaped clusters were then collapsed into profile groups. Severity-related clusters were defined as those for which the range of scores on Sx, K and Ds scales was less than or equal to 1.0, the SD of each scale.

A discriminant analysis was repeated on the new groupings (of clusters into profiles) to ensure that no significant amount of information was lost due to the grouping procedure. Because clusters making up any particular profile differed in severity, it was necessary to correct mathematically for severity before performing the discriminant analysis. Correction for elevation or severity is a common procedure in profile analysis (Bernstein 1988).

Profile groups were then compared on numerous demographic and disease-related variables.

### Relations Between Groups and Measures of Disease

#### Magnetic Resonance Imaging (MRI)

MRI scans were rated by a radiologist for location, size and shape of lesions. The radiologist was not informed of the disease status of individuals before rating their scans. However, given the nature of MS lesions, it cannot

be said that the radiologist was truly blind to whether a subject was MS or control. Presence or absence of lesions was recorded on a standard form specifying possible lesion sites, with provision for the recording of other abnormalities and related observations. These data were then entered into a line file using an interactive program written for this purpose.

a) Reduction of the Number of Lesion Sites to be Examined

Criteria for inclusion of possible lesion sites was as follows. The initial list of sites was, by design, overinclusive and consisted of 50 anatomical regions. To reduce that number, the following regions were not analysed: (1) those at the midbrain or below, because they are less likely than higher regions to mediate cognitive and affective behaviours; (2) those with a relatively high incidence of lesions in this sample of MS patients ( $>65\%$ ), because such regions were not likely to shed light on cluster-specific problems, and (3) those with a relatively low incidence in this sample of MS patients ( $<5\%$ ).

The aim of these criteria was to reduce the number of lesion sites as much as possible without loss of critical information, thereby reducing the number of chance correlations between lesion sites and clusters. Reducing the number of sites decreased the experiment-wise error rate, namely the probability of encountering a Type I error due to the number of tests of significance performed.



b) Relation of Psychological Profiles to Extent of Lesions

For each profile, an addition was made of the total number of sites with lesions. This measure was distinct from total lesion burden or lesion load, since it did not attempt to take into account lesion size. It could instead be called extent of lesions, or extent of biological disease. Statistical analysis entailed the following. A one-way analysis of variance was done across profile groups, to answer the question: do any profiles differ from others in number of sites with lesions? If a significant F-value was found, the groups were compared using Tukey's a posteriori pair-wise comparison technique (Hays 1988).

c) Relation of Psychological Profiles to Lesion Location

This analysis aimed to identify any anatomically-specific lesions which might contribute to a psychological profile. Chi-squared analyses were done, site by profile, to answer the question: for a given site, do a large number of members of any one profile have lesions there, while members of other profiles do not? Ideal data were first conceptualized, as illustrated in figure II, with groupings based on results of the cluster analysis. The figure shows a site in which all Depressed patients, but no others, have a lesion. Such a situation was both intuitively and statistically significant; chi-squared analysis showed an associated p-value  $\leq 0.0001$ . It illustrates the simple

## FIGURE II

### MRI Lesion-location analysis: hypothesized ideal data

An example of ideal data, in which all members of one profile (14/14 Depressed patients) have lesions in the site in question, and in which zero members of other profiles have lesions in that site.  $p \leq 0.0000$

	'Depression'	Denial	Exag.Som.	Severity
Presence of lesion	14	0	0	0
Absence of lesion	0	32	22	31

model in which any given lesion is associated with one, and only one, profile.

However, there was expected to be noise in the system, both "positive" (>0% of members of other profiles showing lesions in the site in question) and "negative" (<100% of members of the profile in question showing lesions in that site). Sources of such noise could have included the following:

Positive. (1) MRI lesions can be clinically silent. This is particularly true for the transient lesions which have been revealed by serial scanning, and which are frequently asymptomatic (Isaac et al. 1988); (2) lesions judged to be in the site in question may in fact be located slightly differently. Due to the size of sites, any two lesions both deemed to be in a particular anatomical site in two different patients may not always be in precisely the same nucleus or fiber tract.

Negative. (1) Some members of a profile may be reactive, not organic; (2) not all MS patients, even those with CDMS, show detectable MRI abnormalities (Paty et al. 1988).

The question therefore arose: how close must data come to the ideal, to be considered strong evidence for an organic basis to the profile? The data in Appendix B address the question: how many members of a profile must have a given lesion, when there is no noise from other profiles, for statistical significance? These data

illustrate that when even a small number of members of one profile, but not other profiles, show lesions in a given site, a significant difference can be found.

However, anticipating the existence of "positive" noise from other profiles, further data in Appendix B address the question: with varying degrees of noise how many members of one profile must have a given lesion for statistical significance?

Based on the chi-squared calculations in Appendix B, it was suggested that an alpha  $\leq 0.005$  should constitute statistical significance for the MRI lesion-location analysis. This alpha level avoids the potentially high false-positive (Type I error) rate which would be associated with a higher alpha.

In the analysis of groups by lesion location, it was decided that outcomes would be examined which (1) showed a statistically significant difference among the groups for a site, and which also (2) were conceptually interpretable within the hypothesis that lesions can contribute to a psychological profile. Conceptual interpretability required that (1) members of one and only one psychological profile stood out from others; (2) a profile differed from others by the presence, not by the absence of a lesion. Presumably, it is the existence rather than the non-existence of a lesion which can contribute to a psychological abnormality. Therefore, when chi-squared tests revealed statistically significant differences between profiles, only those with

the indicated directionality were to be considered, and only those in which one profile was distinct from others.

As mentioned, it was considered possible that some members of any profile had a reactive rather than an organic basis to their behaviour. Intuitively, this idea is sensible: in a group of severely depressed individuals, some may possess that profile because of lesions, while others may possess it because their apparently mild disability has a disproportionate impact on their lives - either real or perceived - as in the case of a pianist with minor sensory loss to the hands. Therefore, as another step in the analysis, for any one profile, patients with common characteristic lesions were to be separated from those without such lesions. Members of one or the other subgroup (with lesions or without) may have displayed common cognitive problems which members of the other subgroup did not.

### Cognitive measures

#### a) Selection of Tests to be Analysed

Tests were chosen which examine a wide variety of cognitive functions, and which have been shown to detect impairment in MS (Peyser et al. 1980a; Heaton et al. 1985; van den Burg et al. 1987; Minden et al. 1990; Klonoff et al. 1991). As well, tests were chosen which have minimal motor and sensory components (Tables 1 and 2), and which therefore

isolate cognitive functions as much as possible, so that any of the patients' motor and sensory impairments would not confound results.

#### b) Relation of Psychological Profiles to Cognitive Performance

The profiles were divided into subgroups based on MRI results, separating those which appeared to have an organically-based profile from those which appeared to have a reactively-based one. Figure III illustrates that this analysis could potentially be done with eight groups, depending on the outcome of the MRI analysis. Unlike in the case of the MRI analysis, data from normal controls were examined, so that controls formed one group. In the MRI analysis, data from controls was not examined due to the low number of lesions in these individuals. However, in the case of cognitive data there was variability among individuals. Therefore, it was useful and important to compare MS patients' scores with those of normals.

As in the case of MRI lesion data, profiles were examined test-by-test to see whether scores on specific tests were related to profile membership. Ultimately, for every cognitive test, the question was asked: do members of one profile produce scores significantly worse than members of other profiles? Ideal data were conceptualized and are illustrated schematically in figure IV, suggesting

### FIGURE III

#### Potential profile groups for neuropsychological analysis

If MRI results indicate that any of the original four profile groups have organic and reactive subgroups, then analysis of cognitive data will be done with up to eight subgroups, as shown.

1. 'Depressed', organic
2. 'Depressed', reactive
3. Denial, organic
4. Denial, reactive
5. Exaggerated Somatic, organic
6. Exaggerated Somatic, reactive
7. Severity
8. Normal controls

#### FIGURE IV

##### Neuropsychological data analysis: hypothesized ideal data

An example of ideal data, in which all members of one profile have low performance on a cognitive test, while members of other profiles have either medium or high performance on that test. Underlining indicates that those groups are not significantly different.

(low performance on cognitive test) <----- (high performance)

ANY ONE PROFILE GROUP                      ALL OTHER MS GROUPS                      CONTROLS

OR

ANY ONE PROFILE GROUP                      ALL OTHER MS GROUPS                      CONTROLS



situations in which one profile group stands out from others with significantly lower performance on a cognitive test.

Before test-by-test analysis, however, it was first necessary to do an omnibus test for overall significance, in the form of a Multivariate Analysis of Variance (MANOVA) (for  $\leq 8$  profile groups as independent variables, and 19 continuous dependent variables in the form of scores on the selected cognitive tests). If the MANOVA resulted in a significant F-value, ANOVAs could subsequently be performed on individual cognitive tests. If Analysis of Variance (ANOVA) resulted in significant F-values ( $p \leq 0.05$ ) for certain cognitive tests, then Tukey's a posteriori tests could be performed to see where between-group differences existed. Of available tests, Tukey's was suitable because it maintains alpha over all pair-wise comparisons (Winer 1962), thereby controlling for experiment-wise error.

The number of subjects in this study was large by clinical research standards. Nevertheless, the neuropsychological variables in the study were also sufficiently numerous that the subject-to-variable ratio was smaller than multivariate analysts would advise. However, the validation study served as a check in this regard.

## CHAPTER FOUR

### RESULTS

#### Subject Characteristics

The subjects consisted of 99 patients and 56 normal controls. Of the 99 patients, 69 (69%) were female and 30 (30%) were male. The patients had a mean age (standard deviation) of 36.3 (7.9) years, and a mean education of 13.8 (2.3) years. Mean age of first symptoms for these patients was 25.5 (7.1) years, while mean age of diagnosis was 30.6 (8.4). Number of relapses since the diagnosis averaged 5.3 (2.6), so that the average number of relapses per year for this group was 0.93. Results of neurological examinations further suggest that this is an MS group with relatively mild physical problems. Mean (SD) Kurtzke EDSS for all patients was 2.03 (1.38) (on a scale of 0.0-10.0 in which 10.0 represents death from MS). No patients scored higher than 6.0, which was part of the selection criteria. A summary of patient characteristics is given in Table 3.

Controls were well-matched with MS patients on demographic variables, as shown in Table 4. T-tests for the continuous variables, and chi-squared tests for the categorical variables, showed that there were no significant differences between the two groups on all but one of these variables. The only variable on which patients differed

**TABLE 3**  
**Characteristics of MS subjects**

**Number of subjects = 99**

**Sex (female/male) = 69/30**

<b>variable</b>	<b>mean</b>	<b>SD</b>
age	36.3	7.9
education (yrs.)	13.8	2.3
age of first symptoms	25.5	7.1
age of Dx	30.6	8.4
number of relapses since Dx	5.3	2.6
number of relapses/year	0.93	
EDSS	2.03	1.38

TABLE 4

Comparison of MS subjects with normal controls  
on demographic variables

variable	MS	Controls
sex (% female)	69.0	66.7
age	36.3	35.9
education (yrs.)	13.8	13.8
marital status:		
married	51.5	50.9
single	19.2	30.2
separated/divorced	28.3	18.9
occupation:		
prof/semi-prof	22.0	22.2
managerial	7.0	9.3
clerk/skilled	49.0	46.3
unskilled	14.0	14.8
homemaker	1.0	-
no occupation	3.0	-
student	4.0	7.4
employment status:		
full-time	36.4	57.1
part-time by choice	24.2	21.4
unemployed due to health	19.2	-
other	20.2	21.5

significantly from controls was current employment status (chi-sq=18.54; df=9;  $p \leq 0.029$ ).

#### Derived Measures: Sx and Ds

The MMPI items used on the Sx and Ds scales are given in Appendix C. Final numbers of items were 31 for the Sx scale and 47 for the Ds scale. It was not necessary to delete any items for which more than 5% of responses were missing, since no such items were found. However, one potential Sx item had to be deleted for lack of variability. All subjects, both MS and controls, responded positively to "I feel tired a good deal of the time", which may have said more about modern life than about MS. The item analysis showed that the vast majority of items on each scale correlated highly with the overall scale; however, three items on each scale were deleted because the correlation with the total score was less than 0.15. Following the item analysis, internal consistency coefficients were over 0.9 for both scales (Sx:  $r=0.901$ ; Ds:  $r=0.900$ ).

Tests for criterion-related validity showed that the Sx scale separated the two samples well. On the Sx scale, MS patients scored significantly higher than controls (MS: mean=13.9, SD=5.9; controls: mean=4.3, SD=3.5,  $t=12.83$ ;  $p \leq 0.001$ ). The Kolmogorov-Smirnov z-test showed that scores on Sx were normally distributed for MS but were significantly different from normal for controls ( $z=1.6$ ;  $p \leq 0.01$ ). The

discriminant analysis also revealed a correct classification rate for the Sx scale of 83.4% of all subjects.

The Ds scale also separated MS subjects from controls, with MS patients scoring significantly lower (indicating more distress) than controls (MS: mean=35.4, SD=8.1; controls: mean=38.9, SD=6.7;  $t=-2.72$ ;  $p \leq 0.005$ ). Scores on Ds were also normally distributed for MS patients but were significantly different from normal for controls ( $z=1.5$ ,  $p \leq 0.03$ ). The discriminant analysis showed a classification rate of 58.9% on Ds. These data are summarized in Table 5.

Correlations between pairs of measures, calculated for MS patients ( $n=99$ ) were as follows: K and Sx:  $r=0.30$ ,  $p \leq 0.002$ ; K and Ds:  $r=0.10$ ,  $p \leq 0.15$ ; Sx and Ds:  $r=0.47$ ,  $p \leq 0.001$ . Correlations were also calculated between Sx and Functional System (FS) scales, and between Ds and FS scales, and none were significant.

### Cluster Analysis

A 10-cluster solution was statistically optimal. For that solution, 81.5% of total multivariate variability was between groups, with the remaining 18.5% within groups. The discriminant analysis of this solution yielded a 97.98% correct classification rate, suggesting clear separation between the clusters in multivariate space. None of the clusters contained fewer than five subjects.

**TABLE 5**  
**Sx- and Ds-scale analyses**

	<b>Sx</b>	<b>Ds</b>
reliability coefficient	0.9	0.9
Mean score:		
MS patients:	13.9	35.4
Controls:	4.3	38.9
t-value for difference:	12.83	-2.72
associated p-value:	$\leq 0.001$	$\leq 0.005$
Classification rate of scale:	83.4%	58.9%

Empirically-derived clusters are graphed, as can be seen in figure V, which also shows the number of subjects in each cluster. The 10 clusters were collapsed into four profile groups based on visual similarity. After a correction for severity, a discriminant analysis on the four-profile grouping revealed that the classification rate remained 97.98%, indicating that no information was lost in the grouping of 10 clusters into four profiles.

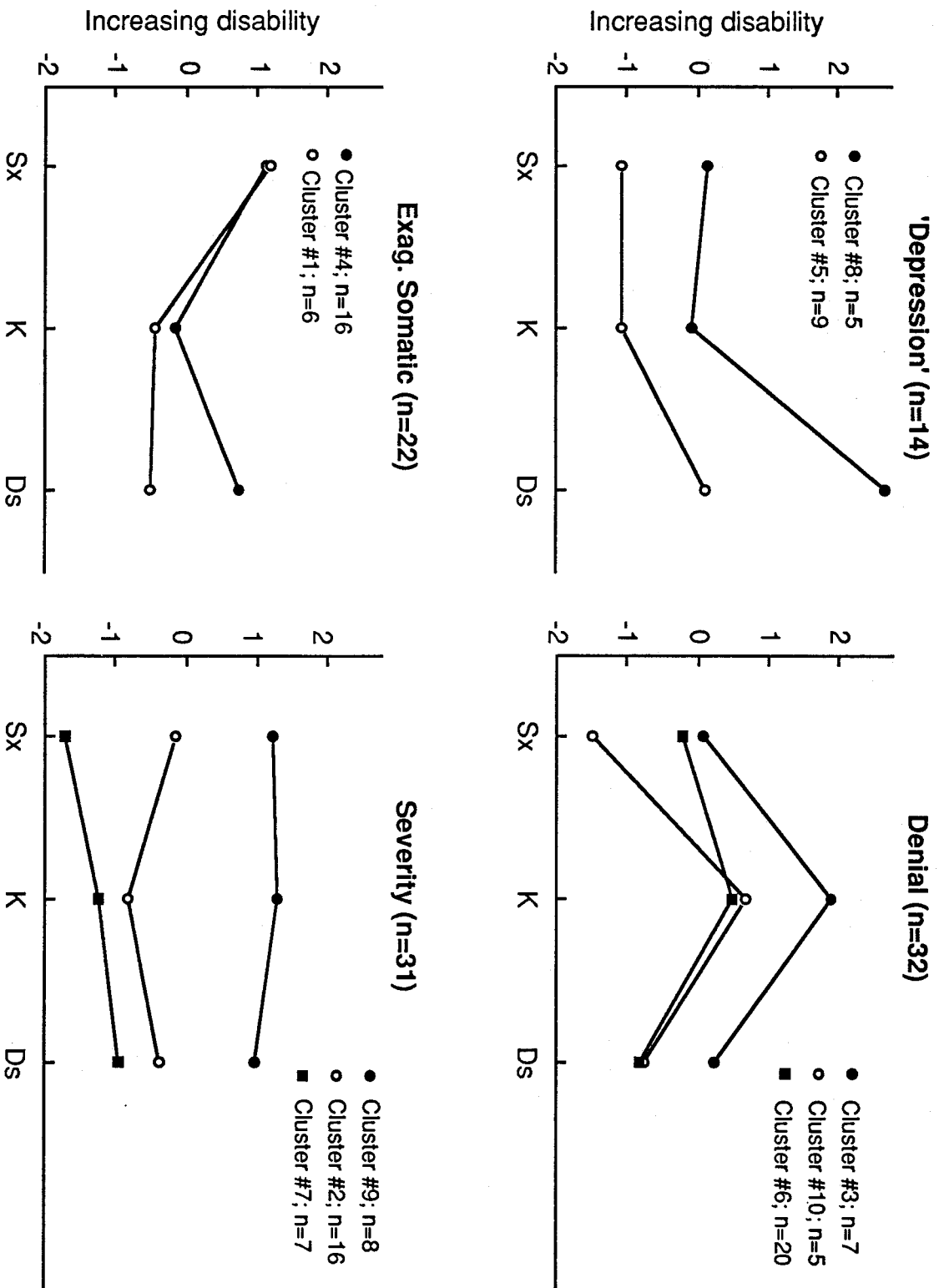
1. The 'Depression' profile contained 14 patients, in two clusters. As can be seen from the graphs (figure V), 'Depressed' patients scored high on Ds reflecting a distress out of proportion to their relatively low scores on objective assessment of disability (K). These patients are also distressed despite their acknowledgement, as evidenced by their low Sx scores, that they do not have many physical problems.

2. The Denial profile contained 32 patients, in three clusters. These patients were characterized by low scores on both of the self-rating scales (Ds and Sx) but relatively high scores on objective assessment of disability (K), indicating that they do have physical problems, but report that they do not have problems either physical or psychological.

3. The Exaggerated Somatic profile contained 22 patients, in two clusters. This group was characterized by relatively high scores on Sx, compared to their scores on K, signifying that these patients report their physical problems



**FIGURE V**  
**Results of cluster analysis: psychological profiles in MS**



as considerably worse than do their neurologists. Scores on Ds were slightly elevated for some patients.

4. The Severity profile contained 31 patients, in three clusters. Characteristic of this group was that the mean z-score for a group on all three measures was within one standard deviation of one another. This score indicates that these patients' assessments of their physical problems were generally concordant with assessments by their neurologists, and that patients with few problems experienced a small amount of distress while patients with many problems experienced more distress.

Analyses of variance on profile groups by education showed no difference among groups. ANOVA on groups by age showed some differences ( $F_{3,95}=2.72$ ;  $p \leq 0.049$ ). The mean age for 'Depressed' patients was lowest (31.5 years), for Severity-related patients was 35.4 years, for Exaggerated Somatic patients was 37.4 years, and for Denial patients was 38.1 years. A Tukey's a posteriori test showed a significant difference between 'Depressed' and Denial patients but not between other pairs of groups.

Several related analyses were also done. ANOVAs showed that groups did not differ on any of (1) age of onset of first symptoms, (2) age of diagnosis, (3) number of years since diagnosis. Groups did differ on number of years since onset of first symptoms, with Deniers (who are also oldest) having lived with their symptoms slightly longer than other groups. These data, for mean (SD) number of years since onset of first

symptoms, are as follows: 'Depressed': 6.6 (6.2); Exaggerated Somatic: 11.9 (7.1); Denial: 13.5 (7.3); Severity: 8.8 (5.6).

Analyses of profile groups by sex showed that 13/14 (93%) of 'Depressed' patients were female, although the sample was 69% female (69/99). Chi-squared analysis showed that this overrepresentation was not significant ( $p \leq 0.056$ ). Women were not overrepresented in any other group, including Exaggerated Somatic.

Scores on the Beck Depression Inventory were markedly different among groups, as shown by an ANOVA ( $p \leq 0.001$ ) with 'Depressed' patients scoring higher than members of other profiles, thus supporting criterion-related validity for the 'Depressed' profile.

### MRI Analysis

#### Relation of Psychological Profiles to Number of Sites With Lesions

An analysis of variance was done to compare all four profile groups on total number of sites with lesions, of the 50 anatomical sites. The groups were not significantly different ( $F_{3,93}=2.14$ ;  $p \leq 0.101$ ). Means (SDs), for number of sites with lesions, were as follows: 'Depressed': 16.3 (8.2); Denial: 13.6 (5.8); Exaggerated Somatic: 11.5 (6.4); Severity: 11.7 (6.2), as presented in Table 6.

TABLE 6

Profiles did not differ significantly  
on number of sites with lesions

$$F_{3,93} = 2.14$$

$$p \leq 0.101$$

group	mean	SD
'Depression'	16.3	8.2
Denial	13.6	5.8
Exag. Somatic	11.5	6.4
Severity	11.7	6.2

### Relation of Psychological Profile to Lesion Location

For the initial analysis, the list of 50 sites was reduced based on criteria discussed in Chapter Three. A total of 23 sites were excluded: nine because they were at or below the level of the midbrain, seven because more than 65% of MS patients had lesions there, and another seven because fewer than 5% of MS patients had lesions there. Therefore, 27 sites were analysed. (Data on the percentages of patients and controls who had lesions in given locations are in Table 7.) Site-by-site chi-squared analysis showed that 26 of the 27 sites did not satisfy the statistical criterion of  $p \leq 0.005$ .

One site, the gray matter/white matter junction of the right parietal lobe, did satisfy the criterion. In that site, half the 'Depressed' group (7/14) had lesion(s), while smaller percentages of other groups had lesion(s) there. These data are summarized in Table 8. The largest percentage of any other group with a lesion there was 5/24 (20.8%) for Severity patients.

These data prompted several further analyses. One set of analyses compared the two 'Depressed' subgroups, one whose members had the lesion and one whose members did not, on demographic variables (age, sex, and education) as well as severity of impairment/disability (EDSS) and total number of sites with lesions. Another set of analyses compared the two groups of patients who had lesions in that site, one group 'Depressed' and one group composed of all non-'Depressed'

TABLE 7

Percentage of subjects with lesions in each brain area.  
Asterisks indicate sites used for chi-squared analysis.

Slice	Region	MS	Controls
Supraventricular:	1) Frontal: R	17.5*	0
	2) L	17.5*	0
	3) Frontal/Parietal: R	18.6*	0
	4) L	19.6*	0
	5) Parietal: R	30.9*	0
	6) L	30.9*	0
Periventricular:	7) Frontal Horn: R	82.5	21.4
	8) L	83.5	26.8
	9) Occipital Horn: R	77.3	17.9
	10) L	77.3	16.1
	11) Temporal Horn: R	40.2*	1.8
	12) L	43.3*	0
	13) Parietal Body: R	84.5	5.4
	14) L	83.5	3.6
Deep White:	15) Frontal Horn: R	17.5*	1.8
	16) L	12.4*	0
	17) Occipital Horn: R	6.2*	0
	18) L	4.1	0
	19) Temporal Horn: R	3.1	0
	20) L	5.2*	0
	21) Parietal Horn: R	39.2*	0
	22) L	42.3*	1.8
Internal Capsule:	23) R	16.5*	0
	24) L	15.5*	0
Gray/White Junctions:	25) Frontal: R	22.7*	0
	26) L	17.5*	0
	27) Parietal: R	17.5*	0
	28) L	19.6*	0
	29) Occipital: R	5.2*	0
	30) L	2.1	0
	31) Temporal: R	11.3*	0
	32) L	11.3*	0
Deep Gray:	33) Insula: R	9.3*	0
	34) L	6.2*	0
	35) BG: R	2.1	0
	36) L	1.0	0
	37) Thalamus: R	1.0	0
	38) L	2.1	0
Brain Stem:	39) Midline:	25.8	1.8
	40) Cerebellum: R	20.6	1.8
	41) L	10.3	0
	42) Pons: R	23.7	0
	43) L	20.6	0
	44) Mid Brain: R	14.4	0
	45) L	16.5	0
	46) Medulla: R	10.3	0
Corpus Callosum:	47) L	7.2	0
	48) Body	71.1	14.3
	49) Genu	35.1*	0
	50) Splenium	39.2*	1.8

TABLE 8

Gray matter-white matter (GM-WM) junction of the right  
parietal lobe: chi-squared analysis

(chi-sq: 13.34;  $p \leq 0.004$ )

'Depression'		Denial	Exag.Somatic	Severity
presence	7	4	1	5
absence	7	28	21	24

patients with that lesion, on Beck Depression Inventory scores, on cognitive impairment as reflected in scores on neuropsychological tests, and on finer detail of anatomical location in the right parietal lesion site. Results of these analyses are summarized in the section entitled Post Hoc Analyses.

In summary, analyses of MRI lesion location data showed that the majority of patients in three out of four profile groups were not distinguished by having lesion(s) in particular sites. A subset of the 'Depressed' group was distinguished by lesion(s) in the right parietal lobe.

#### Neuropsychological Analysis

Neuropsychological analysis was done on six groups subdivided according to the MRI data.

- (1) 'Depressed'-lesion
- (2) 'Depressed'-no lesion
- (3) Denial
- (4) Exaggerated Somatic
- (5) Severity
- (6) Normal controls

A MANOVA produced a significant multivariate F ( $F=1.68$   $df=(120,570)$ ;  $p \leq 0.001$ ), indicating overall differences between the six groups on 22 measures (19 neuropsychological tests and three IQ measures).



Test-by-test ANOVAs showed: (1) no significant differences at  $p \leq 0.05$  on 12 neuropsychological measures, or on Verbal IQ; (2) significant differences at  $p \leq 0.05$  on Performance IQ ( $p \leq 0.0001$ ) and Full-scale IQ ( $p \leq 0.0022$ ); (3) significant differences on seven neuropsychological tests, as shown in Table 9.

An examination of the data showed that the 'Depressed' group with the lesion performed worse than other groups on all seven of the above tests for which significant differences were found. Tukey's comparisons were done, and in some cases showed significant differences between the 'Depressed' group with the lesion and other groups, as illustrated in figure VI. Differences were in some cases not significant because of the small size of the two 'Depressed' subgroups (each  $n=7$ ).

Group scores on the above-mentioned seven neuropsychological tests are illustrated graphically in figure VII. For this graph, groups' scores were standardized using a z-score transformation, so that each test had a mean of 0.0 and an SD of 1.0. As can be seen in figure VII, scores for the 'Depressed' group with the lesion were consistently low. As can also be seen, normal controls' scores are generally relatively high, though not always higher than all MS groups. The 'Depressed' group without the lesion had variable scores - sometimes low, but in several cases higher than those of normals. The 'Depressed' group without the lesion performed better than normal controls on five of the 19 tests: Paired

TABLE 9

Neuropsychological tests on which ANOVAs showed significant differences among groups

Test	F-value	p-value
Paired Associate Learning	$F_{5,150}=6.33$	0.0000
Object Assembly (WAIS)	$F_{5,150}=4.24$	0.0013
Word Fluency	$F_{5,150}=3.74$	0.0032
B. Visual Retention	$F_{5,150}=3.50$	0.0051
Block Design	$F_{5,150}=3.14$	0.0100
Memory for Objects	$F_{5,150}=2.79$	0.0195
Speech Perception	$F_{5,150}=2.49$	0.0340

# FIGURE VI

## Results of Tukey's tests for neuropsychological tests on which ANOVAs showed significant differences among groups

Pairs of groups which were significantly different on Tukey's ( $p \leq 0.05$ ) are denoted by (\*)

DL = 'Depressed' with right parietal lesion  
DNL = 'Depressed' without right parietal lesion  
EXAG = Exaggerated somatic  
DEN = Denial  
SEV = Severity  
N = Normal controls

Pairs:

	DL	DEN	EXAG	SEV	N	DNL
DL				*	*	*
DEN					*	
EXAG						
SEV	*					
N	*	*				
DNL	*					

OA:

	DL	DEN	EXAG	SEV	N	DNL
DL					*	
DEN						
EXAG						
SEV						
N	*					
DNL						

FIGURE VI continued:

Results of Tukey's tests. Groups which were significantly different ( $p \leq 0.05$ ) are denoted by (\*)

DL = 'Depressed' with right parietal lesion  
DNL = 'Depressed' without right parietal lesion  
EXAG = Exaggerated somatic  
DEN = Denial  
SEV = Severity  
N = Normal controls

WF:

	DL	DEN	EXAG	SEV	N	DNL
DL						
DEN					*	
EXAG						
SEV						
N		*				
DNL						

BVRT:

	DL	DEN	EXAG	SEV	N	DNL
DL						
DEN						
EXAG					*	
SEV						
N			*			
DNL						

FIGURE VI continued:

Results of Tukey's tests. Groups which were significantly different ( $p \leq 0.05$ ) are denoted by (\*)

DL = 'Depressed' with right parietal lesion  
DNL = 'Depressed' without right parietal lesion  
EXAG = Exaggerated somatic  
DEN = Denial  
SEV = Severity  
N = Normal controls

BD:

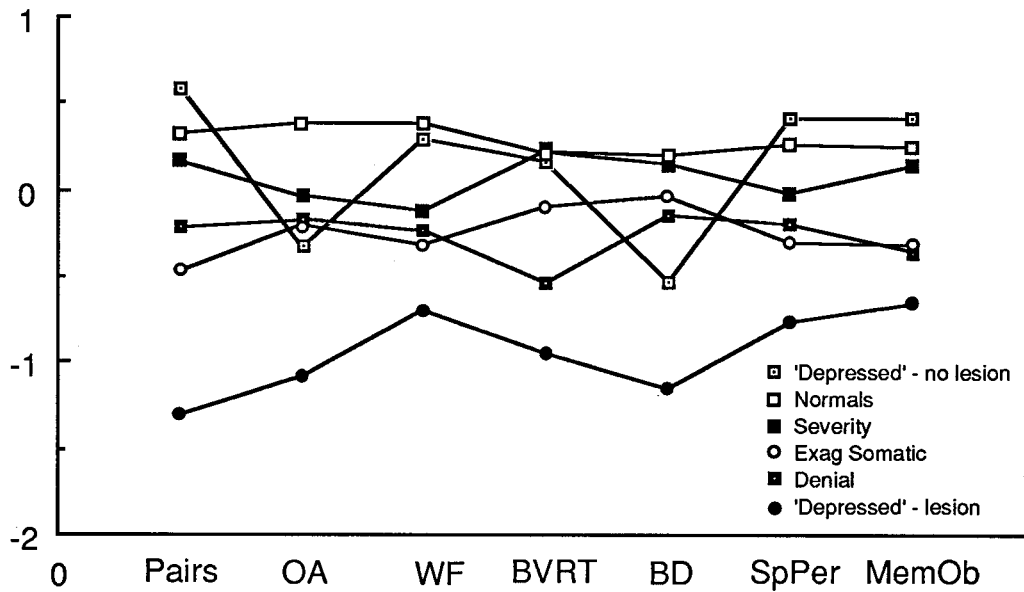
	DL	DEN	EXAG	SEV	N	DNL
DL				*	*	
DEN						
EXAG						
SEV	*					
N	*					
DNL						

SpPer: No significant differences on pair-wise comparisons

MemOb: No significant differences on pair-wise comparisons

**FIGURE VII**  
**Comparison of groups on neuropsychological tests**

The graph shows that scores were consistently low for the 'Depressed' group with the lesion. The tests illustrated are those on which ANOVAs revealed significant differences between groups: Paired Associate Learning (Pairs), Object Assembly (OA), Word Fluency (WF), Benton Visual Retention Test (BVRT), Block Design (BD), Speech Perception (SpPer), and Memory for objects (MemOb).



Associate Learning, Categories, Speech Perception, Picture Completion, and Memory for Objects.

The 'Depressed' group with the lesion performed worst of all groups on all three IQ measures and on the majority (18 out of 19) of other neuropsychological tests as well. Scores for the 'Depressed' group with the lesion showed more impairment than other MS groups on all tests except Digit Span, on which the other 'Depressed' group without the lesion performed worst.

An examination of group means on all neuropsychological tests showed that MS patients generally performed worse than normals.

For descriptive purposes, correlations between neuropsychological tests were calculated, and are shown in Table 10. Correlations were calculated for those seven tests on which ANOVAs showed significant differences among the groups.

#### Post Hoc Analyses

Because the MRI lesion-location analysis distinguished several groups of patients on the right parietal lesion site, it was considered appropriate to do further analyses for characterization of these groups. Three groups were distinguished which warranted further examination: (1) 'Depressed' patients with the right parietal lesion (n=7);

**TABLE 10**

**Correlations between tests on which ANOVAs showed  
significant differences among groups**

**MS/Controls**

	Pairs	OA	WF	BVRT	BD	SpPer	MemOb
Pairs	1.00	.38/ .25	.27/ .21	.43/ .29	.33/ .34	.37/ .29	.47/ .21
OA		1.00	.27/ .13	.48/ .21	.61/ .55	.23/ .10	.23/ .03
WF			1.00	.18/ .07	.36/ .13	.16/ .05	.23/ .31
BVRT				1.00	.66/ .48	.30/ .21	.29/ .11
BD					1.00	.31/ .20	.18/ .17
SpPer						1.00	.12/ .23
MemOb							1.00



(2) 'Depressed' patients without that lesion (n=7); (3) Non-'Depressed' patients with that lesion (n=10).

#### Comparisons Between the Two 'Depressed' Groups

The two 'Depressed' groups, one with the lesion and the other without the lesion, were compared on demographic variables. They were compared on age and education (t-tests), and on sex (chi-squared). No significant differences were found.

The two groups were compared on severity of clinical signs (EDSS score), and no significant difference was found. Mean (SD) scores were: 'Depressed' with the lesion: 1.07 (1.2); Non-'Depressed' with the lesion: 1.00 (0.58).

The two groups were also compared on total numbers of sites with lesions. Means were as follows: 'Depressed' with the lesion: 22.3 (6.1), 'Depressed' without the lesion: 10.3 (5.1), as shown on an ANOVA across these groups as well as across two further groups: Non-'Depressed' with the lesion: 20.1 (5.0), and all other MS patients: 11.3 (5.4). As can be seen, it was not the two 'Depressed' groups who were similar on this variable. Rather, it was the two groups with the characteristic lesion, both of whom had a large number of other lesions as well. The ANOVA showed a significant difference among the groups ( $F_{3,93}=15.59$ ;  $p \leq 0.0001$ ); a Tukey's test showed that the 'Depressed' group with the lesion and the Non-Depressed group with the lesion were both

significantly different from the two other groups. Data on this variable are summarized in Table 11.

These data therefore show that 'Depressed' patients with the lesion have considerably more lesions overall than do 'Depressed' patients without that lesion. Other patients with that lesion also have a large number of lesions overall.

Comparisons Between the two Groups With the Lesion,  
'Depressed' and Non-'Depressed'

These two groups were compared on the Beck Depression Inventory (BDI), to assess whether both groups were depressed in a way not captured by the original profile definitions. The two groups were compared with all other MS patients, and with normal controls. All MS groups were found to have some BDI-measured depression compared with normals. Mean scores are summarized in Table 12. (BDI scores measure amount of depression as follows: 0-4=none or minimal; 4-7=mild; 8-15=moderate;  $\geq 16$ =severe (Beck and Beamesderfer 1974)). A Tukey's test showed differences between normal controls and all MS groups except Non-'Depressed' with the lesion. Because these groups contain small numbers of patients, significance tests may not have the power to show differences, in this case between normal controls and Non-'Depressed' with the lesion. These data indicate that all MS patients are more depressed than normal controls, and that patients who are Non-'Depressed' with the lesion have virtually no more depression

TABLE 11

Comparison of groups on total number of sites with lesions,  
for groups subdivided in reference to  
right parietal lesion

( $F_{3,93}=15.59$ ,  $p \leq 0.0001$ )

	mean	SD
'Depressed' with lesion (n = 7)	22.3	6.1
'Depressed' without lesion (n = 7)	10.3	5.1
Non-'Depressed' with lesion (n = 10)	20.1	5.0
Other MS (n = 75)	11.3	5.4

**TABLE 12**

**Comparison of two 'Depressed' Groups, Other MS Subjects, and Controls, on Beck Depression Inventory (BDI)**

	<b>mean</b>
Normal Controls	3.66
'Depressed' with lesion	11.4
Non-'Depressed' w/ lesion	7.1
Other MS	6.5

than most MS patients. The group that is Non-*'Depressed'* with the lesion also has less depression than does the group of *'Depressed'* patients with the lesion, although differences between MS groups are not significant.

As stated in the previous section, the *'Depressed'* group with the lesion scored worse than other groups on most neuropsychological tests (21/22). These data prompted the question: are all patients with the right parietal lesion cognitively impaired? ANOVAs were re-done on all neuropsychological tests on the following groups: *'Depressed'* with the lesion, Non-*'Depressed'* with the lesion, other MS, and Normal controls. The Non-*'Depressed'* group with the lesion was not noticeably impaired on any test. That is, scores for the Non-*'Depressed'* with lesion group were consistently close to those of other MS subjects (except *'Depressed'* patients with the lesion whose neuropsychological scores were low) and no significant differences were found between the Non-*'Depressed'* with the lesion group and other MS.

It was also reasoned that the two groups with the lesion - one *'Depressed'* and one not - might differ on finer detail of anatomical location of their lesions in the indicated right parietal site. For example, the *'Depressed'* group with the lesion may have lesions more anterior to, or more posterior to, those of the Non-*'Depressed'* patients. Therefore, a visual inspection was done of the original MRI scans, by the Ph.D. candidate, together with the radiologist. There were no

obvious similarities within the 'Depressed' group, nor were there any marked differences between the two groups on anatomical location within the site.

## CHAPTER FIVE

### VALIDATION STUDY: METHODS

#### Subjects

For the validation study, data were available from 43 additional MS patients assessed after the initial study. All patients had clinically definite MS (CDMS) with a relapsing-remitting course, and satisfied the same criteria (detailed in Chapter Three) as initial subjects. Data were also available from 20 normal controls assessed after the 56 controls of the initial study. All met the same criteria as did earlier controls.

Subjects were assessed in the manner described in Chapter Three, with a neurological examination, an interview, a series of MRI brain scans, and psychological tests.

Demographic data were obtained, and comparisons were made between MS and controls, on age and education (t-tests), sex, marital status, occupation and current employment status (chi-squared).

#### Sx and Ds Scales: Reliability and Validity

Sx and Ds scales, which had been analysed for reliability (internal consistency) on the initial 99 subjects, were re-

analysed for internal consistency (Cronbach 1951) on the validation subjects.

Subsequently, Sx and Ds were re-assessed to show whether the scales distinguished the MS subjects from controls. On each scale, a t-test was done for a difference in means between the two groups.

### Cluster Analysis

The 43 MS patients were then cluster-analysed. First, raw scores were standardized to z-scores for the three measures (Sx, Ds and K) which formed the basis of the cluster analysis. The analysis was then undertaken, using Ward's method (Ward 1963). Selection of the optimal cluster solution (number of clusters) was based on statistical criteria: minimization of within-group variability and maximization of between-group variability, with the additional goal that there should be a small number of clusters and that each cluster should contain at least two members. Clusters with similar scores were collapsed into profile groups, and a discriminant analysis done to ensure that the groups showed a high classification rate. Group means were graphed.

Profile groups were compared on age (ANOVA), sex, marital status, occupation and employment (chi-squared).



### MRI Analysis

In light of results from the initial study, which showed that groups differed significantly on number of lesions in the GM-WM junction of the right parietal lobe, the analysis was repeated on that site. Only that site was examined. It was predicted that validation subjects with 'Depressed' profiles would show significantly higher numbers of lesions in that site than would subjects with other profiles.

Chi-squared analysis was performed between profile groups. For this analysis, the statistical criterion was  $p \leq 0.05$ , rather than  $p \leq 0.005$  as in the earlier analysis. There were several reasons for the use of a more liberal p-value in the validation study. Firstly, because only one chi-squared analysis was done, experiment-wise error was not a potential problem. Secondly, group sizes were small in the validation study, so a higher alpha was needed for increased power.

An added analysis checked the results of the initial study showing that groups do not differ significantly on number of sites with lesions. An ANOVA was done across groups on this variable.

### Neuropsychological Analysis

A further analysis was needed to validate the neuropsychological finding from the initial study, that is,

cognitive impairment among 'Depressed' patients who have the right parietal lesion.

Cognitive tests were examined on which significant group differences had been found in the initial study. Therefore, nine measures were analysed - two IQ (Performance IQ and Full-scale IQ) and seven neuropsychological measures: Paired Associate Learning (Pairs), Object Assembly (OA), Word Fluency (WF), Benton Visual Retention (BVRT), Block Design (BD), Memory for Objects (MemOb), and Speech Perception (SpPerc). On all seven of these tests, in the earlier analysis the 'Depressed' group with the lesion was most impaired; it was therefore predicted that 'Depressed' members of the validation group (and particularly any 'Depressed' patients with the right parietal lesion) would have significantly greater impairment on these tests than would other patients.

ANOVAs were done on each of the nine measures. For ANOVAs which resulted in significant F-values ( $p \leq 0.05$ ), Tukey's a posteriori tests were performed to see which pairs of groups were significantly different.

## CHAPTER SIX

### VALIDATION STUDY: RESULTS

#### Subjects

Of the MS subjects, 33 (76.7%) were female and 10 (23.3%) were male. The patients had a mean age (standard deviation) of 34.2 (6.7) and a mean education level of 13.6 (2.0) years. Mean age of onset of the disease for these patients was 26.3 (6.4). Results of the neurological examinations showed that the mean (SD) Kurtzke EDSS score for this group was 1.87 (1.16). A summary of patient characteristics is given in Table 13. Characteristics of this patient group are similar to those of the MS patient group in the initial study.

Comparison of MS subjects and normal controls (n=20) on demographic variables showed that the patients did not differ significantly from controls on age, sex, education, marital status, or occupation when employed. However, the groups did differ on current employment status ( $\chi^2=12.6$ ;  $df=6$ ;  $p \leq 0.049$ ), with more MS than controls unemployed for health reasons, as was the case in the main study. On demographic variables (Table 14) the validation sample was very similar to the sample in the main study.

**TABLE 13**

**Validation study: Characteristics of MS subjects**

**Number of subjects = 43**

**Sex (female/male) = 33/10**

<b>variable</b>	<b>mean</b>	<b>SD</b>
age	34.2	6.7
education (yrs.)	13.6	2.0
age of first symptoms	26.3	6.4
EDSS	1.87	1.16

TABLE 14

Validation study: Comparison of MS subjects and normal controls on demographic variables

variable	MS	Controls
sex (% female)	76.7	85.0
age	34.2	34.1
education (yrs.)	13.6	14.0
marital status:		
married	79.1	60.0
single	16.3	25.0
separated/divorced	4.7	10.0
occupation:		
prof/semi-prof	20.9	25.0
managerial	4.7	20.0
clerk/skilled	58.1	45.0
unskilled	9.3	5.0
homemaker	2.3	-
student/other	4.7	5.0
employment status:		
full-time	37.2	75.0
part-time by choice	20.9	5.0
unemployed due to health	16.3	-
other	25.6	20.0

### Sx and Ds Scales

Reliability analyses for internal consistency on Sx and Ds scales resulted in correlation coefficients of 0.84 for Sx, and 0.92 for Ds.

T-tests showed that the scales separated the two samples. On the Sx scale, MS patients scored significantly higher than controls (MS: mean=14.0, SD=5.8; controls: mean=4.1, SD=3.4,  $t=8.66$ ;  $p \leq 0.001$ ). On the Ds scale, MS patients' scores were significantly different from those of controls (MS: mean=32.8, SD=9.3; controls: mean=41.0, SD=6.2;  $t=-3.58$ ;  $p \leq 0.001$ ). Controls had higher Ds scores in the raw data because that was the directionality assigned to the scale. In the case of Ds, the z-scores were reflected (i.e.,  $x=-x$ ) so that all three scales had the same directionality. These data are summarized in Table 15.

### Cluster Analysis

The statistically optimal solution contained 10 clusters. For that solution 86.5% of multivariate variability was between groups, and the remaining 13.5% of variability was within groups. None of the clusters contained fewer than two subjects.

Profiles for empirically-derived clusters were compared, and similar clusters collapsed into four profile groups. A discriminant analysis on the four-profile

TABLE 15

Validation study: Sx- and Ds-scale analyses

	Sx	Ds
reliability coefficient	0.84	0.92
Mean score:		
MS patients:	14.0	32.8
Controls:	4.1	41.0
t-value for difference:	7.12	-3.58
associated p-value:	$p \leq 0.001$	$p \leq 0.001$

grouping showed a classification rate of 95.35% (2/43 subjects misclassified).

Group means were graphed (figure VIII). As can be seen from these graphs, profiles were similar to those of the initial study, and were consistent with the labels 'Depression', Denial, Exaggerated Somatic and Severity. None of the four groups contained fewer than nine subjects.

Cluster groups did not differ significantly on sex ( $\chi^2=4.77$ ;  $df=3$ ;  $p \leq 0.19$ ), marital status ( $\chi^2=19.23$ ;  $df=18$ ;  $p \leq 0.38$ ), occupation ( $\chi^2=20.61$ ;  $df=21$ ;  $p \leq 0.48$ ), or employment status ( $\chi^2=21.91$ ;  $df=18$ ;  $p \leq 0.24$ ).

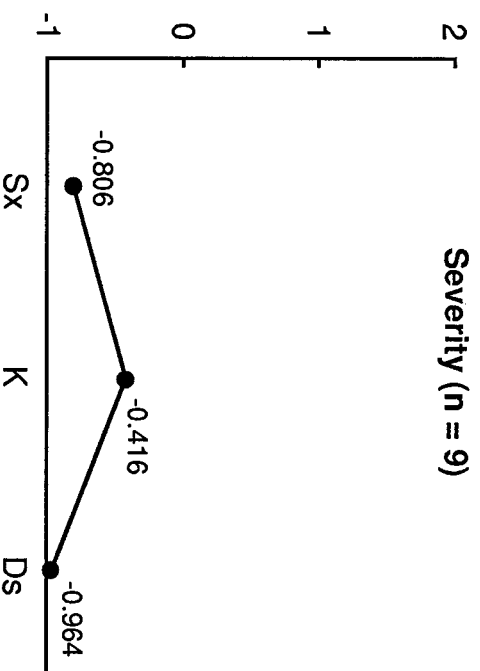
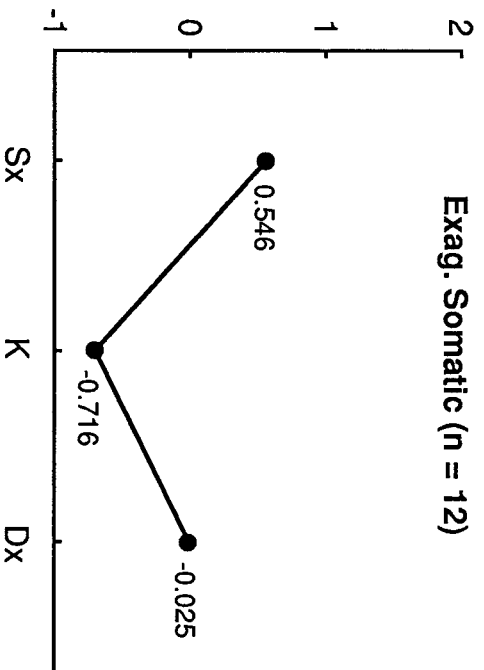
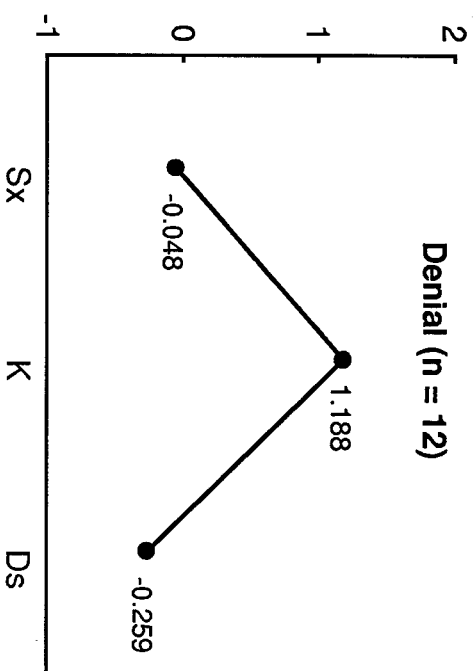
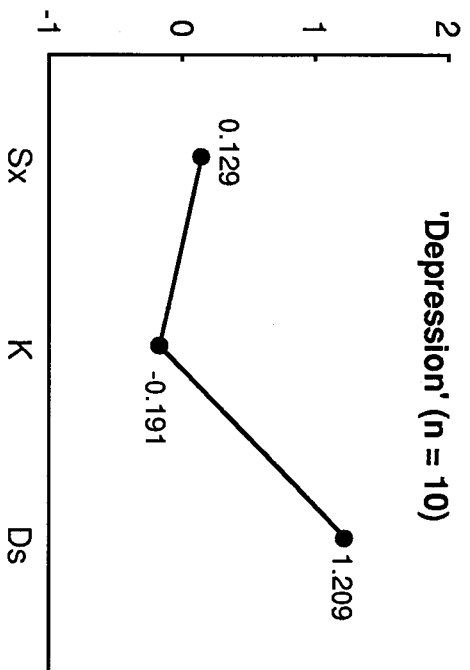
Analysis of profile groups by age yielded a significant F-value ( $F_{3,39}=3.29$ ;  $p \leq 0.031$ ). The mean (SD) age for 'Depressed' patients was 29.2 (6.96), for Denial was 33.8 (7.27), for Exaggerated Somatic was 36.3 (5.79), and for Severity was 37.2 (4.29). A Tukey's test showed a significant difference at  $p \leq 0.05$  between 'Depression' patients, and Severity patients. As in the main study, the 'Depressed' group had a slightly lower average age than did other groups. However, the group with the highest average age was not Denial, as in the main study, but Severity.

### MRI Analysis

An analysis of variance compared the four profile groups on number of sites with lesions, on all 50 anatomical



**FIGURE VIII**  
Validation Study: results of cluster analysis



sites. The groups were not significantly different ( $F_{3,37}=2.06$ ;  $p \leq 0.12$ ). Means (SDs) were: 'Depression' 17.7 (5.8), Denial 12.3 (7.1), Exaggerated Somatic 11.6 (5.1), and Severity 11.6 (8.4), as outlined in Table 16.

Statistical analysis was done on the site (GM-WM junction of the right parietal lobe) on which a significant difference had earlier been found. A larger percentage of members of the 'Depressed' group (4/10=40%) had lesions in that site than did members of other groups (Denial=25%; Exaggerated Somatic=9%; Severity=0%). That difference was not significant by chi-squared analysis at  $p \leq 0.05$  (chi-sq=6.27; df=3;  $p \leq 0.099$ ). However, there was clearly a trend. Kendall's tau is also an appropriate statistic. It requires directionality of scale in one or more variables; in this case the dependent variable (whether or not an individual had a lesion) can be directional. The distribution was significant using Kendall's tau (tau=-0.277;  $p \leq 0.028$ ). The data for groups at this site is shown as a matrix in Table 17.

### Neuropsychological Analysis

This analysis was done on four groups: (1) 'Depressed' with the lesion, (2) 'Depressed' without the lesion, (3) All other MS subjects, (4) Normal controls. It was not necessary to do this analysis on six groups, as in the main study: the intent of this part of the validation study was

TABLE 16

Validation study: Profiles did not differ significantly  
on number of sites with lesions

$$F_{3,37} = 2.06$$

$$p \leq 0.123$$

group	mean	SD
'Depression'	17.7	5.8
Exag. Somatic	11.6	5.1
Denial	12.3	7.1
Severity	11.6	8.4

TABLE 17

Validation study: GM-WM junction of the right parietal lobe:  
chi-squared analysis

(Kendall's tau B = -0.277;  $p \leq 0.028$ )

'Depression'		Exag. Somatic	Denial	Severity
presence	4	1	2	0
absence	6	11	8	9

to focus on the group of 'Depressed' patients with the lesion.

One-way ANOVAs on the two IQ measures and seven neuropsychological tests showed the following results.

Significant differences among groups were found on Performance IQ ( $F_{3,59}=4.91$ ;  $p \leq 0.004$ ); Full-scale IQ ( $F_{3,59}=3.39$ ;  $p \leq 0.024$ ); Object Assembly ( $F_{3,59}=3.44$ ;  $p \leq 0.023$ ); Benton Visual Retention ( $F_{3,59}=2.97$ ;  $p < 0.039$ ); Block Design ( $F_{3,59}=3.03$ ;  $p \leq 0.036$ ); and Paired Associate Learning ( $F_{3,59}=3.07$ ;  $p \leq 0.035$ ), but not on Word Fluency, Memory for Objects or Speech Perception. However, in none of the Tukey's comparisons were the scores of 'Depressed' patients with the lesion significantly lower than others. Because the power of a statistical test increases with increasing sample size, the small size of the 'Depressed' group with the lesion ( $n=4$ ) precluded findings of significance in some tests. 'Depressed' patients with the lesion did worst of all groups on Full-scale IQ, Benton Visual Retention, Memory for Objects, and Paired Associate Learning. Overall, however, 'Depressed' patients with the lesion did not stand out as being markedly more impaired than other groups.

## CHAPTER SEVEN

### DISCUSSION AND CONCLUSIONS

#### Methodological Considerations

Before conclusions are drawn from this study, a number of methodological issues should be reviewed. First, the MS sample in this study was deliberately restricted, so that subjects had mild clinical symptoms, a relapsing/remitting MS course, and no complicating factors such as other diseases or drug use. Because of this selective sampling, inferences can be drawn with confidence for MS patients with mild physical problems. However, results cannot be extrapolated to patients with more severe disease. For example, the finding that psychological response may be largely a reaction to stress for this sample does not preclude the possibility of organically-based psychological response in the later stages of the disease. Further to the issue of sampling is the fact that patients for the study all had EDSS  $\leq 6.0$ . The chief reason for restricting the range in this manner was that patients with higher EDSS scores would more likely have had dementia, and motor or sensory problems, which could have invalidated their scores on a variety of tests. As well, because relations between a restricted range of a variable, and other variables, can be attenuated, the fact that psychological profiles were

identified in this range is further evidence for the existence of these profiles.

The second consideration involves test reliability and the results of the cluster analysis. Cluster analyses are only as reliable as the measures on which subjects are clustered. This study demonstrated high reliability coefficients for derived scales  $S_x$  and  $D_s$ , in the main study and in the validation study. Although no such coefficient was available for the K (EDSS) scale (studies have examined whether two or more raters assign the same EDSS score to a patient, rather than whether raters' overall assignments correlate well), reasonable agreement has been shown between raters' EDSS assignments (Francis et al. 1991). Despite drawbacks of the EDSS (Willoughby and Paty 1988), it remains the best available method for assessing disability or impairment in MS. The EDSS also has the advantage of providing a single numerical summary of an individual's physical problems. Another aspect of the cluster analysis regards the use of Ward's method and its particular inherent bias. This method tends to identify spherically-shaped clusters, which in the current study refers to Severity groups. The fact that salient-features profiles were also identified, and validated, gives confidence that such groups exist. However, because Ward's method is not as sensitive to outliers as are some cluster methods, it is possible that small patient groups, showing different coping styles, may not have been identified.

The third consideration involves validity, for experimental inference (internal and external validity) (Campbell and Stanley 1966) and for the instruments used in the study (construct, content, and criterion-related validity, with construct validity the most important) (Meehl 1973; Kerlinger 1986; Messick 1989). In the realm of experimental inference, the study strove for high internal validity in terms of careful selection of patients, in the choice of MRI sites most likely both to show variability and to underlie psychological change, and in the setting of a stringent alpha for significance in the MRI lesion-location analysis. There can be a trade-off (Kerlinger 1986) between internal and external validity, because internal controls which give confidence can also potentially limit generalizability. However, several arguments can be made for generalizability of the results of this study to other similar MS populations. Selection of patients was done on a basis that would apply in other MS centers; for example, the criteria for a diagnosis of CDMS (Poser et al. 1983) are widely used. As well, the exclusion of certain anatomical sites from the MRI analysis was not done for reasons specific to this sample. Of the 23 sites which were excluded, nine sites were excluded for theoretical reasons. Seven sites were excluded because more than 65% of patients had lesions there; these sites were almost all periventricular, and all seven sites were in regions which have been reported as high incidence in MS (Escourolle and



Poirier 1978; Valk and van der Knaap 1989). Another seven sites were excluded because fewer than 5% of patients had lesions there; most of these sites were gray-matter, and all are known as low incidence in MS (Escourolle and Poirier 1978; Valk and van der Knaap 1989).

In the realm of the validity of instruments used, the construct validity of Sx and Ds are supported for the following reasons: (1) items for Sx and Ds were chosen from the MMPI to satisfy theoretical constructs - the patient's view of physical difficulties arising from MS (the Sx scale) and distress (the Ds scale). Judgments were made independently by the two raters, and agreement was required for inclusion of any item on either scale. (2) the Sx and Ds scales do not measure the same phenomena yet do have a relation to each other, as evidenced by their correlation of 0.47. (3) patients in the Depressed group, who score high on Ds, also score high on the Beck Depression Inventory. (4) MS and controls scored significantly differently from each other on both Sx and Ds.

The validity of the K (EDSS) scale as a measure of MS clinical problems must be assumed, not only because it is the most widely used clinical evaluation tool in MS, but because this scale partly defines the diagnosis of MS. There is also divergent validity between Sx and K, and between K and Ds, pairs of measures which, as expected from the literature, do not correlate highly. The low correlation between Sx and K is consistent with reports

that, as physicians are well aware, patient self-report does not always agree with results of clinical assessment (Taylor 1991); a specific example from MS was demonstrated by Beatty and Monson (1991) in which many patients' opinions of their memory difficulties were considerably different from results of objective memory tests. The lack of correlation between K and Ds is supported by previous evidence that there is no significant relation between degree of disability as measured by the EDSS, and the presence of depressive disorder (Joffe et al. 1989).

In the case of MRI, issues of validity are less applicable than in the case of the scales cited above in which abstract concepts are being measured. Nevertheless, MRI could be said to have validity for this study because its distinction between different tissues is based largely on water-content, which changes in MS as a result of the breakdown of myelin. The validity of MRI is supported by the fact that this imaging process reveals the same lesions as does CT (Bydder et al. 1982) as well as many more lesions, and by the fact that MRI data concur with those of post-mortem assessment. Stewart et al. (1984, 1986) have shown that areas of increased signal intensity on MRI correspond to regions of MS pathology in post-mortem MS brains. Although the correlation between MRI lesion sites and physical problems is far from perfect (Isaac et al. 1988; Paty et al. 1988), there is a relation between confluence of lesions and course of disease, with chronic

progressive MS patients showing notably more confluence than patients with benign disease (Koopmans et al. 1989). As well, examination of MS patients using sensitive neuropsychological tests has demonstrated that cerebral lesions may not, in fact, be silent and that total MRI lesion area can predict cognitive dysfunction (Rao et al. 1989a).

Regarding neuropsychological tests, the validity of the WAIS-R as a measure of global intelligence has been well-established, in comparisons of WAIS scores to other measures of academic success and to alternative tests of intellectual functioning (Wechsler 1981). The WAIS (1955) and its successor the WAIS-R (1981) have been used in thousands of studies to measure intelligence in its various aspects. Though originally standardized on normal individuals, the WAIS-R has been used extensively in clinical populations (Lezak 1983) including MS (Rao 1986) and can be valuable in assessment of such groups (Strub and Black 1985). One potential problem in the use of intelligence tests in neurological patients is that patients' illnesses may lead them to score badly for reasons not related to intelligence. However, this potential problem should not be a factor in the current study, because tests with strong sensory or motor components were not used in the analysis, and because the patients had relatively mild physical problems from their illness.

Further to the issue of validity is that a validation study was done on the positive results of the main study, providing replication and thereby reducing threats to both experimental and instrumental validity. At the level of instruments used, Sx and Ds scales were again analysed in the validation study for reliability (internal consistency), and for their ability to distinguish MS subjects from controls in the new group of subjects used. At the experimental level, the cluster analysis was again performed, as were MRI and neuropsychological analyses which showed significance in the main study.

A fourth methodological consideration in the current study was the following. As in any anatomical localization study of "experiments of nature," this investigation was constrained by the practical need to delineate anatomical regions as separate one from another. In this case, 50 sites were pre-determined based on previous experience with MRI and MS. However, biological lesions do not always fit neatly into such logical schemes. Lesions frequently overlap site boundaries. In other cases two or more lesions may be located in one site. Similarly, lesions frequently vary in volume, and may not be fully captured in the axial direction.

The fifth consideration is the relationship between white matter lesions and behavior. Current understandings of the brain are based largely on the role of gray-matter nuclei. Because white matter consists of tracts carrying

information between and among many nuclei, the effects of white matter lesions on behavior are even more complex, and less understood, than similar effects of gray matter lesions. As an example, the (largely white matter) lesions of MS frequently do not correspond to clinical signs (Paty et al. 1985; Stevens et al. 1986; Isaac et al. 1988; Koopmans et al. 1989), especially when lesions are above the brainstem. Numerous studies have probed the consequences of white matter lesions. Rao et al. (1989a) showed that total lesion area did predict cognitive dysfunction in MS, and that smaller size of the corpus callosum predicted lower test performance on measures of mental processing speed. Rao et al. (1989b) showed that corpus callosum atrophy affected dichotic listening performance, suggesting decreased efficiency of inter-hemispheric information flow in MS. Research into relations between white-matter changes and behavior is also being conducted in other disorders such as Alzheimer's Disease (Harrell et al. 1991). However, our understanding of such relations is limited.

Sixth, although the overall sample size was large, there was no way of ensuring that all groups to be analysed would be large. In the clustering portion of the study, all profile groups had 14 or more subjects. However, in the subsequent MRI analysis, the 'Depressed' group (n=14) divided into two equal subgroups - those with the right parietal lesion and those without that lesion. Therefore, two groups of seven subjects were used in the

neuropsychological analyses. In the validation study, the 'Depressed' patients again divided into two subgroups: those with the lesion (n=4) and those without the lesion (n=6). Because these groups were small, outliers may have had profound effects on the statistical tests.

The seventh consideration involves Type I and Type II error. The probability of Type I error (false rejection of the null hypothesis) in a significance test is controlled by the setting of the alpha level. The levels of alpha set in this study were guided by a desire to obtain results which were interpretable within the proposed model. In the MRI analysis, for example, alpha was set at  $p \leq 0.005$ , so that any connection between profile and lesion site could be viewed with confidence, and so that a theory would not be developed based on weak tests of significance. Hypothetical outcomes, discussed in Chapter Three and outlined in Appendix B, indicated that  $p \leq 0.005$  was a point at which data were becoming compelling and interpretable within the model. Although many scientific studies employ an alpha level of  $p \leq 0.05$ , it should be emphasized that this level is arbitrary. The choice of alpha is at the discretion of the experimenter, and is based on the ramifications of making either a Type I error or a Type II error (Hays 1988). For example, when a new drug, with potential side-effects, is being tested, one would want to see treatment effects at a relatively stringent (low) alpha before calling the drug effective; on the other hand a relatively innocuous

treatment such as art therapy might be worth implementing even if effects were significant at only a less stringent (higher) alpha. Regarding the chi-squared analyses of the current study, the contrast-wise significance level was chosen as the level at which results would be meaningful. However, even though the contrast-wise error rate was set at  $p \leq 0.005$ , the experiment-wise error rate for the MRI analysis was potentially high. Given that this study was exploratory, it was deemed better to make an experiment-wise error than a Type II error, because there was no expense or danger associated with a Type I error.

However, another aspect of setting the alpha level is the underlying scale of measurement, and expected variation. In the MRI data, except for small periventricular lesions, there is little or no variation in the normal sample, which should be virtually lesion-free. In contrast, in cognitive test results, considerable variation is expected in the normal sample. Therefore, alpha levels for the neuropsychological analysis were set at  $p \leq 0.05$  because of the need to detect subtle differences in test scores in which large inter-subject variability is present.

The eighth and final issue of concern is experiment-wise error, which is the increased chance of Type I error whenever numerous tests of significance are performed. In the current study, it is difficult to determine the level of experiment-wise error, due to the number of independent analyses involving multiple measures. For the main study,

clearly experiment-wise error was high. Therefore, a validation component was included to give a higher level of confidence in the results. Positive findings were those which were replicated in the validation study. Initial positive results which were not replicated remain ambiguous. Based on this procedure, the overall results of the study are illustrated schematically in figure IX, which shows results from the cluster analysis, MRI analysis and neuropsychological analysis. For each profile group, results in a given part of the study are shown as a plus or minus. So, if an analysis showed positive results in the main study which were replicated in the validation study, this is shown as (++); if a finding was positive in the main study but not validated, it is shown as (+-). If an analysis was not done in the validation study because the original result was negative, it is represented as (nd).



# FIGURE IX

## Schematic illustration of overall results

(+) = positive results  
 (-) = negative results  
 (++) = positive results in both the main study and the validation study  
 (nd) = analysis not done

	'Depression'	Denial	Exag.Som.	Severity
Cluster Analysis	++	++	++	++
MRI Analysis	++	-nd	-nd	-nd
Neuropsych Analysis	+-	-nd	-nd	-nd

## Findings

The cardinal finding of the current study supports Hypothesis one, that distinctive psychological profiles of accommodation exist and can be identified. Specifically, the finding involved the empirical identification and validation of four psychological profiles or coping responses in patients with MS. These profiles are consistent with qualitative descriptions of psychological responses in MS patients, namely 'Depression', Denial, Exaggerated Somatic and Severity.

The 'Depressed' group showed high distress relative to disability; frequency of this profile was 14/99 (14%) in the main study and 10/43 (23%) in the validation study. The Denial group showed low scores on both self-rating scales relative to their higher scores on K (EDSS); this profile occurred in 32/99 (32%) patients in the main study and 12/43 (28%) in the validation study. The Exaggerated Somatic group showed high scores on Sx relative to scores on K; this profile occurred in 22/99 (22%) patients in the main study and 12/43 (28%) patients on validation. The Severity group showed similar scores on all three measures, whether low or high; this profile occurred in 31/99 (31%) patients in the main study and 9/43 (21%) on validation.

The second finding supports Hypothesis two, that membership in psychological groups is not related to extent of pathology as measured by number of sites with lesions.

Data from the study show that psychological groups are not distinguished by number of sites with lesions, suggesting that membership in groups is not a function of amount of biological disease.

Hypothesis three, that membership in profile groups was related to location of lesions, was not supported for three of the four profiles. That is, no relations were found for the Denial, Exaggerated Somatic and Severity groups, and site of lesion. However, for a subgroup of the 'Depressed' profile, a significant relation was found. Specifically, seven out of 14 of the 'Depressed' subjects (50%) in the main study, and four out of 10 subjects (40%) in the validation study had lesion(s) in the gray matter-white matter junction of the right parietal lobe. Therefore, the relation was found in both the main study and the validation study, in 11/142 patients (7.7%). A relation between 'Depression' and right-hemisphere lesions accords with some past reports on gray matter (GM) lesions, because relations have been suggested between right-hemisphere lesions and depression (Folstein et al. 1977; Lezak 1983). However, the bulk of the neurology literature has associated left-hemisphere lesions with depression (Robinson and Price 1982, Lezak 1983), and right-hemisphere lesions with denial and anosagnosia (Lezak 1983). Nevertheless, any apparent discrepancy between the finding of this study, and the bulk of the literature on brain lesions, emphasizes how little is known about the behavioural consequences of white matter

lesions. There is no reason to believe that white matter lesions in the parietal lobe, affecting tracts which may be transferring information from, for example, the occipital lobe to the frontal lobe, will affect functions classically associated with the parietal lobe.

Hypothesis four of the study, that group membership would be related to performance on cognitive tests, was not supported for most MS patients. That is, for the majority of MS groups, no relation was found between group membership and specific cognitive impairment. However, there was a strong indication in the main study that the 'Depressed' group with the right parietal lesion had widespread cognitive impairment, because this group scored lowest of all groups on 18/19 neuropsychological tests. The validation study did not confirm this cognitive impairment, so that the finding remains unclear. The potentially important symptom triad of 'Depression', a right parietal lesion, and general cognitive dysfunction, nevertheless warrants further study. As discussed earlier, the small size of the 'Depressed' group with the lesion in the validation study (n=4), could have precluded findings of significance.

### Implications

The first implications to be discussed concern the profiles illustrated in the first vertical line of figure IX. Clearly, the profiles were not defined by K (EDSS) scores, as several pairs of clusters had similar K scores yet fell into separate profile groups based on differences in Sx and Ds scores. This fact underscores a central theme of this study, that amount of clinical disease (level of disability or impairment) does not alone determine psychological response. Therefore, not only could an MS patient display any of a number of different responses, but any one response is not necessarily characteristic of a certain stage of clinical disease.

These data on profiles do not support the position that there is an "MS personality". Rather these unique profiles suggest an interaction between pre-morbid personality or coping style and the diagnosis of MS. The only possible exception in the current study is the case of the 11 subjects with 'Depression' and a lesion at the gray matter-white matter junction of the right parietal lobe.

The identification of separate groups also supports the concept that individuals faced with life crises do not all respond similarly. Heterogeneity of response to illness has been demonstrated in rheumatoid arthritis (McFarlane et al. 1987; Keefe et al. 1989), head injury (Nockleby and Deaton 1987; Moore et al. 1989), spinal cord injury (Frank et al.

1987), coronary bypass surgery (Clark and Klonoff 1988), and other illnesses as well as in non-medical crises (Kessler et al. 1985). Moreover, the coping mechanisms suggested in these studies are similar to those reported in other diseases (Kessler et al. 1985). Therefore, in general, one would propose an interactive model based on adjustment strategy prior to diagnosis, coupled with increased stress.

Such a model is further buttressed by the MRI data summarized on the second line of figure IX. For the MS subjects, particularly in the Denial, Exaggerated Somatic and Severity profiles, no relation was found between profile membership, and site of lesions. This study therefore tested the possibility of an organic basis to patients' responses, and did not support such an organic model. One possible explanation must be that the majority of MS patients with mild physical problems who experience psychological difficulties do so as a reaction to the stress of MS rather than as a direct result of lesions.

The exception to this model was the 'Depressed' group. For 11 of 24 of these subjects, 'Depression' was associated with a certain lesion in the right parietal lobe. Therefore, for the individual subject with 'Depression', there may or may not be an organic basis.

The lack of significant relations between profiles and lesion sites need not contradict previous reports that psychological change such as euphoria may be organically-based (Rabins et al. 1986; Minden and Schiffer 1990a).

Though denial and euphoria share features in common, it may be that denial in patients with mild physical problems is most often a reactive response, while euphoria in more severely disabled patients is the result of disruption of brain function. Given the selective sampling procedures, questions about severely disabled patients could not be directly addressed in this study. However, for mild MS patients, the denial response appears to be reactive.

For the neuropsychological data summarized in the third line of figure IX, it was predicted that the Denial profile group would do poorly on tests requiring insight. This prediction was not borne out; Deniers scored lower than most, but not all, other groups on Similarities and Categories tests. Similarly, it was predicted that 'Depressed' groups would do poorly on tests requiring new learning and memory. This prediction was also not clearly supported, as there were no memory tests on which the two groups of 'Depressed' patients scored significantly lower than did other groups.

Neuropsychological data from this study are relevant to the general issue of the relation between depression and cognitive impairment. While one group (n=7) of 'Depressed' patients in the main study showed significant cognitive impairment, the other group (n=7) did not. In fact, the latter group ('Depressed' but without the characteristic lesion) performed better than normal controls on several tests, while the group with the lesion performed worse than

the other groups. There is a considerable literature on the link between depression and cognitive impairment (reviewed in Weingartner and Silberman 1982). In theory, causation (if such exists) could run in either direction, with depression causing cognitive dysfunction or cognitive dysfunction causing depression. In contrast, the performance of 'Depressed' patients in the current study shows that depression, as defined here, need not necessarily cause cognitive impairment. This contention is consistent with the work of others who have concluded that depression and cognitive dysfunction can be independent in MS (DePaulo and Folstein 1978; Peyser et al. 1980a).

This study was not designed to examine or evaluate therapies for psychological problems. However, several speculative statements can be made. Patients whose psychological response is problematic, and for whom there is evidence of a biological basis to the response, may be strong candidates for treatment of the MS disease process itself. Patients whose psychological problems have no identifiable biological basis may be strong candidates for psychiatric treatment, either medication or psychotherapy or a combination thereof. Either group of patients (likely-organic, and likely-reactive) can, however, be considered for both anti-MS and psychiatric therapy.

In the realm of psychiatric treatment, there is evidence that both chemotherapy and psychotherapy can be useful to MS patients. Schiffer and Wineman (1990) showed



that the anti-depressant medication desipramine has a modest beneficial effect in serious depression associated with MS. Several research groups have shown benefits from psychotherapy for MS patients (Larcombe and Wilson 1984; Schiffer 1987). Crawford and McIvor (1985) demonstrated that group psychotherapy for MS patients resulted in decreased depression and anxiety, and increased self-concept and self-direction. Frank et al. (1987) have suggested that well-designed psychotherapeutic treatment may assist patients to forge their own most effective attitudes toward the disease. Several authors add that the existence of psychological problems which apparently have an organic basis are not a contraindication to psychotherapy (Talbott et al. 1988; Minden and Moes 1990).

Further research may clarify the existence of a subgroup of organically 'Depressed' patients, and possible treatment implications. For now, while this study will be of interest to clinicians, its data are too preliminary to form the basis for a recommendation of regular testing at the MS Clinic.

#### Further Comments

Although four profiles were found, there is still the question of whether other, different, profiles might also exist. Though the existence of alternative profiles is theoretically possible, any such groups would have contained

fewer than five subjects, the smallest cluster size. Therefore, error in failing to identify such clusters would have been small. As well, the many reports in the literature which have commented on psychological profiles in MS do not suggest notable alternatives to the four profiles identified here.

The study has not attempted to place value judgments on any or all psychological responses to MS, or to say that one response is more appropriate than another. All responses are appropriate in the view of individuals who show them. Although it is possible that one response might have different long-term effects on the course of the illness than another, if, for example, relapsing disease is related to perceived stress, such an assessment would require a long-term study. However, the coping response in all probability does affect accommodation to diagnosis and subsequent enjoyment of life.

The 'Depression' in this study was defined as an increase in the level of distress relative to the individual's level of physical difficulty from the disease. This definition was thought to be appropriate, because one might expect a general increase in distress in MS patients. The 'Depression' of this study, then, was not the same as the depression defined by the psychiatric Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). In the DSM-III-R, criteria for diagnosis of major depression are (1) depressed mood, (2) markedly diminished interest in normal

activities, (3) significant weight loss or gain, (4) hypersomnia or insomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or excessive guilt, (8) diminished ability to think or concentrate, or indecisiveness, (9) recurrent thoughts of death; plans for suicide. The Ds scale of this study, an important component of the definition of 'Depression', contains items referring to all nine of these DSM-III-R criteria. Therefore, although the 'Depression' of this study does not use the criteria of psychiatric depression, there is expected to be considerable overlap between the two definitions.

The division of 'Depressed' patients into two subgroups suggests the terms 'reactive' and 'endogenous', which have been used to describe, respectively, depression with a clear precipitating stressor, and depression which may instead have an organic basis. Clearly, the two categories are ends of a continuum, and do overlap (Kaplan and Sadock 1991). However, in a general sense it may be that 'Depressed' patients with the parietal lesion are displaying an endogenous depression, while 'Depressed' patients without the lesion are displaying a reactive depression. For those with reactive depression, the stressor is the diagnosis of MS. For those with endogenous depression, their lesion may have contributed to their mood. This distinction does not, however, exclude either group from any possible therapy, nor does it specify treatment. For example, although

psychiatric patients with apparently endogenous depression are considered good candidates for anti-depressant medication or electro-convulsive therapy, one cannot assume that such therapies will be effective for these MS patients, because the cause of their depression may be different. Nevertheless, a distinction between reactive and endogenous depression is useful. Such a distinction recalls the central point of the study, and a central point in psychiatry - the quest to know whether a patient's psychological problems are, or are not, organically-based.

This study emphasized the importance of patients' personal views of their illness, which form the basis of the two self-report measures of the three measures used in the cluster analysis. A patient's belief about his/her level of illness can differ considerably from the physician's belief, as illustrated in this study in the differences between K and Sx for many patients. Beatty and Monson (1991), in a study on memory problems in MS, have also shown that patients' reports can differ markedly from those of their physicians. In the present study, there is a stronger correlation between Sx and Ds ( $0.47; p \leq 0.001$ ) than between K and Ds ( $0.10, p \leq 0.15$ ), demonstrating that patients' views of reality influence their mood considerably more than do objective measures of reality. Clearly, it is enlightening to consider a patient's perception of the illness.

Profiles identified in this study represent coping strategies, although this study did not attempt to examine all possible methods of coping, which are cognitive and behavioural efforts to master, tolerate or reduce demands which tax a person's resources (Lazarus and Folkman 1984). The term "coping" is used broadly in the literature to include not only attitudes and behaviours towards illness such as the psychological profiles of this study, but also explanatory strategies such as those involving religious conviction (Matson and Brooks 1977). Many coping methods could not be examined in this study, the purpose of which was to cite from the literature, and empirically identify, responses common in MS.

Data from this study add to those of investigators who have questioned the widespread application of stage theories to models of coping. Stage theories assume that individuals progress through predictable levels during, or following, important life processes or events. Such theories have been influential in psychology, for descriptions of cognitive development in children (Piaget 1929), moral maturation (Kohlberg 1958), responses to death and dying (Kubler-Ross 1969), and progress through male adulthood (Levinson 1978). However, several recent authors (Kessler et al. 1985; Frank et al. 1987) have commented that such models are not strongly supported by empirical evidence. Because stage models frequently imply that patients must work through a series of attitudes before coming to accept their

situations, Frank et al. (1987) also say that stage models have encouraged passivity on the part of clinicians, and have retarded the development of modes of treatment which would help patients control their own responses.

The stage concept was applied to MS by Matson and Brooks (1977) who proposed a model in which patients were said to pass through four stages of coping with their illness. It was suggested that MS patients more recently diagnosed behaved differently toward their illness than did patients diagnosed long before. Similarly, Jouvent et al. (1989) reported that depression was more common in patients who had lived with the disease for less than two years, than in patients who had lived with MS for more than six years. Data from the current study show that psychological profile groups differ slightly on number of years since onset of first symptoms, but do not differ significantly on number of years since diagnosis. Data from the current study, then, do not clearly support a stage model based on length of time an individual has been living with the disease. Age data do not clearly support a stage model either, because the Denial group was oldest in the main study, but the Severity group was oldest in the validation study.

Data from the current study do not, however, show that psychological response is often a function of site-of-lesion in patients with early-stage MS. What other models, then, might be considered to explain different psychological responses? As mentioned, several studies suggest that

depression is most common among patients recently diagnosed. But because more-recently diagnosed patients are usually also younger than patients less-recently diagnosed, it may be that patients respond differently based on their "stage of life". Such a model could be investigated further. However, while there were significant differences between ages of profile groups in this study, the fact that all groups had mean ages in their 30s suggests that groups were not at markedly different stages of maturity.

Data from this study do not support a stage model based on either level of clinical disease as measured by EDSS score, or level of biological disease as measured by number of sites with lesions. It is nevertheless theoretically possible that patients might change their response at some point based not on clinical or biological stage, but for other, psychological, reasons. That is, a patient may use denial for a time, find it inadequate, and collapse into depression. An alternative possible model to explain the existence of various profiles is that of individual differences in dimensions of personality, which lead to a variety of ways of coping with stress.

Contributions of the Study;  
Suggestions for Future Research

This study has made contributions in both evidence and methodology. In the realm of evidence, the study has empirically validated the existence of a heterogeneity of coping styles in MS. These data should caution researchers not to expect any one psychological outcome in MS. Data from this study also suggest that different profiles may not be the result of stage of biological disease. These data could encourage more active psychotherapeutic intervention for MS patients, on the basis that patients need not traverse an inevitable series of psychological crises in dealing with their MS.

In the larger health field, support for heterogeneity of response to a given situation fits with an important issue in medicine and psychology, and in the relatively new field of health psychology. It has been observed in numerous kinds of crises that individuals respond differently one from another. So, for example, when two individuals are both rendered paraplegic, one may sink into despair and dependence, while another may become more active and seek independence. This phenomenon occurs, then, in a number of different situations, even in ones in which the brain has not been affected. Data from the current study cannot address the larger issue of reasons for different responses, but the study does remind researchers and



clinicians not to expect certain physical or psychological outcomes in individuals based on a single agent or event.

In the realm of methodology, the study avoided many of the problems for which past psychological studies in MS have been criticised (VanderPlate 1984; Rao 1986; Minden and Schiffer 1990; Peyser et al. 1990). The study had a large sample, chosen from a clinic population of more than 2,000 patients. The sample was well-characterized and fully described. The study tested only relapsing/remitting patients, and controlled for the cyclic nature of the disease by testing solely individuals in remission. Also in the realm of methodology, the study provided further evidence of the utility of cluster analysis for clarifying concepts involving several variables.

There are numerous questions which could be asked in future work, including: (1) Are various therapies more effective in MS patients if it is first determined whether there might be an organic basis to any psychological change? (2) For 'Depressed' patients with the characteristic lesion in the right parietal lobe, does cognitive dysfunction often arise? (3) Do different coping responses have different effects on the course of the illness?

## APPENDIX A

### CORRELATIONAL STUDIES WHICH HAVE BEEN DONE IN MS, BETWEEN PSYCHOLOGICAL VARIABLES AND PHYSICAL/DISEASE VARIABLES

#### A. Affective Problems and Extent of Disability

##### a) Studies Suggesting Correlations

(1) Cleeland et al. (1970) showed that depression, as gauged by the MMPI, is greater for patients in exacerbation than those in remission.

(2) McIvor et al. (1984) showed that depression, as gauged by the Beck Depression Inventory (BDI), is greater in more-disabled spinal MS patients than in less-disabled ones.

It should be noted that both the BDI and the Depression scale of the MMPI contain items which could be endorsed purely on the basis of physical symptoms of MS.

##### b) Studies Suggesting Little or No Correlation

(1) Joffe et al. (1989) found no direct relationship between degree of disability and mood disorders. Patients with major depression were generally less disabled than those without such psychiatric diagnosis.

(2) Minden et al. (1989) reported no relationship between severity of disability and depression as measured by the BDI.

## B. Cognitive Function and Extent of Disability

### a) Studies Suggesting Correlations

(1) Beatty and Gange (1977) suggested a relation between memory dysfunction and motor dysfunction, showing that correlations between motor and memory performance were consistently higher in MS patients than in controls.

(2) Surridge (1969) showed a significant association between intellectual deterioration and physical disability.

(3) Stenager et al. (1989b) suggested that aspects of cognition including verbal and visual memory decline with increasing score on the Expanded Disability Status Scale (EDSS), a measure of disability/impairment for MS (Kurtzke 1983).

### b) Studies Suggesting Little or No Correlation

(1) Van den Burg et al. (1987) showed no relation between most intellectual abilities and MS progression, and only weak relations between memory measures and the disease.

(2) Rao et al. (1984) reported no relation between degree of memory disturbance and EDSS score.

(3) Lyon-Caen et al. (1986) found no correlation between cognitive difficulties, and degree of illness as measured by EDSS.

## C. Affective Problems and MRI Lesion Measures

### a) Studies Suggesting Correlations

(1) Honer et al. (1987) reported that MS patients with psychiatric disorders had more temporal-lobe lesions than

patients with no such disorders. However, the authors reported no relation between total lesion burden and the presence of psychiatric disorder in MS patients, which suggests that lesion site (rather than amount) may be critical.

(2) Rabins et al. (1986) showed that MS patients with brain involvement had more depression than MS patients with only spinal-cord involvement.

b) Studies Suggesting Little or No Correlation

(1) Logsdail et al. (1988) and Ron and Logsdail (1989) reported no significant associations between total MRI lesion scores and severity of psychiatric problems.

D. Cognitive Problems and MRI Lesion Measures

a) Studies Suggesting Correlations

(1) Callanan et al. (1989) reported that IQ deficit and defective auditory attention were significantly correlated with the degree of brain pathology detected by MRI.

(2) Franklin et al. (1988) showed a relation between cognitive impairment and total brain-lesion area.

(3) Rao et al. (1989a) showed that several MRI measures, particularly total lesion area, were significantly different in cognitively impaired patients from patients not impaired.

b) Studies Suggesting Little or No Correlation

(1) Huber et al. (1987) reported no correlation between amount of dementia in MS patients and any of the following

MRI measures: number of lesions, size of lesions, and extent of generalized cerebral atrophy. However, the authors reported a modest correlation between dementia and corpus callosum atrophy.

## APPENDIX B

### MRI LESION-LOCATION ANALYSIS: HYPOTHETICAL DISTRIBUTIONS OF SUBJECTS WITHIN GROUPS, AND ASSOCIATED P-VALUES

**Appendix B.1.** With zero noise in 3/4 profile groups, how many members of a profile group must have lesions for significance?

(# = number of members w/lesion) (asterisk =  $p \leq 0.005$ )

	n = 14		n = 22		n = 32	
#	matrix	p-value	matrix	p-value	matrix	p-value
1	$\frac{1}{13} \mid \frac{0}{32} \mid \frac{0}{22} \mid \frac{0}{31}$	.105	$\frac{0}{14} \mid \frac{0}{32} \mid \frac{1}{21} \mid \frac{0}{31}$		$\frac{0}{14} \mid \frac{1}{31} \mid \frac{0}{22} \mid \frac{0}{31}$	
2	$\frac{2}{12} \mid \frac{0}{32} \mid \frac{0}{22} \mid \frac{0}{31}$	.0062	$\frac{0}{14} \mid \frac{0}{32} \mid \frac{2}{20} \mid \frac{0}{31}$	.067	$\frac{0}{14} \mid \frac{2}{30} \mid \frac{0}{22} \mid \frac{0}{31}$	.233
3	$\frac{3}{11} \mid \frac{0}{32} \mid \frac{0}{22} \mid \frac{0}{31}$	.0003*	$\frac{0}{14} \mid \frac{0}{32} \mid \frac{3}{19} \mid \frac{0}{31}$	.0127	$\frac{0}{14} \mid \frac{3}{29} \mid \frac{0}{22} \mid \frac{0}{31}$	.091
4			$\frac{0}{14} \mid \frac{0}{32} \mid \frac{4}{18} \mid \frac{0}{31}$	.0022*	$\frac{0}{14} \mid \frac{4}{28} \mid \frac{0}{22} \mid \frac{0}{31}$	.0331
5			$\frac{0}{14} \mid \frac{0}{32} \mid \frac{5}{17} \mid \frac{0}{31}$	.0004*	$\frac{0}{14} \mid \frac{5}{27} \mid \frac{0}{22} \mid \frac{0}{31}$	.0116
6					$\frac{0}{14} \mid \frac{6}{26} \mid \frac{0}{22} \mid \frac{0}{31}$	.0039*
7					$\frac{0}{14} \mid \frac{7}{25} \mid \frac{0}{22} \mid \frac{0}{31}$	.0013*
8					$\frac{0}{14} \mid \frac{8}{24} \mid \frac{0}{22} \mid \frac{0}{31}$	.0004*

**Appendix B.2.** With minimum noise in 3/4 profile groups, how many members of a group must have lesions for significance?

n = 14		n = 22		n = 32		
#	matrix	p-value	matrix	p-value	matrix	p-value
1						
2						
3	$\frac{3}{11} \mid \frac{1}{31} \mid \frac{1}{21} \mid \frac{1}{30}$	.078	$\frac{1}{13} \mid \frac{1}{31} \mid \frac{3}{19} \mid \frac{1}{30}$	.366		
4	$\frac{4}{10} \mid \frac{1}{31} \mid \frac{1}{21} \mid \frac{1}{30}$	.0092	$\frac{1}{13} \mid \frac{1}{31} \mid \frac{4}{18} \mid \frac{1}{30}$	.133		
5	$\frac{5}{9} \mid \frac{1}{31} \mid \frac{1}{21} \mid \frac{1}{30}$	.0000*	$\frac{1}{17} \mid \frac{1}{17} \mid \frac{5}{17} \mid \frac{1}{17}$	.038	$\frac{1}{13} \mid \frac{5}{27} \mid \frac{1}{21} \mid \frac{1}{30}$	.281
6			$\frac{1}{16} \mid \frac{1}{16} \mid \frac{6}{16} \mid \frac{1}{16}$	.0092	$\frac{1}{26} \mid \frac{6}{26} \mid \frac{1}{26} \mid \frac{1}{26}$	.138
7			$\frac{1}{15} \mid \frac{1}{15} \mid \frac{7}{15} \mid \frac{1}{15}$	.0019*	$\frac{1}{25} \mid \frac{7}{25} \mid \frac{1}{25} \mid \frac{1}{25}$	.061
8			$\frac{1}{14} \mid \frac{1}{14} \mid \frac{8}{14} \mid \frac{1}{14}$	.0004*	$\frac{1}{24} \mid \frac{8}{24} \mid \frac{1}{24} \mid \frac{1}{24}$	.025
9					$\frac{1}{23} \mid \frac{9}{23} \mid \frac{1}{23} \mid \frac{1}{23}$	.0093
10					$\frac{1}{22} \mid \frac{10}{22} \mid \frac{1}{22} \mid \frac{1}{22}$	.0033*
11					$\frac{1}{21} \mid \frac{11}{21} \mid \frac{1}{21} \mid \frac{1}{21}$	.0011*
12					$\frac{1}{20} \mid \frac{12}{20} \mid \frac{1}{20} \mid \frac{1}{20}$	.0003*

**Appendix B.3.** With a large amount of noise (50%) in 3/4 groups, how many members of a group must have lesions for statistical significance?

n = 14		n = 22		n = 32	
matrix	p-value	matrix	p-value	matrix	p-value
$\frac{14}{0}   \frac{16}{16}   \frac{11}{11}   \frac{16}{15}$	.0073	$\frac{1}{7}   \frac{16}{16}   \frac{22}{0}   \frac{16}{15}$	.0005 *	$\frac{7}{0}   \frac{32}{0}   \frac{11}{0}   \frac{16}{0}$	.0000 *
$\frac{13}{1}   \frac{16}{0}   \frac{11}{0}   \frac{16}{0}$	.0326	$\frac{7}{0}   \frac{16}{0}   \frac{21}{1}   \frac{16}{0}$	.0024 *	$\frac{7}{1}   \frac{31}{1}   \frac{11}{0}   \frac{16}{0}$	.0001 *
$\frac{12}{2}   \frac{16}{0}   \frac{11}{0}   \frac{16}{0}$	.1103	$\frac{7}{0}   \frac{16}{0}   \frac{20}{2}   \frac{16}{0}$	.0091	$\frac{7}{2}   \frac{30}{2}   \frac{11}{0}   \frac{16}{0}$	.0005 *
		$\frac{7}{0}   \frac{16}{0}   \frac{19}{3}   \frac{16}{0}$	.0291	$\frac{7}{3}   \frac{29}{3}   \frac{11}{0}   \frac{16}{0}$	.0019 *
		$\frac{7}{0}   \frac{16}{0}   \frac{18}{11}   \frac{16}{0}$	.078	$\frac{7}{4}   \frac{28}{4}   \frac{11}{0}   \frac{16}{0}$	.0058
				$\frac{7}{5}   \frac{27}{5}   \frac{11}{0}   \frac{16}{0}$	.0156
				$\frac{7}{6}   \frac{26}{6}   \frac{11}{0}   \frac{16}{0}$	.0374
				$\frac{7}{7}   \frac{25}{7}   \frac{11}{0}   \frac{16}{0}$	.0800



## APPENDIX C

### MMPI ITEMS COMPRISING Sx AND Ds SCALES

#### **Sx scale:**

- 007: My hands and feet are usually warm enough.
- 009: I am about as able to work as I ever was.
- 018: I am very seldom troubled by constipation.
- 023: I am troubled by attacks of nausea and vomiting.
- 036: I seldom worry about my health.
- 047: Once a week or oftener I feel suddenly hot all over,  
without apparent cause.
- 051: I am in just as good physical health as most of my  
friends.
- 061: Parts of my body often have feelings like burning,  
tingling, crawling, or like 'going to sleep'.
- 062: I have had no difficulty in starting or holding my  
bowel movement.
- 067: I hardly ever feel pain in the back of my neck.
- 100: I have little or no trouble with my muscles twitching  
or jumping.
- 116: My speech is the same as always (not faster or slower  
or slurring: no hoarseness.)
- 150: During the past few years I have been well most of the  
time.
- 157: I have never felt better in my life than I do now.
- 160: I do not tire quickly.
- 172: I seldom or never have dizzy spells.

- 179: I am afraid of losing my mind.
- 182: My hearing is apparently as good as that of most people.
- 183: I frequently notice my hand shakes when I try to do something.
- 184: My hands have not become clumsy or awkward.
- 185: I can read a long while without tiring my eyes.
- 186: I feel weak all over much of the time.
- 189: I have had no difficulty in keeping my balance in walking.
- 191: I have had attacks in which I could not control my movements or speech but in which I knew what was going on around me.
- 239: I have few or no pains.
- 268: I have numbness in one or more regions of my skin.
- 269: My eyesight is as good as it has been for years.
- 276: I do not often notice my ears ringing or buzzing.
- 313: I have never been paralyzed or had any unusual weakness of any of my muscles.
- 314: Sometimes my voice leaves me or changes even though I have no cold.
- 393: I have had no difficulty starting or holding my urine.

**Ds scale:**

- 002: I have a good appetite.
- 003: I wake up fresh and rested most mornings.
- 008: My daily life is full of things that keep me  
interested.
- 010: There seems to be a lump in my throat much of the time.
- 016: I am sure I get a raw deal from life.
- 022: At times I have fits of laughing and crying that I  
cannot control.
- 040: Most any time I would rather sit and daydream than to  
do anything else.
- 041: I have had periods of days, weeks or months when I  
couldn't take care of things because I couldn't get  
going.
- 043: My sleep is fitful and disturbed.
- 046: My judgement is better than it ever was.
- 066: I wish I could be as happy as others seem to be.
- 075: Most of the time I feel blue.
- 083: These days I find it hard not to give up hope of  
amounting to something.
- 085: I am certainly lacking in self-confidence.
- 087: I usually feel that life is worthwhile.
- 101: I don't seem to care what happens to me.
- 104: I am happy most of the time.
- 139: I certainly feel useless at times.
- 149: Most nights I go to sleep without thoughts or ideas  
bothering me.

155: I cry easily.

207: I can sleep during the day but not at night.

213: I frequently find myself worrying about something.

226: I hardly ever notice my heart pounding and I am seldom short of breath.

232: I brood a great deal.

234: I have periods of such great restlessness that I cannot sit long in a chair.

238: I believe I am no more nervous than most others.

247: No one cares much what happens to you.

252: I usually expect to succeed in things I do.

294: Life is a strain for me much of the time.

297: Even when I am with people I feel lonely much of the time.

300: I seem to make friends about as quickly as others do.

318: I feel anxiety about something or someone almost all the time.

320: Most of the time I wish I were dead.

340: Sometimes some unimportant thought will run through my mind and bother me for days.

347: I am not unusually self-conscious.

351: I very seldom have spells of the blues.

354: People often disappoint me.

356: My plans have frequently seemed so full of difficulties that I have had to give them up.

359: I have sometimes felt that difficulties were piling up so high that I could not overcome them.

- 364: I am usually calm and not easily upset.
- 368: I am apt to take disappointments so keenly that I can't put them out of my mind.
- 370: At times I think I am no good at all.
- 404: I feel like giving up quickly when things go wrong.
- 408: I must admit that I have at times been worried beyond reason over something that really did not matter.
- 421: The future seems hopeless to me.
- 433: I sometimes feel that I am about to go to pieces.
- 439: In the past 12 months, I have seriously thought about taking my life as a solution to personal problems.

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