PREDICTORS OF PSYCHOSOCIAL FUNCTIONING IN MULTIPLE SCLEROSIS: COGNITIVE IMPAIRMENT, DEPRESSION AND PHYSICAL DISABILITY

by

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ABSTRACT

A number of reports suggests that multiple sclerosis (MS) leads to certain changes in psychosocial functioning. Whether these changes are the direct result of specific symptoms of MS such as: physical impairments, depression or deficits in cognitive function, is not yet clear. Few studies have examined the relative effects of each of these symptoms on various measures of social and vocational activities. Therefore, the purpose of this study was to determine: 1) in a sample of MS patients in the early stages of a relapsing-remitting disease course, the prevalence of cognitive impairment and depression; 2) whether these two dimensions were independent of physical disability; and 3) whether cognitive impairment, depression, or physical disability was most predictive of the decline of psychosocial functioning.

In order to discover whether each of the symptoms existed within the sample, the MS group was divided according to cutting scores established by the performance of the normal control group. First, a group of MS patients who were cognitively impaired was identified by scoring lower than the fifth percentile of the normals’ scores on the Word Fluency Test. Thirty seven patients (20%) of the MS group scored in the impaired range. Validation of this impairment was assessed by performance on other neuropsychological tests. Neither disease-related nor demographic variables could account for the deficit. Similarly, a group of patients with a high level of depressive symptoms was identified by using the ninety-fifth percentile of
the normals' scores on the Beck Depression Inventory (BDI) as a cut-off. Thirty eight (21%) patients were classified as depressed according to the above criterion. Finally, those patients with highest levels of physical disability (top 20%) were identified from their scores on the Kurtzke EDSS. Thirty four (19%) of the MS group were considered physically impaired. Of the total MS sample, only 11% were impaired on a combination of two or more dimensions.

The dependent variable for the final question, psychosocial functioning, was assessed by activity in the work force (employed vs unemployed), level of social/recreational activity, and outlook for the future (either optimistic or pessimistic).

The results of this investigation suggest four things. First, cognitive impairment does exist in the early stages of MS and is independent of disease-related or demographic variables. Second, evidence for depressed mood was also found in a portion of this sample. Third, these observed symptoms as well as degree of physical disability are independent phenomena in the early stages of the disease. Fourth, being cognitively impaired is related to both a decrease in vocational and recreational activities and a greater pessimism towards the future. If a MS patient is depressed, it is more likely that he or she is unemployed and also less socially active. Interestingly, the degree of physically disability does not seem to be related to these three areas of psychosocial functioning.
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I am indebted to the staff of the UBC MS clinic as well as to all the MS patients (and controls) who gave their time and effort so that this project could be.
A number of studies suggest that multiple sclerosis (MS) leads to changes in psychosocial functioning. Whether these changes are a direct result of deficits in certain symptoms of MS such as: cognitive impairment, depression or physical disability, is not yet clear. Simply, there are no published investigations examining the relative effects of each of these three symptoms on various measures of quality of life. The literature on this subject is limited to studies which assess the effects of only one of the symptoms on social and vocational outcome measures.

A possible explanation for the limited focus in the social functioning literature is a debate concerning the relationships (or lack thereof) among the three symptoms. For example, some researchers have argued for the role of depression (Weingartner & Silberman, 1982) as well as motor/sensory losses (Beatty & Gange, 1977) in the manifestation of cognitive change. While other investigators have disagreed, arguing for the independence of the three (Rao, Leo, Bernardin, & Unverzagt, 1991a; Reitan, Reed, & Dyken, 1971). Similarly, depression has been reported to be a grief reaction to the loss of physical functions (Vanderplate, 1984) and is thus intimately linked to the physical symptoms. Here too, controversy has prevailed (Minden, Orav & Reich, 1987).
Each of the three symptoms (cognitive impairment, depression and physical disability), whether interacting or acting independently, may have detrimental effects on an individual’s ability to cope in every day life situations. Separating out the independent effects of each is of clinical importance. Therefore, reflecting the nature of the issues, the purposes of this study were threefold. The first purpose was to determine, in a sample of mild relapsing-remitting (R/R) MS patients, whether cognitive problems and depression exist. Given that these two dimensions exist, the second purpose will be to find out whether they are independent of each other, and of physical disability. The final purpose was to discover whether cognitive impairment, depression or physical disability is most predictive of the decline of psychosocial functioning. Psychosocial functioning was measured by the patient’s activity in the work force, the number and type of social/recreational activities undertaken by the patient and whether the patient has a pessimistic future outlook.

**Cognitive Impairment**

Although the frequency and patterns of cognitive problems in MS are still unresolved, there is general agreement that cognitive impairment is a feature of the disease (reviewed in Rao, 1986). Early investigations of MS suggest that cognitive impairment does occur (Charcot, 1877; Ombredane, 1929; Cottrell & Wilson, 1926) but there was no agreement in terms of the
prevalence rate or specific features. These prevalence rates ranged from 2 to 72% but in general cognitive impairment was confined to the later stages of the disease. More recent research has suggested that cognitive problems do exist in approximately 50% of patients (Sandford & Petajan, 1990) but bear no relation to disease duration (Rao et al., 1991a) or level of physical disability (Franklin, Nelson, Filley & Heaton, 1989).

Moreover, Canter (1951b) argued that cognitive problems could be observed early in the disease, and this fact has been subsequently validated by other investigators (Klonoff, Clark, Oger, Paty & Li, 1991; Beatty, Goodkin, Monson, & Beatty, 1989). Not only did Klonoff et al. (1991) and Beatty et al. (1989) indicate that cognitive impairment can be an early stage effect, they also argue that it can occur in some patients with relapsing-remitting (R/R) course while in remission.

The cognitive problems that have been reported in MS are changes in memory function, in abstract conceptual reasoning, in word fluency, and in speed of information processing (Minden, Moes, Orav, Kaplan & Reich, 1990). Primary language abilities and recall of overlearned material, on the other hand, seem to be spared (reviewed in Rao, 1986; Peyser & Poser, 1986).
Depression

In addition to problems with cognition, emotional problems are common in MS. The prevalence of depression has been estimated between 27-54% (Minden & Schiffer, 1990). The reported prevalence has been variable from study to study perhaps due to the lack of standardized terminology and assessment tools. Depression has been postulated as being of the reactive type early in the disease course due to the problems of adjusting to the diagnosis of a progressively disabling disease (VanderPlate, 1984), whereas depression seen in the later stage is presumed to be organic, reflecting lesions in the cerebrum (Schiffer, Caine, Bamford & Levy, 1983).

Relation Between Cognitive Impairment and Depression

The relationship of cognitive impairment and depression has not been clearly established. Some researchers have argued that the poorer performance by MS patients on neuropsychological tests was a secondary reaction to depression (Weingartner & Silberman, 1982, Goldstein & Shelly, 1974). Moreover, it is conceivable that causation could run in the opposite direction with cognitive impairment being a precipitating factor in the appearance of depressive symptoms. Schiffer et al. (1983) and Rao, Leo, Ellington, Nauertz, Bernardin, Unverzag, (1991b) have argued that cognitive impairment and depression might bear no relation to one another.
Motor/Sensory Effects on Cognitive Impairment

There is a further complicating issue to the debate concerning the underlying causes of cognitive impairment. The issue is that motor/sensory deficits, the cardinal symptoms of MS, have been proposed to be a possible contributing factor (Beatty & Gange, 1977; Rao, 1986). There are numerous reports in the literature indicating that tests of motor/sensory function are performed less efficiently by MS patients (Klonoff et al., 1991; Minden et al., 1990). However, physical impairment can not account for poorer performance on other tests which have virtually no motor/sensory component. Reitan et al. (1971) have indicated that MS patients perform more poorly than normal controls on tests of motor function, but also did poorly on tests not requiring motor functions.

Role of Cognitive Changes, Depression, and Motor/Sensory Losses on Social Disability

MS, with its debilitating symptoms and fluctuating course, can interfere with the ability of MS patients to perform everyday activities. Sandford and Petajan (1990) review the impact of MS on daily life activities. They indicate that MS patients are less proficient at managing the household, less apt to undertake recreational activities, and have more difficulty with their jobs (if they are still working). Sandford and Petajan (1990) do not speculate on the underlying basis of the reduced ability to
function in social settings, but they do indicate that cognitive and affective problems may be partly to blame.

Clearly, the physical symptoms of MS (motor/sensory losses) may contribute to social disability in MS patients. However, it is possible that the accompanying depression may be more socially disabling for the patient. Furthermore, cognitive impairment may also give rise to social disability. This question warrants investigation. Specifically, which of the three manifestations of the disease (motor/sensory losses, depression, or cognitive impairment) is most social disabling for the MS patient.

A study was undertaken by Rao et al. (1991b) to determine the effects of cognitive impairment on the psychosocial functioning in MS patients. They identified a subgroup of MS patients who were cognitively impaired according to their criteria. The impaired group was compared with a cognitively intact group on measures of social functioning indicated by employment status and level of recreational activity. The cognitive impaired group was more likely to be unemployed and less likely to partake in recreational activities. Furthermore, the two groups did not differ in terms of level of depression. Their results suggest that cognitive impairment is a major factor determining life satisfaction for the MS patient in terms of remaining socially active and in the work force.
The Rao et al. (1991b) study was instrumental in motivating the present study. Although similar in methodology, the current study differs from the Rao et al. (1991b) investigation in many respects. In the Rao et al. (1991b) study, patients were selected who represented differing disease courses. In addition, these patients were at various stages of the disease. Finally, the patients were older and more physically disabled than those patients in the current study. The subjects in the present investigation were young, early stage R/R MS patients with mild physical disability. The strict entry criteria provided a sample free from potentially confounding variables that have been problematic in other research (for example, severe physical disability or relentless disease course). The research question was to determine whether cognitive impairment (if it exists) interferes with the daily life activities of MS patients who are at most mildly physically disabled early in the disease course.

**Rationale**

The relationship between cognitive impairment and depression has been addressed in the literature in many different ways. For example, DePaulo and Folstein (1978), using a cross sectional design, presented evidence in support of the independence of the two phenomena. However, only 6 of the 126 neurological patients were MS patients. Their research method consisted of using two tests known to screen for cognitive impairment and emotional disturbance and to determine whether poor performance on one test
necessarily means poor performance on the other. Only 13% of their sample were impaired on both tests. Another approach, which was taken by Peyser, Edwards, Poser, and Filskov (1980) involved correlating the extent of cognitive impairment with the level of depression and finding no significant relation between the two. The current study will use a unique approach. The sample will be divided into two groups based on cognitive performance and subsequently, the level of psychosocial functioning will be compared. This approach will be used because previous studies have suggested that cognitive impairment is confined to a sub-sample of MS patients (Rao, Hammeke, McQuillen, Khatri & Lloyd, 1984). Similarly, a group of depressed patients will be identified by their scores on the Beck Depression Inventory as compared to the similar normal controls and assessed on psychosocial outcome measures. A group of patients with the highest levels of physical disability will also be identified and compared on psychosocial measures.

This particular research design will also overcome another potential problem. Many of the neuropsychological tests used to assess intellectual functioning have some degree of motor involvement. In the current study, subjects with possible impairment will be identified by performance on the Word Fluency Test. This test requires the subject to produce words starting with a specific letter (F,A,S). The Word Fluency Test was chosen as it has very little motor component and is thus a relatively pure measure of cognitive function. The assertion that this
group has cognitive impairment will be validated by examining performance on other cognitive tests. Moreover, the performance of the two groups will be compared in terms of motor sensory tests.

The current study will attempt to minimize the kinds of methodological problems which have been criticized (Rao 1986; Heaton, Nelson, Thompson, Burks & Franklin, 1985; Peyser, Rao, LaRocca, & Kaplan, 1990) in earlier papers. As 181 MS and 90 normal controls have been assessed, the resulting estimates should be stable. Since all subjects were recruited during their annual visit to a Hospital MS clinic and are by definition "mild" (Kurtzke EDSS less than or equal to 6), this avoided a potential problem of preselecting hospitalized individuals (who are likely to be more seriously ill). Finally, the effects of acute exacerbations and medication are avoided by testing only those patients who are in remission at time of testing and are relatively drug free (having had at least one week drug holiday).

Overview of Research Design

Specific Questions

Three questions will be examined in this study.
**Question one.** Given that cognitive dysfunction does exist in a sample of early relapsing remitting MS patients with mild physical disease course (Good et al., in Press), what is its relation to depression or physical disability.

**Question two.** Does the decline of intellectual functions relate to a decrease in psychosocial functioning? Psychosocial functioning will be measured in terms of activity in the work force, number and type (for example active sports vs. hobbies) of leisure activities in which the patient engages per week, and their level of optimism for the future.

**Question three.** What is the relative effect of cognitive impairment on psychosocial functioning in comparison to physical disability and depression. Specifically, this analysis will try to determine whether depression can interfere with the number of leisure activities, the employment status and level of optimism for the future. Furthermore, the same questions will be asked with respect to physical disability.

The above analyses will be performed in order to answer the larger question: Are the three symptoms independent of each other, and which of these symptoms is associated most strongly with a decline in psychosocial functioning.
Method

Sample description. The data was drawn from an existing database. The subjects were considered for inclusion into a larger study at their annual visit to the UBC MS clinic. Subjects were included if they met the criteria of being in the early/mild stage of a relapsing-remitting disease course, and in remission at time of testing; diagnosed as clinically definite; young, aged less than 50 years and having been diagnosed before the age of 40 years. The MS patients must not have had any psychiatric diagnosis predating the onset of the disease, nor any complicating medical problem or drug regimen concurrent with MS. Each MS patient was asked to recruit a same-sex, educationally and socio-economically matched non-relative who met the same criteria where applicable to act as a control.

Measures and design. Data collected on each subject (both MS and controls) included scores from an extensive neuropsychological battery, interview data, an MRI (magnetic resonance imaging) scan, and in the case of the MS patients, disease related information including their level of physical disability from the Expanded Disability Status Scale (EDSS). The neuropsychological battery included 23 tests which assessed a wide range of functions. The Word Fluency Test was administered and it will be used as a screening device in order to detect patients with possible cognitive impairment.
To ensure that these patients will not be selected solely because of lower premorbid ability, subjects will then be compared on highest level of vocational achievement, and educational status. In order to be certain that the lowered cognitive efficiency is not a result of poor sensory/motor skills, performance on the tests of sensory/motor function (Grooved Pegboard, a test of motor speed and coordination) will be examined.

The cognitively impaired subgroup will then be compared with the cognitively intact group on such measures as employment status, amount and type of social/recreational activity in which the patients engage and patients’ level of pessimism towards the future. Finally, the relative effects of cognitive impairment, depression, and physical disability will be examined. It was hypothesized that cognitive impairment might have an effect on each of these areas, but level of physical disability or depression may also play a role. Therefore, these variable will be examined in order to determine which variable is able to predict the social disability that these patients face.

Contributions and Significance

The motor/sensory deficits associated with MS and their debilitating effects are well recognized in the literature and usually used to explain subsequent problems in adaptation in normal living. However, if cognitive changes occur in the early
stages of the disease, the recognition of these changes and their resultant effects on the individual clearly has a direct bearing on treatment planning.

This study should contribute to our understanding of the effects of various MS related symptoms on psychosocial functioning, specifically whether cognitive change may be the most socially disabling. The results of this study may underscore the need for timely and accurate neuropsychological assessment. Cognitive deficits can interfere with the performance of normal daily activities and in particular can lead to cessation of employment, regardless of level of physical disability. Neuropsychological assessment can give information that may be beneficial to family members, friends, employers so that adaptations can then be made in working and living conditions. With respect to working conditions, cognitive retraining programs could be beneficial for the MS patient to make use of mental processes spared by the disease. Alternately, retraining to take on a new less mentally challenging position which minimizes the cognitive component needed for job performance. In terms of leisure activities, changes can be made in order to lessen the impact of impaired cognitive functioning on ultimate life satisfaction. Should depression be found to be socially disabling, recognizing and treating the cause might lead to favorable outcomes in terms of social and vocational life-style.
A detailed neuropsychological battery which covers a wide range of functions, including an assessment for the level of depression, should be used in assessing cognitive functions early in the course of the disease, and information from this assessment should be used in planning realistic life goals for the MS patient and his/her family.

**Overview of Subsequent Chapters**

This thesis has been divided into five chapters. The following section provides a rough overview of the chapters to follow.

Chapter two serves as a review of the literature, examining issues which are pertinent to the research question. It has been broken down into two sections: 1) early findings in MS, and 2) the current status of our knowledge. The second section has been further subdivided into seven sections. These are: 1) diagnostic criteria; 2) physical disability; 3) cognitive impairment; 4) interaction of cognitive impairment and physical changes; 5) depression; 6) interaction of cognitive impairment and depression; 7) social disability.

Chapter three provides a detailed methodological section outlining subject selection, assessment techniques, methodology, and analyses. Chapter four reviews the obtained results of the analyses.
Chapter five provides a detailed discussion of the findings and draws conclusions based on the obtained results. Furthermore, implications of these results on the everyday lives of the MS patients are discussed as well as presenting ideas for future research.
CHAPTER II
BACKGROUND TO THE STUDY

The purpose of this study is to determine the relative effects of motor/sensory impairment, cognitive deficits and depressed mood in multiple sclerosis, on the individual’s ability to live a normal life. Therefore, this chapter will first review the reported cognitive and mood changes in multiple sclerosis with specific reference to the early or mild stages of the disease. Subsequently, our current understanding of the social impact of this disease will be outlined. To date, however, there are few studies attempting to delineate the relative effects of impairment in these three spheres (motor/sensory, cognitive or mood) on daily function although clear recognition of the potential effects of such impairment is evident in the literature.

Early Findings in MS Research

Given the variability of symptoms which characterize the disease, diagnosing the MS patient, particularly early in the history of the disease, has been difficult (Matthews, Acheson, Batchelor, & Weller, 1985). The pathology underlying the disease became apparent with post mortem analysis, but definitive diagnosis was only possible at autopsy (DeJong, 1970). Jean Cruveilhier has been credited for first describing MS clinically in 1835. He referred to the pathology as "sclerose en taches" or
"en iles" but described it as a disease of the spinal cord (DeJong, 1970). At about the same time, Robert Carswell made a number of drawings of the pathological states of MS (DeJong, 1970). However, it was not until later in the century that Jean Martin Charcot (1877) recognized MS as its own entity, separate from other neurological diseases such as neurosyphilis (Hashimoto & Paty, 1986).

Diagnosis and Symptoms

Problems of diagnosis. Due to the nature of the disease, diagnosis is difficult and many patients have been misdiagnosed (Burnsfield & Burnsfield, 1982). In the past, patients with other neurological diseases may have been included in clinical studies of MS (for a review, Rao, 1986). Conversely, individuals who may have been afflicted with MS may have been misdiagnosed as suffering from psychiatric conditions such as hysterical conversion reaction (Langworthy, 1948). For example, Buzzard claimed in his 1897 paper that due to the transient nature of the symptoms and the seemingly spontaneous recovery without treatment, many patients (especially women) were considered to be suffering from hysteria. This lack of diagnostic precision may have resulted in inaccurate prevalence estimates of psychological problems in MS patients. Although these diagnostic issues are not fully resolved, more formal clinical diagnostic criteria have been employed and are used in conjunction with more definitive
laboratory tests (Poser, Paty, Scheinberg, McDonald, Davis, Ebers, Johnson, Sibley, Siberberg, & Tourtellotte, 1983).

Cognitive Impairment

Early investigators found that in addition to motor/sensory problems, intellectual and cognitive deterioration could be a feature of the disease (Ombredane, 1929). Charcot (1877) indicated that MS patients had a particular mental state which he described as "...Marked enfeeblement of memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality" (page 194). Ombredane (1929) observed 72% of his patients to have deterioration of memory ranging from minimal to severe. Emphasizing the occurrence of intellectual deficits, Surridge (1969) found almost two thirds of his patients to have intellectual impairment. Jambor (1969) found his patients to have general and specific intellectual impairments. The most marked deficits were general intellectual efficiency, non-verbal reasoning and memory functions. In contrast to these high rates of cognitive impairment, Cottrell and Wilson (1926) noted the relative rarity of intellectual deficits in their patients and suggested that cognitive impairment occurred only in long standing cases, and that even then it was confined to a small subgroup of patients.

The variations in definition or scope of mental symptoms which are reported in the earlier literature make it difficult to
determine the relative prevalence of cognitive and affective symptoms. For example, no distinction was drawn between cognitive and emotional disturbances; rather, they were typically grouped under the general rubric of 'mental symptoms' (Dercum, 1912). Although early reports recognized often both phenomena the two were not always separated in the presentation of data (Berger, 1905). Charcot's (1877) original descriptions alluded to both types of symptoms with his reference to "foolish laughter for no cause" and "marked enfeeblement of memory". Although such qualitative description may capture the clinical presentation of some patients, the lack of separation between cognitive and emotional problems in empirical studies does not allow for accurate estimates of emotional or cognitive impairment in the MS population (for a review, Rao, 1986).

The variation in these reports of so-called "mental" symptoms indicated the need for a clearer definition of psychological and affective disorders in MS. Recent studies have attempted to clarify this issue by using more formal and diverse assessment techniques (Rao, 1984; Minden & Schiffer, 1990).

Emotional Symptoms: Mood and Personality Changes

Early researchers were aware of the changes in mood that accompanied the disease (Trimble & Grant, 1982). Since the time of Charcot, the mood state known as euphoria has been associated with MS. Brown and Davis (1922) stated that a large percentage
of their patients (71\%) seemed too cheerful and unconcerned about their disease. In addition, Cottrell and Wilson (1926) found 63\% of their sample to be euphoric and 84\% appeared to be eutonic (a sense of physical well being as opposed to mental well being). One problem regarding the definition of euphoria was the subjective rating by the clinician as to what might constitute being "too cheerful". In addition, emotional lability (inappropriate changes in mood for no apparent reason) has been discussed (Charcot, 1877; Cottrell & Wilson, 1926).

Early studies on the subject of depression revealed that depression was more common in MS (reviewed in Minden et al, 1987) in comparison to the general population (3-9\%, Gregory & Smeltzer, 1983). Cottrell and Wilson (1926) found 10\% of their sample to be depressed while Sugar and Nadell (1943) found seven of their 28 patients (25\%) to be depressed. Ombredane (1929) believed that depression did occur but occurred only early in the disease. However, depression gave way to euphoria later in the disease and tended to be accompanied by intellectual slowing. In antithesis to the above findings, Brown and Davis (1922) were unable to find any evidence of depression in their sample.

The idea of a premorbid personality which predisposes certain persons to develop MS was discussed by Langworthy (1948). He suggested that MS patients had poor premorbid adjustment, characterized by immaturity in interpersonal relationships and emotional displays. A later trend in
personality research stemmed from the appearance of the Minnesota Multiphasic Personality Inventory (MMPI). MS patients tended to have elevated scores on the so-called "neurotic triad" (Baldwin, 1952). Specifically, MS patients tend to have elevated scores on the hypochondriasis, depression and hysteria scales.

The older research was plagued by confounding variables, imprecise definitions and inconsistent assessment measures. Some problems addressed in earlier research are not yet clear. However, definite progress has been made with more recent investigations using more explicit criteria and more sensitive measurement techniques.

Current Understanding of MS

Diagnostic Criteria

MS is a difficult disease to diagnose but in recent years diagnosis has been facilitated by the introduction of a set of guidelines (Matthews, Compston, Allen, & Martyn, 1991). The first systematic attempt to establish a criteria for diagnosis was published in 1965 (Schumacher, Beebe, Kibler, Kurland, Kurtzke, McDowell, Nagler, Sibley, Tourtellotte, & Willmon, 1965). This diagnostic system was used to select only patients who had definite MS for clinical trials and thus permitted better generalization of findings. Six requirements must be fulfilled in order for the diagnosis of clinically definite MS to be made.
These are as follows: 1) there must be objective abnormalities on physical examination; 2) these abnormalities must reflect primarily white matter dysfunction; 3) from neurological exam or history, there must be evidence of involvement of two or more separate parts of the central nervous system that occurred at separate times (disseminated in time and space); 4) the onset of symptoms is within the expected age range (10-55 years); 5) the pattern must fit into one of the following courses: at least two clear-cut episodes of functionally significant worsening, each lasting over 24 hours and separated by at least one month, or a slow progressive development over at least 6 months; 6) a competent physician must be satisfied that no other disease can explain the symptoms (Schumacher et al., 1965).

More recently, a set of criteria was proposed by Poser et al. (1983) which expanded on Schumacher's and included greater specificity. This new set of guidelines incorporates the results of ancillary tests such as magnetic resonance imaging (MRI) for enhancing the confidence in the diagnosis and include both probable and possible diagnostic categories. Although medical researchers have begun to limit clinical trials to including only those with a "definite" or "probable" diagnosis, these additional groups can be used to add greater flexibility to the research design (Rao, 1986).

The confidence in diagnosis of MS has been an ongoing concern and misdiagnosis is not limited to older research. A
high false positive rate still occurs in the diagnosis of MS. Herndon and Brooks (1985) report that up to 10% of people diagnosed as having the disease in fact do not have MS but in actuality have other specific diagnoses. More recent research has suggested that the symptoms of MS are still occasionally mistaken for psychiatric disorders. Skegg, Corwin & Skegg (1988) found that 16% of their sample of 91 MS patients were initially referred to psychiatrists before a subsequent diagnosis of MS was made. To date, no specific laboratory test has been found to unequivocally identify MS. Although new laboratory tests such as oligoclonal banding or evoked potentials can be helpful, the diagnosis remains a clinical one (Hashimoto & Paty, 1986). So until a laboratory test is found to differentiate MS from other clinical entities with certainty, this problem remains.

Motor/Sensory Losses

Impairment of motor and sensory systems are the hallmark symptoms of MS (Matthews, Compston, Allen, & Martyn, 1991). The sensory losses may be double vision, optic neuritis (loss of vision in all or parts of the visual field), loss of tactile discrimination ability, bladder and bowel dysfunction and poor limb position sense whereas motor problems may be weakness, pariesis, or loss of coordination (Gulick, 1991). According to Matthews et al. (1991), the incidence of initial symptoms has been broken down as follows: motor weakness 40%; optic neuritis
22%; paraesthesiae 21%; diplopia 12%; vertigo 5%; bladder and bowel disturbance 5%.

Assessment of physical disability. The physical signs and symptoms are the basis of clinical diagnosis (Sibley, 1990). A scale was developed to identify the extent of neurological disability in MS patients (Kurtzke, 1955) and is the accepted system for comparing subjects. Eight functional systems are examined with this scale: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, mental, and other. Each of the functional systems with the exclusion of the "other" scale, is graded from normal (grade 0) to maximally impaired (grade 5 or 6), while the "other" scale is graded as a 0 (none) or 1 (present). The functional systems are mutually exclusive in terms of neuroanatomy. A later expansion of the scale (Kurtzke, 1983) included a scale for evaluating overall physical disability in MS. This 10 point rating scale, termed the expanded disability status scale (EDSS), graded by increments of 0.5 classifies MS patients from 0 (no disability) to 10 (death due to MS). A turning point occurs at the 6 point mark indicating that the patient needs a cane/crutches for ambulation.

Cognitive Impairment

Cognitive changes are now a recognized feature of the disease process in Multiple Sclerosis (for a review see Rao, 1986). The literature suggests that: 1) there is little doubt
that cognitive dysfunction is often associated with MS (VanderPlate, 1984) and 2) cognitive impairment is more prevalent than early researchers had estimated (Rao et al., 1991b); and 3) there is a general consensus as to which functions are affected and which functions are spared (Matthews et al., 1991).

**Frequency of cognitive impairment.** The method by which cognitive disability is assessed has profound effects on the observed prevalence (Peyser et al., 1980). Standard neurological mental-status examination generally produce lower estimates of cognitive impairment than do more extensive neuropsychological tests. In earlier estimates of cognitive impairment, cognitive problems may have been missed due to the emphasis placed on sensory/motor impairments or were assumed to be the direct result of the sensory/motor impairment (Reitan et al., 1971).

Several studies have employed the neurological mental status exam or neurological exam in order to assess the nature or degree of cognitive problems in MS (Rabins, Brooks, O’Donnell, Pearlson, Moberg, Jubelt, Coyle, Dalos, & Folstein, 1986; Beatty & Goodkin, 1990). These screening devices tended to yield rather low results. A study by Kahana et al. (1971), using a neurological examination, found 25% of their sample of MS patients to be intellectually impaired. Peyser et al. (1980) found only 13% of their sample to be cognitively impaired on the standard neurological examination.
Neurological screening devices, although quick and relatively inexpensive, have been found to be insufficiently sensitive to detect cognitive impairment in the MS patient (Peyser et al., 1980). For example, Peyser et al. (1980) found that half of those patients who were described as having intact mentation on a standard neurological assessment in fact were impaired on neuropsychological examination. More recent studies have found that the prevalence of cognitive problems in MS is greater using more sensitive neuropsychological tests than with a standard mental status exam (Franklin et al., 1989). Staples and Lincoln (1979) studied 29 MS patients with severe, long standing disability with 29 muscular dystrophy patients matched for age, sex, and socioeconomic status. Sixty percent of the MS patients were found to have some evidence of memory impairment. Furthermore, Rao et al. (1984) found that 43% of their sample of chronic progressive MS patients had mild disruption of memory while 21% exhibited moderate to severe memory problems.

Research has shown that not only is intellectual deterioration a feature of the disease process, but it may also be evident in the early stages of the disease (van den Burg, Zomeren, Minderhoud, Prange, & Meijer, 1987; Klonoff et al., 1991; Beatty et al., 1989). A study by Canter (1951) was instrumental in determining that cognitive deficits are evident in the early stages of the disease. Canter examined army veterans who developed MS after entering the service. Significant intellectual losses were reported in these
individuals on the Army General Classification Test even though they were in the early stages of the disease. In addition, intellectual impairment was evident in a test retest situation after a six month period on the Wechsler-Bellevue Memory Test, further suggesting that cognitive deficits are seen early in the disease. Ivnik (1978) reinforced these findings with his longitudinal study indicating that deterioration of a number of cognitive functions was evident on average three years later.

**Pattern of cognitive impairment.** Reviews of the literature suggest that there is general agreement to the cognitive abilities that are spared and those that are impaired in MS (Matthews et al. 1991). For example, several authors have demonstrated differential impairments in memory both verbal and non-verbal and immediate and delayed recall (Jambor, 1969; Rao & Hammeke 1984; Staples & Lincoln, 1979). A review by Rao (1986) summarizes that the capacity of short term memory tends to be spared, while retrieval strategies from short and long term memory tend to be impaired. Minden et al. (1990) have found 30% of their patient sample to have severe memory impairment, 30% to have moderate impairment of memory and 40% to have mildly or unimpaired memory. Similarly, Rao et al. (1984) found 21% of their sample to have moderate to severe memory impairment, 43% to have mild problems and the remaining 36% to be comparable to normals with no apparent memory deficits. These findings suggest that MS patients can be differentially affected with respect to memory functions.
Several researchers have indicated that the performance Intelligence Quotient (IQ) is affected, possibly due to the reliance on motor skills whereas Verbal IQ is less affected in MS (Reitan et al., 1971; for a review see Rao, 1986). Accordingly, the Full scale estimate will be lower. In a review of the literature, Rao (1986) demonstrated that in a large number of studies (eight), both the Verbal IQ and the Performance IQ were deficient, however, the average Verbal IQ was higher than the Performance IQ by seven to 14 points. The results of the literature review suggest that although Verbal IQ and Performance IQ decline in MS, verbal/linguistic performance may not be as severely affected as visuomotor processes.

Furthermore, deficits in abstraction or conceptualization have been reported (Beatty & Gange, 1977). Specifically, MS patients tend to perseverate, have difficulty shifting sets and responding to feedback (Peyser et al., 1980; Rao, 1986).

Although a chronic-progressive (C/P) disease course is associated with greater impairment of cognitive functioning, the pattern of impairment in the relapsing-remitting (R/R) disease course is similar to that seen in the C/P form (Heaton, Nelson Thompson, Burks & Franklin., 1985). As a general rule, memory functions, both verbal (Klonoff et al., 1991) and nonverbal (Grant, McDonald, Trimble, Smith & Reed, 1984), verbal fluency (Beatty et al. 1989), and perceptuomotor speed (van den Burg et al., 1987) seem to be impaired in early stage R/R MS. This
typical pattern tends to leave verbal intellectual and primary language abilities unaffected (Rao, 1986).

Several studies in the MS literature have shown MS patients perform more poorly on the Word Fluency Test than normal controls or other neurological disease control groups (Beatty et al., 1989; Caine, Bamford, Schiffer, Shoulson & Levy, 1986; van den Berg et al., 1987). This test is of particular interest because performance should not be impaired by the motor/sensory losses associated with MS. In the Word Fluency Test, the patient names as many words as he/she can think of that begin with a specific letter in one minute. This procedure is done for three letters, F, A, and S. This particular test is known to be sensitive to brain damage (Benton 1968).

Relation Between Motor\Sensory Loss and Cognition

Usually the greatest difference in mean scores on neuropsychological tests between MS patients and normal controls occur on tasks that load on motor/sensory functioning (for a review, Peyser & Poser, 1986; Ivnik., 1978). Beatty and Gange (1977) found that their MS patients performed much worse than controls on tests such as Finger Tapping, Foot Tapping, Grip Strength, Grooved Pegboard, Static Steadiness, all of which have a substantial motor component. Klonoff et al. (1991) found similar results on variables measuring motor functions in their early stage R/R patients.
A study by Reitan et al. (1971) addressed the relationship of motor impairment and cognitive skills. They state that the inconsistencies in the literature on the prevalence of cognitive impairment is dependent on the types of tests used. They argue that if assessment of cognitive function is based on tests measuring verbal information skills, MS patients would show little impairment. However, if tests of motor/problem solving were used for assessing these same patients, their performance would appear to be greatly deficient. With this rationale, their study divided all tests of the Halstead neuropsychological battery into categories depending on which functions each test was assumed to assess. The categories ranged from groups of tests which involve primarily motor skill (finger tapping), to those tests that have a large percentage of motor component but involve a problem solving component as well (Tactual Performance Test, Digit Symbol), finally, to tests which have virtually no motor component which load on such functions as memory or abstract conceptualizations (Halstead Category Test). Results of this study indicated that on all 29 tests, the MS group had lower mean scores. However, the greatest difference was found on the categories containing tests involving motor components. The MS group also performed significantly worse than the controls on all other tests, even tests without substantial motor component. The results of this study suggest that motor impairment may worsen performance on tasks requiring these skills, but the poorer performance on cognitive tests by MS patients cannot be attributable to deficits in motor/sensory functions.
Cognitive impairment can be detected in MS patients who exhibit no appreciable physical symptoms (Klonoff et al., 1991). However, if examination is not comprehensive, this impairment may not be detected. In early stage MS patients, Jouvent, Montreil, Benoit, Lubetzki, Tournier-Lasserve, des Lauriers, Widlocher, Lhermitte and Lyon-Caen (1989) found 46% to have cognitive impairment and Klonoff et al. (1991) found their mild (Kurtzke EDSS \(\leq 6.0\)) R/R patients to be deficient relative to the control group on 50% of the neuropsychological tests. Therefore, it is fairly clear that patients with mild physical disease can have intellectual deterioration.

The literature suggests that there is a non-significant or weak relationship between the degree of the patient's physical disability and his/her intellectual/cognitive ability. Several studies have now investigated this relationship and found no correlation between Kurtzke scores and cognitive ability. A study by Marsh (1980) assessed 48 definite MS patients representing varying disease courses and found no significant correlation between severity of illness and cognitive impairment. van den Burg et al. (1987) examined 40 mild stage MS patients and also found no relationship between intellectual ability and MS advancement - namely length of illness and disability status scores. A study by Lyon-Caen, Jouvent, Hauser, Chaunu, Benoit, Widlocher, & Lhermitte, (1986) also supports this finding. They found no correlation between degree of handicap (EDSS scores) and cognitive impairment in their sample of 21
probable and definite MS patients and nine patients with recent onset optic neuritis.

Other investigations have found a significant but weak correlation between performance on neuropsychological tests and disability status. Beatty et al. (1990) found that EDSS correlated weakly with the Symbol Digit Modalities test, a test with a heavy motor component (r = .62). However, when the motor component is removed, as in the immediate recall from short term memory, the correlation drops to r = .31. Some of the above studies examined selected ranges of disability scores and may suffer from attenuation. Hence, the resulting correlations which include the entire spectrum of physical disability may be the better estimate of the relationship between physical disability and cognitive ability.

Furthermore, it has been suggested that the longer individuals have had the disease, the more likely they are to have psychological problems (Marsh, 1980). With increased sophistication of specific neuropsychological tests this statement has not been consistently verified (Beatty et al., 1990). Due to the great variability of the disease, people who are in the early stages of the disease may have many physical and cognitive problems whereas others who have had the disease for a number of years may follow a relatively benign course (Matthews et al., 1985). A study by Beatty et al. (1989) found evidence to suggest that the length of time a person has had the disease is
related to but not a good predictor of the degree of cognitive impairment. Other studies using cross sectional designs also have not revealed a relationship between cognitive decline and duration of illness (Ivnik, 1978, Marsh, 1980; Rao et al., 1991a). The lack of a significant relationship between cognitive functioning and duration of illness underscores two major themes of this project. First, cognitive impairment need not be a late stage effect but may in fact be present at disease onset (Young, Saunders & Ponsford, 1976). Second, the cognitive impairment may occur in the absence of profound motor/sensory deficits (Franklin et al., 1989).

Depression

Depression is a frequent concomitant of MS (Schiffer et al., 1983; Minden & Schiffer, 1990). MS patients are thought to be more depressed than would be expected given their level of disability (Rabins et al., 1986) and more depressed than patients with other disabling diseases such as Muscular Dystrophy (Surridge, 1969), mixed neurological disease (Whitlock & Siskind, 1980), or spinal cord injured (Dalos, Rabins Brooks, & O’Donnell, 1983). In a recent study and review of the literature, it was noted that the true prevalence of depression in MS lies in the range of 27-54% (Minden & Schiffer, 1990).

Depression as an early and late stage effect. Depression has been recognized as an early (Young et al., 1976) as well as a
late stage effect of MS (Minden et al., 1987). In fact some researchers have speculated that depression may be one of the presenting symptoms of the disease (Goodstein & Ferrell, 1977). Furthermore, Whitlock and Siskind (1980) examined MS patients and other neurological controls and found that the MS patients they examined were more likely to have had psychiatric episodes predating the onset of their disease. Their results led Whitlock and Siskind to speculate that the early depressive episodes may in fact have been initial MS symptoms.

Definition and Description of depression. It is clear that depressed mood is a common occurrence in MS (Whitlock & Siskind, 1980; Schiffer et al., 1983; Minden et al., 1987;). In terms of definition of depression, the mood change reported by these patients in some cases may not be classified as clinical depression. Most studies which identify "depression" in an MS group employ a self report measure such as the Beck Depression Inventory (BDI) or Zung Self-Rating Depression Scale (Whitlock & Siskind, 1980; Rao et al., 1991a). The reported differences in these depression measures between the MS group and normal controls may be statistically significant but the resulting mean scores may still be in the normal range. For instance, one study (Beatty et al., 1989) reported a significantly increased level of depression (as assessed by the BDI) in R/R patients but yet the resulting mean on the BDI was only 7.5. According to Beck, Ward, Mendelson, Mock and Erbaugh (1961), a score of 7.5 is indicative of "mild" depression, and not until a score of approximately 20
would a person be classified as having "severe" depression. In contrast, Schiffer et al. (1983) found that 37% of their MS group had had at least one major depressive episode according to the third edition of the Diagnostic and Statistical Manual (DSM-III). The different results between these two studies may stem from the fact that Beatty et al. (1989) looked only at mild stage R/R patients whereas the latter study was interested in older, more diverse sample.

In addition to the varied definitions of depression found in the MS literature, the choice of rating scales has been problematic. Items included in certain self report measures of depression may well be confounded with the symptoms of the disease (Minden & Moes, 1990). This problem may present itself with the MS patient reporting more so called depressive symptoms thereby artificially inflating their depression scores. In the Beck Depression Inventory, three of the 21 items may be confounded with the disease, the Zung self-rating scale has two items corresponding to psychomotor problems, and a further eight items which tap into physiological disturbance (Lezak, 1983). The Zung has a total of 20 items and the proportion of items which might be assessing the physical symptoms of MS is high (40%), thereby making this measure a questionable choice for determining the extent of depression in MS patients. The depression scale of the MMPI as well contains a large number of items which could possibly measure somatic body complaints characteristic of those found in MS. Schiffer (1990) has stated
that the MMPI is a poor choice for use in medical populations. Therefore, when interpreting the results of such studies, caution must be used as the estimate of depression often contains items that are actual symptoms of the disease (Marsh, Hirsh, & Leung, 1982).

Interaction Between Depression and Cognitive Impairment

Evidence for a relationship between cognitive impairment and depression in MS can be found in the literature (Goldstein & Shelly, 1974; Weingartner & Silberman, 1982). It has been documented that depressed patients can have lowered scores on cognitive tests. A review by Weingartner and Silberman (1982) discuss the effects of depression on cognition. They summarize evidence suggesting that depression can lead to decreased memory, attention and information processing ability. Depression can produce both qualitative and quantitative changes in thought processes. A correlational study by Stenager, Knudsen and Jensen (1989) found that as physical disability (EDSS) increases, so do depression scores and furthermore, patients who are most severely physically disabled are those with the greatest impairment in cognitive function. Unfortunately, this study does not supply the correlation coefficients that lead to the conclusions. Therefore, it is not possible to determine the strength of these relations.
Some authors have argued that cognitive deficits are at least partly attributable to the affective disorders seen in MS. Goldstein and Shelly (1974) found that cognitive tests were unable to discriminate between MS and neuropsychiatric patients and from reviewing the literature, they found that MS patients show affective disturbance on the MMPI. These two facts lead them to speculate that affective disturbance may be partly at the root of the intellectual deficits (Goldstein & Shelly, 1974). However, as previously mentioned, the MMPI may not be the best scale to assess affective disturbance in the MS patients that these researchers observed (Marsh et al., 1982).

Several studies concluded that depression and cognitive deficits are not related (Schiffer et al., 1983; Peyser et al., 1980). Schiffer et al. (1983) compared two groups of MS patients: those who had primarily cerebral involvement and those who had spinal cord and cerebellar involvement. The cerebral group was found to be more depressed and to have had more depressive episodes than the spinal cord/cerebellar group. There were no differences in intellectual functioning between the two groups suggesting that depression is not predictive of cognitive dysfunction. Furthermore, a study by Peyser et al. (1980) came to similar conclusions that cognitive dysfunction and depression are independent of one another. They found that 54.7% of their MS group were considered cognitively impaired but found no evidence to suggest that this impairment was due to depression (Peyser et al., 1980). Finally, Staples and Lincoln
(1979) summarized results of several studies concluding that "Intellectual deterioration occurs in MS as a result of central nervous system (CNS) involvement and is not found as a result of mood changes..." (Staples & Lincoln, 1979 p. 153).

The interaction of cognitive impairment, depression, and motor/sensory problems in MS has not yet been elucidated. There are few studies in the literature dealing with the relative effects of both motor/sensory losses and depression on cognitive ability especially in the mild stages of the disease. Jambor (1969) has addressed this issue, but only superficially. The patients he studied had intellectual impairment and he stated that "MS patients tend to get symptoms of anxiety and depression in the early stage of their lower intellectual efficiency" (Jambor, 1969, p. 773).

Social Disability

What can MS patients no longer do? MS can impose limits on a person's ability to live a normal life (Sandford & Petajan, 1990). For example, getting around can be a major drawback for those MS patients who have motor/sensory problems (Gulick, 1991). Similarly, bowel and bladder problems can discourage patients' participation in activities because of possible incontinence (Gulick, 1991). Depression generically is characterized by a reduced motivational state resulting in an inability to interact with others (DSMIII-R). Moreover, cognitive losses such as
memory problems, or impaired ability to think abstractly may interfere with the quality of life experienced by these persons. These three spheres (sensory/motor losses, depression, or cognitive problems) have been recognized as having disabling effects on the quality of life of the MS patient (Sandford & Petajan, 1990; Stenager et al., 1989). The relative effects of the impairments faced by MS patients on social disability have not yet been established. Table 2.1 summarizes the literature on the subject of the symptoms of MS and their effects on the daily living activities of the patient.

The daily living problems of the MS patient have been discussed in Chapter 1. Sandford and Petajan (1990) have tried to quantify the effects of MS on daily living activities with the Sickness Impact Profile (SIP). The SIP is a scale which characterizes the effects of an illness on physical and psychosocial activities. They state that MS patients are significantly more dysfunctional on 13 of the 15 areas of daily living than are rheumatoid arthritis patients, cancer patients and normal controls.

**Quality of life can be influenced by employment status.** When assessing a person's quality of life, their occupation is of great importance. Neff (1985) indicated that work fulfills human needs for a feeling of personal worth and self esteem and
it contributes to one's identity. Work is needed: 1) in order to obtain material goods, 2) to be active, and 3) to be respected by others. A disease like MS, with its unpredictable course, can interfere with the ability for one to carry out what used to be normal aspects of employment. The changes that occur can force changes in typical work patterns and possibly lead to reduced work load or cessation of employment.

A survey conducted in the US indicated that four out of ten MS patients were dismissed from their positions or left their employment as a result of their disease. A further one out of ten persons with MS changed jobs due to their disease. The survey went on to point out that those MS patients who remained employed continued to work but worked fewer hours than other, non MS, co-workers (US Department of Health and Human Services, 1985). In fact this figure may underestimate the prevalence of unemployment as another study quoted that 77% of their sample of MS patients were unemployed (LaRocca, Kalb, Kendall & Scheinberg, 1982).

These results suggest that MS can interfere with a person's ability to carry on with productive employment at any stage of the disease. According to Neff's (1985) definition, a person who has ceased employment should be negatively affected by this change of status resulting in a lowered opinion of personal worth and self esteem. The ill effects of forced cessation of employment on MS patients has not been adequately studied.
The effects of cognitive impairment on social functioning. There are few reports in the literature dealing with the effects of cognitive problems on the ability of MS patients to remain active in the work force. A study by Franklin et al. (1989) looked at individuals who were minimally impaired (Kurtzke EDSS=3.2) (Kurtzke, 1983). Two thirds were sufficiently cognitively impaired to preclude productive employment. An investigation which examines the impact of cognitive dysfunction on psychosocial functioning in MS is a study by Rao et al. (1991b). Rao et al. (1991b) identified a cognitively impaired subgroup of MS patients who were in the mild stage of the disease as measured by the EDSS (4.1)(Kurtzke, 1983). Their criteria for cognitive impairment was four or more failed tests on their 31 test battery so their MS group was divided into "impaired" and "intact" groups. There were no differences between the impaired group and the intact group in demographics or length of illness. The impaired group, however, was less likely to be employed and moreover, engaged in fewer social activities.

A further investigation performed by Stenager, Knudsen and Jensen (1991) has looked at the effects of cognitive dysfunction on how socially active a group of MS patients were. These researchers divided their MS group according to EDSS scores and compared the resulting five groups on the Katz Adjustment Scale (a scale designed to estimate the amount of social/spare time activities). They found that physical disability alone was able
to account for the diminished level of social activities. They found that those patients who were minimally impaired (Kurtzke EDSS 1-2) had no decrease in social activities whereas with increasing levels of physical disability, the level of social activities declined. They go on to state that earlier research (Stenager et al., 1989) indicated that there is a high correlation between physical disability and cognitive functioning. Therefore they reasoned that the level of social activities declines with decreasing cognitive ability (Stenager, et al., 1991).

The effects of depression and physical disability. The results of the above studies lend credence to the hypothesis that cognitive dysfunction has its effects on the ability of the MS patient to remain socially active. However, depression and physical disability may also play a role. Table 2.1 summarizes a number of relevant investigations which deal with this issue. Physical disability has been found to have an effect on employment status. LaRocca et al., (1982) found that higher Kurtzke (EDSS) scores (Kurtzke, 1983) were predictive of unemployment in their sample. However Franklin et al. (1989) found that in their sample where the EDSS scores were very low, cognitive impairment alone was able to account for the high rate of unemployment. With respect to social/recreational activities, Stenager et al. (1991) found that increasing EDSS led to a decreased level of sparetime and recreational activities. However, these researchers found no effect in the Kurtzke
## TABLE 2.1
LITERATURE REVIEW ON THE EFFECTS OF COGNITIVE IMPAIRMENT, DEPRESSION AND PHYSICAL DISABILITY ON VOCATIONAL AND RECREATIONAL ACTIVITY IN MS

### INDEPENDENT MEASURES

<table>
<thead>
<tr>
<th>Employment Status</th>
<th>Cognitive Impairment</th>
<th>Physical Impairment (EDSS)</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+Franklin et al. 1989</td>
<td>+La Rocca et al. 1982</td>
<td></td>
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<tr>
<td></td>
<td>-Stenager et al. 1989*</td>
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<tr>
<td>Leisure Activities</td>
<td>+Stenager et al. 1991</td>
<td>+Stenager et al. 1991</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>+Rao et al. 1991b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outlook For Future</td>
<td>?</td>
<td>+Matson &amp; Brooks 1977**</td>
<td>+ DSM III-R (Symptom)</td>
</tr>
</tbody>
</table>

+ had an effect
- had no effect
? no published studies found

* Employment Status used as the Independent Measure and Cognitive Impairment as the Dependent Measure
** Looked at Self Concept vs. changes in Physical Ability
range 1-2. Physical disability has also been found to influence how an MS patient feels about him or herself. Matson and Brooks (1977) looked at self concept in MS patients and found that increasing EDSS led to a lowered self concept in their sample.

Outcome measures such as social disability in MS as a result of depression have been given no consideration in the literature. Both the well recognized psychiatric manual (DSMIII-R, A.P.A., 1983) and The Beck Depression Inventory (Beck & Beamesderfer, 1974) refer to the symptoms of depression as leading to a pessimistic outlook for the future and work inhibition. But, these areas have not yet been specifically addressed in the MS literature.

Rationale and Motivation for the Current Study

The rationale for the current study is to determine whether cognitive impairment is evident in early stage R/R MS and whether being cognitively impaired is predictive of the level of social functioning. There is a paucity of literature on the subject of social functioning in R/R MS. The selection of mild MS patients with no concurrent medical or psychiatric problems in the relapsing-remitting form was a good choice for the current study for four reasons. The subjects that were studied were mildly (or very slightly) physically disabled. The low level of disability provided a group whose physical functioning would not confound to any great degree any changes in cognitive functioning that were
found. Second, one of the dependent measures of the current study is employment status which could easily be influenced by decreased motor/sensory ability. Third, selecting patients who have no history of drug use or psychiatric problems provided a clean sample, free from confounding factors that have been problematic in other investigations. Finally, selecting only relapsing-remitting patients and testing them solely in remission allowed for an estimate of cognition in the stable form of the disease.

The study by Rao et al. (1991b) was the motivating factor to the current study. The Rao et al. (1991b) study is different from the current study in many respects. The sample which was characterized by the Rao group was not only older (mean age 45.7 years), and hence, having a longer disease duration (9.5 years) but also comprised of patients with relapsing-remitting, chronic-progressive, and chronic-stable (38, 19, and 43% respectively) disease courses. Their results can be generalized to an older, sicker, more heterogeneous population. The question that was asked in the current study was whether cognitive impairment has any effect on psychosocial adjustment in early stage, R/R MS patients.

Another difference in the Rao study and the current study is in the proportion of patients who are medicated (42% were taking prescription medication at time of testing in the Rao study). One of the stipulations for inclusion in the current study was
that no drug regimens are currently in progress thereby eliminating one potentially confounding variable. One of the dependent measures used by the Rao study was the Zung Depression Scale. A further difference was the use of the Environmental Status Scale (ESS) which provides an assessment of social handicap as a result of the disease. The current study used the Beck Depression Inventory (BDI) for the measure of depression and data from a structured interview in order to establish the extent of social disability.

Summary

It can be concluded from this review that cognitive, affective, and motor/sensory problems are manifestations of the disease process of multiple sclerosis even in the early stages. One of the important findings of this review is that MS patients can undergo a social disability that can be seemingly out of proportion with their physical symptoms. The correlations between physical disability, cognitive and affective problems have not been found to be consistently high and it is not clear whether these dimensions are independent. The question that is left unanswered is: if the dimensions are independent, how much does each contribute to the social disability faced by MS patients. Recognizing the basis of the social problems that affect the MS patient is of primary importance for treatment planning particularly in the early phases of the disease.
CHAPTER III

METHODS

This chapter will outline the methods to identify whether cognitive impairment exists in early R/R MS and if it has a relation with motor/sensory losses or depression. Furthermore, this investigation will try to determine whether cognitive impairment, or alternatively depression or motor/sensory losses have any effect on the ability of MS patients to cope with everyday life activities. This chapter provides a detailed methodological section outlining subject selection, assessment techniques, and analyses.

Hypotheses and Predictions

Questions

Analysis I. Does there exist a subgroup of MS patients who are cognitively impaired? Is the cognitive impairment specific or is it a widespread decline of function? The impairment is hypothesized to be unrelated to demographic such as age, level of education, socioeconomic factor or disease-related variables such as EDSS scores or length of disease.

Analysis II. Is the observed subgroup with cognitive impairments less likely to be employed? Is the impaired subgroup less likely to be engaged in social or recreational activities?
Do the types of activities that are undertaken differ as a function of group membership? Is there any relation between group membership and a pessimistic outlook for the future?

Analysis III. Does there exist a subgroup of MS patients who are depressed? How does being depressed interfere with vocational, social/recreational activities and outlook for the future? Do the patients who are the most physically disabled in the MS sample have limited vocational or social/recreational activities or a more pessimistic outlook for the future? How does cognitive impairment rank as a predictor of social disability in comparison to depression and motor/sensory losses? Are these phenomena (cognitive impairment, depression, physical disability) independent or is there much overlap in terms of group membership?

Predictions

The third analysis was performed with respect to certain predictions. The literature search in chapter two (See Table 2.1) was the source from which these predictions were made. Table 3.1 summarizes the predicted outcomes of being in the impaired range for each symptom.

Referring to Table 3.1, It was predicted that being cognitively impaired would have an adverse effect on all three of the social outcome measures. Those who are cognitively impaired
TABLE 3.1
PREDICTED RESULTS OF THE EFFECTS OF COGNITIVE IMPAIRMENT, DEPRESSION AND PHYSICAL DISABILITY ON VOCATIONAL AND RECREATIONAL ACTIVITIES

INDEPENDENT MEASURES

<table>
<thead>
<tr>
<th>COGNITIVE IMPAIRMENT</th>
<th>PHYSICAL DISABILITY (EDSS)</th>
<th>DEPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPLOYMENT STATUS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DEPENDENT PERSPECTIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEISURE ACTIVITIES</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>OUTLOOK FOR FUTURE</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

3/3 1/3 2/3

(+ = Effect)
(- = No Effect)
should be less likely to be employed, the level of social/recreational activities should be reduced and the outlook for the future should be pessimistic. Physical disability, it was predicted, should only affect one of the three measures. Those patients who are physically impaired should be less likely to be employed but the social and recreational status should be unaffected and their outlook for the future should be fairly optimistic. The number and type of social and recreational activities are more able to be changed in order to compensate for increased physical disability. However, the requirements of the work place are less under the control of the individual and thus not able to be changed. These predictions were forecast as motor/sensory problems faced by this particular sample are very minimal. The symptoms of depression can include work inhibition and pessimism (towards the self and future) as some self report measures (Beck & Beamesderfer, 1974) and diagnostic criteria (DSMIII-R, A.P.A., 1983) have suggested. Therefore, it was predicted that being depressed should lead to two of the three measures being affected. Those MS patients who are depressed should be more pessimistic towards the future and be less likely to be employed.

Sampling Procedures

A large database has been established which includes neuropsychological test scores, MRI scans, neurological
assessments and interview data for MS patients and normal control subjects. The MS patients were considered for inclusion to the study during their visit to the UBC MS clinic. One of five neurologists administered a standard neurological exam and rated the severity of disability with the Kurtzke EDSS. If the subject met the criteria, neuropsychological assessment was completed within a month of their clinic visit. If any changes in physical status were reported, the patient underwent another neurological exam on the day of the neuropsychological assessment. The entire neuropsychological procedure, interview and MRI scan required one day to complete. Each subject gave informed consent for the procedure.

**Subjects**

MS patients were selected providing that they met the following criteria: 1) diagnosis of clinically definite MS (Poser et al., 1983) with relapsing remitting course and in remission at time of testing; 2) in the early or mild stage of the disease and functionally independent (Kurtzke ≤6); 3) aged less than 50 years and having been diagnosed before the age of 40 years; 5) having had no complicating drug regimens, medical problems concurrent with MS or psychiatric disorders predating the diagnosis of the disease; 6) no excessive recreational drug use. Each subject was asked to recruit a same-sex, non-relative who was similar in terms of socioeconomic and educational status to act as a control who meets the above criteria where applicable.
Clinically definite MS was defined according to Poser et al. (1983) criteria. According to this criteria, clinically definite MS (CDMS) can be diagnosed if the patient has had two attacks with clinical evidence of two separate lesions or two attacks, clinical evidence of one lesion and paraclinical evidence of another, separate lesion. Paraclinical evidence may be elicited by procedures such as evoked potentials, Computerized Tomography (CT) scans, MRI, oligoclonal banding (abnormal cerebrospinal fluid in the form of a pattern of multiple monoclonal globulins seen in 90% of patients with CDMS) or the hot bath test (the heat of the hot bath can exacerbate the symptoms of MS and this test has been used as a crude diagnostic test). Relapsing remitting MS was defined as a disease course characterized by "relapses" or a worsening of a preexisting symptom or appearance of a new symptom which lasts for at least 24 hours which is followed by a "remission" or recovery or partial recovery of function (Hashimoto & Paty, 1986). Relapses must be separated in time by at least one month for a R/R course to be diagnosed.

Assessment techniques

Neuropsychological Tests of Interest: Administration

The neuropsychological battery that was used to assess cognitive impairment was administered by a trained psychometrician, and the order in which the tests were presented was random. The battery was comprised of 23 different tests.
which measured a variety of cognitive/intellectual and sensory/motor functions of which 13 were chosen for the current investigation. The tests which were chosen have been documented to be performed poorly by MS patients (Klonoff et al., 1991, Rao, 1986) and were representative of a large number of functions tested by the larger battery.

**Word Fluency Test (FAS).** The examiner presents the subject with a letter of the alphabet and instructs him or her to say as many words as he or she can that begin with that letter. The patient then proceeds to recite words in the given category over a one minute trial. The subject is instructed not to use words that are normally capitalized (proper nouns) or to add many suffixes to one root word. The letters F, A, and S were used. The score was the total number of admissible words for the three letters. This test was of interest as it does not seem to have any appreciable sensory or motor component to it. For example, Beatty et al. (1989) reported a correlation of -.37 for the Word Fluency Test and EDSS. Similarly, a correlation of .25 has been found between performance on the Word Fluency Test and the Grooved Pegboard test (both hands) (Good et al., unreported data). In addition, deficits in neuromuscular components of speech production have not been reported to occur early in the disease (Matthews et al., 1991). Therefore, should a low score be obtained, sensory/motor losses cannot adequately explain this deficit. This test was used as a criterion test which divided
the group of MS patients into a cognitively impaired subgroup and a cognitively normal subgroup.

Beck Depression Inventory (BDI). For this self report measure of depression, the subject selects the one statement out of four statements which most generally applies to them. There are a series of twenty one categories in which the statements in each category were rated from 0 to 3. The score is the sum total rating of all the categories. The higher the score, the more depressed the patient. According to Beck, Ward, Mendelson, Mock and Erbaugh (1961) a score of approximately 17 translates to a moderate level of depression and a score over approximately 20 is indicative of severe or clinical depression. The BDI is a good measure of depression for the MS sample as it has only a few items which are sensitive to somatic body complaints (Lezak, 1983).

WAIS-R FIQ, VIQ and PIQ. The Wechsler Adult Intelligence Scale (WAIS-R) (revised in 1981) is a composite battery test composed of eleven subtests. The subtests are categorized into Verbal Intelligence quotient (VIQ) comprised of six subtests and Performance Intelligence quotient (PIQ) which comprises five subtests depending on the underlying ability being measured. The Full scale Intelligence Quotient (FIQ) is a standardized score which is incorporated from all eleven subtest raw scores. These three estimates are standardized according to the age of the subject. This test is used extensively in MS research and is a
good benchmark upon which to compare results of the current study to other MS studies.

**Grooved Pegboard.** A motor sensory task which involves placing small pegs into slotted holes within a board. The pegs are keyhole shape in cross section. The board is a small box with a 5 X 5 grid with each hole able to accommodate each peg. The slotted holes are angled in different directions therefore the pegs must be first arranged in the proper orientation before they can be inserted. The obtained score is the time taken to insert all pegs with 1) right hand; 2) left hand; 3) both hands. This test was chosen as it requires the integrity of the sensory system, speed, and coordination, all three of which tend to be impaired. It is a sensitive test for motor/sensory function in MS patients.

**Category Test (Halstead, Abbreviated form).** A stimulus pattern is presented on a screen in front of the subject which consists of figures usually four in number at one time. The subject also has access to four buttons, numbered one to four. The stimulus figure(s) will, in some fashion, form a pattern which corresponds to one of the numbers on the buttons. For example, the first (practice) pattern involves presenting the subject with the Roman numerals I through IV and the subject must press the corresponding button (1 through 4). A later pattern involves presenting the patient with four objects, three of which are the same. The correct answer is to press the button
corresponding to the position of the odd figure (1st, 2nd, 3rd, 4th). The rules for determining which button to press change periodically in a predetermined fashion. The subject is not told what is the selection rule but he/she can monitor his/her progress as a bell is sounded when a correct button is pressed and a "buzz" is sounded when an incorrect button is pressed. The score is the number of errors and is thought to measure abstracting ability.

Trail Making Test (Trails B-A). Trails A involves joining consecutively numbered spheres in a timed trial. Trails B involves again joining spheres but this time the subject must alternate between numbers and letters in sequential order (1-A-2-B-3-C etc). There are the same number of spheres on each sheet. Trails B is thought to involve a conceptual tracking/information processing component which adds to the time for that trial. By subtracting the time taken for A from the time taken for B, a crude measure of information processing time results.

Sentence Repetition. The sentences are presented to the subject who must repeat them word for word (immediate recall). Each sentence is one syllable longer than the previous one. The beginning sentence has 10 syllables and the longest one has 26 syllables. The score is the number of sentences remembered correctly and is a measure of immediate verbal recall.
Memory for Objects. Fifteen items are placed on a tray and the subject is allowed to view them for one minute. The tray is taken from view and the subject must recall all the items. The score is the number of items that were recalled and measures immediate visual recall.

Benton Visual Retention Test (BVRT). The subject is shown a card which contains (usually) three figures, two large and one small. There is a ten second exposure time and a ten second delay time before the subject is given a piece of paper on which to draw the design. There are ten designs in each form (Form C was administered) and the score is the number of errors made. This test is another measure of visual recall.

Minnesota Multiphasic Personality Inventory (MMPI). The MMPI is a personality test which is comprised of 439 true/false items. The items were coded onto several computer cards and the cards were read by an optic scanner. The 439 items can be divided into a number of scales. A number of items were used to determine the patient's future outlook.

Demographic and Neurological Data

Demographic information on each patient and normal controls was obtained by a semi-structured interview. Personal and demographic information were recorded (age, marital status, education, sex, handedness, employment status, and occupational
status) and the patients’ feelings about the disease, as was factual information (e.g., family history of MS and other diseases). Information regarding neurological status and disease history was obtained from the UBC MS clinic (age at diagnosis, age of onset, number of relapses, Kurtzke Expanded Disability Status Scale (EDSS) and Kurtzke functional scales, duration).

Data Collection and Entry

Fatigue has been often associated with MS and this fact could have potentially confounded results on neuropsychological tests. However, subjects were given predetermined rest periods throughout the lengthy battery. Furthermore, the presentation of neuropsychological tests was randomized so that the tests later in the battery would not always be the same and more prone to effects of fatigue.

The neuropsychological data were entered into an interactive computer program designed specifically for the investigation. The MMPI scores were recorded on computer cards and read by an optic scanner. The demographic and neurological data were entered in computer file. The data were analyzed by the computer program Statistical Package for the Social Sciences (SPSS-X version 3.0) on the UBC main frame system (MTS).
Analyses

Analysis I

The purpose of the first analysis was to identify whether there existed a subgroup of MS patients in this sample who were cognitively impaired. The following questions were then asked: 1) Is the observed cognitive impairment a specific loss of a particular function (in this case spontaneous word generation) or is it a widespread decline of many functions?; and 2) Are the observed cognitive problems a result of demographic or disease-related variables?

In order to divide the MS group into two subgroups, the results of the Word Fluency Test were used. This particular test was chosen because the motor/sensory demands of this task are minimal and thus allow for a relatively pure measure of cognitive function. In the Word Fluency Test, a higher score is indicative of better performance. Therefore, to separate the MS group into a cognitively impaired subgroup and a subgroup whose members have no cognitive problems, the fifth percentile of the distribution of the normal group was the criterion. The fifth percentile was chosen in order to capture the most impaired persons in the MS group and to ensure statistical power. Those MS patients who score below this score were considered cognitively impaired; those who score as well or better were considered cognitively normal. A Chi-squared analysis was done to determine if a
greater than expected number of MS patients fell below the fifth percentile.

Further analysis was performed in order to rule out other potentially confounding factors such as demographics or severity and duration of illness. Age and education were examined using a one-way analysis of variance and Tukey’s post hoc test to determine whether any differences could be attributed to those variables. Similarly, using a Chi-square test, the contribution of sex was examined among the two MS subgroups and the normal control group. The effects of severity (looking at EDSS and all functional scales), duration of illness, age of onset and number of relapses were investigated using a t-test for independent groups on the two MS subgroups.

One way analysis of variance was employed to detect any between group differences on tests of motor sensory capacities such as the Grooved Pegboard. The Grooved pegboard was chosen as a test of motor/sensory ability as it seems to combine a number of functions on which MS patients have been shown to be deficient (speed, motor coordination and tactile discrimination). The hypothesis in question would predict that both MS groups should be significantly worse than the normal controls. Should the impaired group perform significantly worse than the other two groups, it could be argued that motor/sensory problems could be a confounding factor of the observed cognitive impairment.
In order to define the extent of the cognitive impairment, the three groups were compared on all other cognitive tests. This was done in order to determine whether the members of the impaired group have a problem only in spontaneous word generation or whether their cognitive impairment is generalized or global. Again using the one-way analysis of variance and Tukey's post hoc test, the three groups were compared on the following variables: Full Scale IQ, Verbal IQ, Performance IQ, Category test, Paired Associate Learning, Trails B-A, Sentence Repetition, Memory for Objects, and Benton Visual Retention.

It was conceivable that the preselection of patients in terms of so-called cognitive impairment may have been accomplished by selecting those persons who had lower premorbid ability. This was examined by comparing all three groups (normal, cognitively impaired MS, and cognitively normal MS groups) on the highest level of academic achievement and the highest level of occupational status which are thought to be fairly good indicators of level of functioning prior to the onset of the disease (Lezak, 1983). A Chi-square statistic was used.

Analysis II

The purpose of the second analysis was to determine whether the level of social functioning was related to cognitive functioning. Social functioning was measured by the employment status and the nature and number of social/recreational
activities. Furthermore, the level of optimism for the future was assessed to determine whether cognitive dysfunction was related to greater pessimism towards the future.

From the interview data, information regarding employment status was available. Employment status was characterized by four levels: 1) those who were engaged in full time employment which includes those employed in the household (homemakers) and students; 2) those who were employed but were only working part of the time regardless of the reasons given (children, choice, economy, or disease related); 3) those people who were not employed regardless of the specified reasons; and 4) those who have retired (all subjects in the study were less than 50 years at the time of testing). This analysis tried to determine whether the cognitively impaired group were more likely to be unemployed or working part time than the cognitively intact or the normal groups. A Kendall’s Tau was used to compare the three groups in terms of their employment status and a further Kendall’s Tau was used to compare the two MS subgroups on employment status.

Also from the interview data, information was available regarding how leisure time is spent. Both number and type (for example, hobbies vs active sports) of recreational activities that were engaged in by the patients were available from the database. The three groups were compared to see whether there were any differences in terms of the nature of recreational
activities undertaken by each group and to calculate the number of activities performed by the members of each group. A one-way analysis of variance compared the three groups on the number of activities whereas a Chi-squared statistic was used to compare the type of recreational/social activities undertaken by the members of all three groups.

From the MMPI, a scale was derived from items which examine the optimistic/pessimistic outlook for the future. Five items were selected along with an item from the interview (What do you see for yourself in the future) in order to get a rough estimate of the level of optimism for the future. The items from the MMPI were as follows:

16. I think I got a raw deal from life.
83. These days, I find it hard not to give up hope amounting to something.
101. I don't seem to care what happens to me.
252. I usually expect to succeed in the things I do.
421. The future seems hopeless to me.

A composite score was established by recoding each of the items and summing the resulting scores. Items 16, 83, 101, 421, and the interview item were coded in that if "true" was answered, a score of 1 was obtained whereas if "false" was answered, a score of 0 was obtained. For the remaining item (252), the coding scheme was reversed in that a response of "false" led to a score
of 1 and "true" led to a score of 0. The resulting scale had a minimum of 0 (Optimistic for the future) and a maximum of 5 (Pessimistic for the future).

From the theoretically derived scale, a reliability coefficient was computed in order to determine the validity of the scale. The coefficient determined whether the items in the scale indeed measured what was intended (optimism/pessimism). A correlation matrix indicated which items should be deleted (a low covariance) and after the unwanted items were deleted, a new scale was observed. The three groups were compared on this scale using a one-way analysis of variance and Tukey’s post hoc test.

**Analysis III**

The third analysis attempted to delineate whether cognitive impairment, depression, or physical disability was most predictive of any decrease in social functioning.

In the first analysis, the fifth percentile of the distribution of the normal controls’ scores on the Word Fluency Test established a cognitively impaired and a cognitively normal MS group. A similar procedure to that employed in the first analysis was used to identify a group of depressed individuals with the results of the BDI. A cutting score was obtained from the distribution of scores of the normal group. A high score on the Beck Depression Inventory is indicative of higher level of
depression, hence, the ninety-fifth percentile served as criterion. The ninety-fifth percentile was chosen in order to achieve a balance between statistical power and clinical meaningfulness (those patients who report a high level of depressive symptoms). Those MS patients scoring above this level were considered depressed and those scoring the same or lower were considered non-depressed.

The MS group was dichotomized in a third manner according to their scores on the EDSS. No data for the normal controls were available for physical disability, and therefore a slightly different procedure determined the cutting score for "physical disability". A higher score on this scale translates into greater disability. Therefore, those patients with scores in the top 20 percent of the scale were classified as "physically disabled". This procedure ensured that only the most disabled persons be included in this group and statistical power was optimized. All other MS patients were considered to have relatively mild levels of physical disability.

The most disabled persons in each symptom category (cognition, depression and physical status) were able to be compared to their non-impaired counterparts on a number of social outcome measures such as: employment status, level of recreational/social activities and outlook for the future. Refer to Table 3.1 for the predictions on how each of the symptoms of
the disease might affect the social/recreational or vocational activities and the optimism/pessimism for the future.

**Employment status.** A two by two Chi-square was the statistical procedure employed to determine the effect of being in the impaired group in each of the spheres (cognition, depression or physical status) on employment status. Employment status was dichotomized into a working category versus non-working category. The working category included people who were working full time (student and homemaker included) and those working part time. The non-working category included those people who were no longer working (unemployed or retired). Group membership was the independent variable. A significant Chi-square result indicated that group membership had an effect on employment status (for example, being depressed led to a significantly greater proportion of being unemployed). This analysis was performed three times, once for each domain (cognitively impaired MS versus normal cognition MS, depressed MS versus normal depression MS, and physically impaired MS versus normal physically disabled MS).

**Recreational/leisure activities.** The amount of leisure activities was compared in a manner similar to the way employment status was analyzed. The number of leisure activities was totalled. The number of leisure activities was the dependent variable whereas group membership was the independent variable. A t-test for independent groups was performed on the data to
determine whether being in the impaired group led to a decreased number of leisure activities undertaken. A t-test for independent groups was computed for all three domains (cognition, depression and physical status).

**Outlook for the future.** Finally, the contribution of group membership to the outlook for the future was examined for each domain. The level of pessimism for the future was assessed in the same manner as in analysis II. A t-test for independent groups compared the impaired versus the non-impaired groups in each sphere on their pessimism for the future.

**Can these phenomena be independent?** The final analysis will show how the MS group breaks down into categories according to which symptom(s) is/are experienced. The "Extent of disability" will be computed by determining what percentage of the MS patients are 1) globally impaired (fall in the impaired range for cognition, depression and physical disability), 2) those who are in any combination of two of the three symptoms and 3) those who are unimpaired (do not fall into the impaired range for any symptom).

In order to test independence, a Chi square analysis and Phi coefficient were computed for each combination of symptoms (Cognition and Depression; Cognition and Physical disability; and Depression and Physical disability). A high Phi coefficient was
indicative of dependence whereas a low Phi coefficient was indicative of independence.
CHAPTER 4
RESULTS

Sample Demographics

The MS group was selected according to a very specific set of criteria and were comparable to the control group in terms of demographic variables (see Table 4.1). Controls were selected by asking the MS patient to recruit a same-sex non-relative who had a similar personal background. Of the 181 MS patients, 131 (72.9%) were female, whereas 64 of the 90 normal controls (71.1%) were female. The mean age of the MS group was 36.2 (standard deviation of 7.8 years, range 19 to 53) compared to the controls who averaged 35.5 years (standard deviation 7.3, range 21 to 55 years). The groups were almost equivalent in terms of education, with the MS group having had 13.6 years (standard deviation 2.19, range 7 to 19) in contrast to the Normal group having had 13.9 years (standard deviation 2.20, range 10 to 19).

The two groups were also similar on other variables. No differences were found between the two groups in terms of marital status ($X^2_{(2)}=3.57, p>.05$). Similarly, no group differences were found on highest level of occupational achievement ($X^2_{(2)}=1.49, p>.05$). The single variable where a difference was found was employment status ($X^2_{(3)}=21.7, p<.0001$).
<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>CONTROL</th>
<th>T or $X^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (SD)</td>
<td>36.2 (7.8)</td>
<td>35.5 (7.3)</td>
<td>0.69$^1$</td>
<td>NS</td>
</tr>
<tr>
<td>EDUCATION (SD)</td>
<td>13.6 (2.2)</td>
<td>13.9 (2.2)</td>
<td>-1.11$^1$</td>
<td>NS</td>
</tr>
<tr>
<td>SEX (% FEMALE)</td>
<td>72.9</td>
<td>71.1</td>
<td>0.03$^1$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MARITAL STATUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARRIED</td>
<td>109 (60%)</td>
<td>47 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SINGLE</td>
<td>34 (19)</td>
<td>26 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIVORCED</td>
<td>38 (21)</td>
<td>17 (19)</td>
<td>3.57$^2$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>OCCUPATIONAL STATUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROFESSIONAL</td>
<td>35 (19%)</td>
<td>23 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKILLED</td>
<td>117 (65)</td>
<td>55 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNSKILLED</td>
<td>29 (16)</td>
<td>12 (13)</td>
<td>1.49$^2$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>EMPLOYMENT STATUS (CURRENT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FULL TIME</td>
<td>96 (53%)</td>
<td>17 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PART TIME</td>
<td>38 (21)</td>
<td>14 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNEMPLOYED</td>
<td>36 (20)</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RETIRED</td>
<td>11 (6)</td>
<td>3 (3)</td>
<td>21.70$^2$</td>
<td>.0001</td>
</tr>
</tbody>
</table>

LEGEND: 1) t-test used
2) Chi square used
Analyses

Analysis I

The purpose of the first analysis was to determine whether a sample of MS patients who were impaired on several measures of cognition existed and whether disease-related or demographic variables were able to explain this impairment.

The fifth percentile in the normal sample on the Word Fluency test was a total score of 28 or 9.3 words per minute. Twenty percent of the MS group (37 members) scored below this score, and hence were classified as impaired. This percentage was greater than could have occurred by chance ($X^2(1) = 9.06$, $p < .003$). The three resulting groups (MS Impaired, MS Normal, and the Normal Controls) were compared on the following demographic variables: age, education, sex, marital status, highest occupational status (while employed) and handedness. The three groups were not significantly different on these mentioned variables. The resulting means with the statistical tests that were used are found in Table 4.2.

To determine whether a number of disease-related variables such as age of onset, disease duration, disability status score, scores on the functional scales, number of relapses and length of illness could account for the differences in cognitive functioning, the variables were compared between the two MS
### TABLE 4.2
DEMOGRAPHICS FOR THE THREE GROUPS: COGNITIVELY IMPAIRED MS, NORMAL MS, AND NORMAL CONTROLS

|                      | MS IMPAIRED | MS NORMAL | NORMAL CONTROLS | F or X^2 | p 
|----------------------|-------------|-----------|-----------------|----------|------
| AGE (SD)             | 36.5(8.3)   | 36.1(7.7) | 35.5(7.3)       | .28^1    | NS   
| EDUCATION (SD)       | 13.0(2.1)   | 13.7(2.2) | 13.9(2.2)       | 2.09^1   | NS   
| SEX (%FEMALE)        | 75.7        | 72.2      | 71.1            | 0.27^2   | NS   
| HANDEDNESS (%RIGHT) | 94.6        | 91.6      | 92.2            | 2.14^2   | NS   

**MARITAL STATUS**

<table>
<thead>
<tr>
<th></th>
<th>MS IMPAIRED</th>
<th>MS NORMAL</th>
<th>NORMAL CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARRIED</td>
<td>21(57%)</td>
<td>88(61%)</td>
<td>47(52)</td>
</tr>
<tr>
<td>SINGLE</td>
<td>6(16%)</td>
<td>28(19%)</td>
<td>26(29)</td>
</tr>
</tbody>
</table>
| DIVORCED  | 10(27%)     | 28(19%)   | 17(19)          | 1.06^2   | NS   

**OCCUPATIONAL STATUS**

<table>
<thead>
<tr>
<th></th>
<th>MS IMPAIRED</th>
<th>MS NORMAL</th>
<th>NORMAL CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFESSIONAL</td>
<td>7(19%)</td>
<td>28(19%)</td>
<td>23(19%)</td>
</tr>
<tr>
<td>SKILLED</td>
<td>23(62%)</td>
<td>94(65%)</td>
<td>55(61%)</td>
</tr>
</tbody>
</table>
| UNSKILLED | 7(19%)      | 22(15%)   | 12(13%)         | 1.80^2   | NS   

**LEGEND:**
1) One-way ANOVA used
2) Chi-square statistic used
subgroups. Disease-related variables are listed in Table 4.3. T-tests for independent groups revealed that the two groups were not significantly different with respect to the above mentioned variables. EDSS between the two groups were almost the same ($t(46.9) = 1.03, p > .05$), and the two groups were similar on variables such as duration of illness ($t(179) = 0.38, p > .05$); number of relapses ($t(179) = 0.46, p > .05$); age of onset ($t(179) = -0.13, p > .05$); and age at diagnosis ($t(179) = 0.02, p > .05$). As 18 comparisons were made, the Bonferroni correction of 0.006 ($0.10/18$) was used.

In order to validate the presence of cognitive impairment, the performance on other neuropsychological tests was examined. Using a one-way ANOVA followed with Tukey's post hoc test, the following results were found (see Table 4.4 for a summary). Even with the Bonferroni correction of 0.008 ($0.10/13$), all ANOVAs were significant. Of all the neuropsychological tests examined, the cognitively impaired MS group had the poorest performance on all variables. The cognitively impaired group performed significantly worse than the normal MS group and the normal control group on Full Scale IQ, Verbal IQ, the Word Fluency Test, Halstead Category Test and Sentence repetition while the unimpaired MS group and the normal controls did not differ on these variables. All three groups were significantly different on Performance IQ, and the Wechsler Paired Associates learning. However, the MS impaired group was the most deficient in both cases. Tukey's post hoc test showed that the normal control
### Table 4.3
Disease-related variables for the cognitively impaired MS and the normal MS

<table>
<thead>
<tr>
<th></th>
<th>MS Impaired</th>
<th>MS Normal</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEVERITY (EDSS)</strong></td>
<td>2.2</td>
<td>2.0</td>
<td>1.03</td>
<td>NS</td>
</tr>
<tr>
<td><strong>DURATION</strong></td>
<td>5.4</td>
<td>5.1</td>
<td>0.38</td>
<td>NS</td>
</tr>
<tr>
<td><strong>NUMBER OF RELAPSES</strong></td>
<td>5.0</td>
<td>4.7</td>
<td>0.46</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AGE ONSET</strong></td>
<td>26.3</td>
<td>26.5</td>
<td>-0.13</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AGE OF DIAGNOSIS</strong></td>
<td>31.1</td>
<td>31.0</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>KURTZKE FUNCTIONAL SCALES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PYRAMIDAL</td>
<td>1.35</td>
<td>1.15</td>
<td>1.13</td>
<td>NS</td>
</tr>
<tr>
<td>CEREBELLAR</td>
<td>0.57</td>
<td>0.50</td>
<td>0.44</td>
<td>NS</td>
</tr>
<tr>
<td>BRAINSTEM</td>
<td>0.43</td>
<td>0.45</td>
<td>-0.16</td>
<td>NS</td>
</tr>
<tr>
<td>SENSORY</td>
<td>0.78</td>
<td>0.75</td>
<td>0.22</td>
<td>NS</td>
</tr>
<tr>
<td>BOWEL/BLADDER</td>
<td>0.54</td>
<td>0.50</td>
<td>0.32</td>
<td>NS</td>
</tr>
<tr>
<td>VISUAL</td>
<td>0.54</td>
<td>0.55</td>
<td>-0.06</td>
<td>NS</td>
</tr>
<tr>
<td>MENTAL</td>
<td>0.11</td>
<td>0.03</td>
<td>1.47</td>
<td>NS</td>
</tr>
<tr>
<td>Variable</td>
<td>MS IMPAIRED</td>
<td>MS NORMAL</td>
<td>NORMAL</td>
<td>F</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>FIQ</td>
<td>94.2</td>
<td>105.2</td>
<td>108.2</td>
<td>21.3</td>
</tr>
<tr>
<td>VIQ</td>
<td>96.8</td>
<td>106.9</td>
<td>107.4</td>
<td>13.4</td>
</tr>
<tr>
<td>PIQ</td>
<td>92.2</td>
<td>102.2</td>
<td>107.8</td>
<td>23.2</td>
</tr>
<tr>
<td>WORD FLUENCY</td>
<td>21.8</td>
<td>41.0</td>
<td>41.8</td>
<td>67.6</td>
</tr>
<tr>
<td>CATEGORY TEST</td>
<td>27.9</td>
<td>20.9</td>
<td>19.8</td>
<td>5.8</td>
</tr>
<tr>
<td>TRAILS B-A</td>
<td>42.7</td>
<td>36.2</td>
<td>27.0</td>
<td>10.8</td>
</tr>
<tr>
<td>SENTENCE REPETITION</td>
<td>17.4</td>
<td>19.2</td>
<td>19.5</td>
<td>10.6</td>
</tr>
<tr>
<td>MEMORY FOR OBJECTS</td>
<td>11.9</td>
<td>12.3</td>
<td>12.9</td>
<td>6.4</td>
</tr>
<tr>
<td>BENTON (ERRORS)</td>
<td>4.9</td>
<td>4.3</td>
<td>3.1</td>
<td>7.0</td>
</tr>
<tr>
<td>PAIRS (TOTAL)</td>
<td>40.2</td>
<td>44.0</td>
<td>47.7</td>
<td>17.8</td>
</tr>
<tr>
<td>GROOVED PEGBOARD(R)</td>
<td>87.1</td>
<td>77.9</td>
<td>62.4</td>
<td>17.8</td>
</tr>
<tr>
<td>GROOVED PEGBOARD(L)</td>
<td>95.8</td>
<td>87.1</td>
<td>65.6</td>
<td>20.0</td>
</tr>
<tr>
<td>GROOVED PEGBOARD(B)</td>
<td>73.9</td>
<td>64.4</td>
<td>50.9</td>
<td>20.5</td>
</tr>
</tbody>
</table>

_____ Indicates homogeneous subsets
group performed at a higher level than the other two groups on Memory for objects, Trails B-A and the Benton Visual Retention test. No differences for these tasks were found between the two MS subgroups. See Figure 1 for a graphical representation of the performance on neuropsychological tests for the three groups.

In order to determine whether the cognitively impaired group was selected solely on the basis of poorer premorbid ability, the results of the highest level of occupational achievement and years of education were compared. Again, no differences were found on these variables. These data are presented in Table 4.2.

The results of tests of motor/sensory ability showed that the normal control group performed significantly better than both MS subgroups. Tukey's post hoc test found no differences between the two MS subgroups on Grooved Pegboard Left and Right. However, using both hands, not only did the normal controls perform significantly better than the two MS subgroups but there was a significant difference between the two MS subgroups. Results of the above analyses are presented in Table 4.4.

Analysis II

The purpose of the second analysis was to determine whether being cognitively impaired had any effect on the adaptability of the MS patient in terms of 1) vocational, 2) recreational and
Figure 1 - Neuropsychological Performance

- WFTOT*
- FIQ*
- VIQ*
- PIQ**
- CAT TOT*
- TRAIL B-A***
- SENS REP*
- MEM
- BVRT
- PAIRS**

* cognitively impaired significantly different than the normal MS and normal controls
** all three groups significantly different from each other
*** normal controls significantly different than the normal MS and cognitively impaired MS
social activities. In addition, the purpose of this analysis was to determine whether cognitive impairment was predictive of a more pessimistic future outlook.

Using a Kendall's Tau, a measure of the association between two variables similar to a Pearson's correlation coefficient (Howell, 1987), there was a difference in current employment status among the three groups ($T=0.268$, $p<.0001$). Comparing the two MS groups, it was found that they did differ on their current employment status ($T=-.142$, $p<.021$). The MS impaired group were less likely to be working full time (41% versus 56% of the normal MS group were employed full time) and more likely to be unemployed (32 vs 17% MS normal). See Table 4.5.

The question of whether cognitive impairment interferes with social and recreational activities (soc/rec) was examined in two ways. The first analysis examined whether the total number of soc/rec activities was reduced in the cognitively impaired group relative to the other two groups. The results of a one-way ANOVA showed that there was a significant difference among the three groups ($F(2,270)=10.1$, $p<.0001$). Tukey's post hoc test showed that all three groups differed from one another with the cognitively impaired participating in the lowest average number of soc/rec activities (1.97) followed by the MS normal group (2.33) and finally an average 2.62 activities for the normal control group. Again, see Table 4.5.
TABLE 4.5
VOCATIONAL/RECREATIONAL VARIABLES FOR THE COGNITIVELY IMPAIRED MS, NORMAL MS AND NORMAL CONTROLS
ANALYSIS II

<table>
<thead>
<tr>
<th></th>
<th>MS IMPAIRED</th>
<th>MS NORMAL</th>
<th>NORMAL</th>
<th>F or $\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPLOYMENT STATUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FULL TIME</td>
<td>15 (41%)</td>
<td>81 (56%)</td>
<td>71 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PART TIME</td>
<td>7 (19%)</td>
<td>31 (22%)</td>
<td>14 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNEMPLOYED</td>
<td>12 (32%)</td>
<td>24 (17%)</td>
<td>2 (2)</td>
<td>0.268*</td>
<td>.000</td>
</tr>
<tr>
<td>RETIRED</td>
<td>3 (8)</td>
<td>8 (6)</td>
<td>3 (3)</td>
<td>-0.142**</td>
<td>.021</td>
</tr>
</tbody>
</table>

| **TOTAL SOCIAL/RECREATIONAL ACTIVITIES** |             |           |        |               |     |
| NUMBER            | 1.97        | 2.33      | 2.62   | 10.1$^1$      | .0001|

| TYPE              |             |           |        |               |     |
| ACTIVE            | 1 (3%)      | 1 (1)     | 1 (1)  |               |     |
| RECREATIONAL      | 2 (6)       | 5 (4)     | 4 (5)  |               |     |
| AROUND HOME       | 0 (0)       | 4 (3)     | 5 (6)  |               |     |
| HOBBIES           | 9 (25)      | 41 (29)   | 20 (22)|               |     |
| SOCIAL            | 17 (47)     | 57 (40)   | 42 (47)|               |     |
| FAMILY            | 3 (8)       | 16 (11)   | 8 (9)  |               |     |
| VOLUNTEER         | 3 (8)       | 15 (11)   | 6 (7)  |               |     |
| TRAVEL            | 1 (3)       | 2 (1)     | 3 (3)  | 8.25$^2$       | NS  |

| OUTLOOK FOR THE FUTURE |             |           |        |               |     |
| 0.162               | 0.035       | 0.034     |        | 5.43$^1$      | .005 |

**LEGEND:**
1) One-way Anova
2) Chi-square
*used Kendell’s tau
** used Kendell’s tau on the two MS subgroups
_____ indicate homogeneous subsets
The second way in which soc/rec activities were examined was in the type or pattern of activities that was undertaken. A chi square statistic found no systematic relations among each group in terms of what types of soc/rec activities each group preferred (See Table 4.5).

A reliability analysis was performed on the items of the MMPI to determine the overall accuracy of the scale using Cronbach's alpha (Kaplan & Saccuzzo, 1982). The reliability measure was computed by obtaining a correlation matrix among all items on the scale with the estimated variance of the true score in the numerator and the estimated variance of the true score plus the error variance in the denominator. Among MMPI items, correlations ranged from .07 to a maximum of .45 with an overall reliability of .28. The low intercorrelations suggested that each item was measuring a different domain.

There are several potential reasons for this low internal consistency. First, scales with high reliability usually have more than 40 items (Kaplan & Saccuzzo, 1982) and second, when correlating two dichotomous variables with unequal marginal probabilities, the maximum resulting correlation obtained will fall short of a 1.00 values, with more unequal splits leading to a lower maximum correlation (Comrey, 1978). Reviewing the marginal probabilities of each of the items, it was observed that there was great variability and furthermore, only five items were included on the scale. These two facts may well be the reason
why the overall reliability of the scale was low and why the decision was made to drop the MMPI items. Due to this lack of internal consistency, a decision was then made to drop all MMPI items but retain only the interview item "what do you see for yourself for the future?". Using this interview item alone, pessimistic future outlook could be determined and was thus a more accurate measure to address the question.

A one-way ANOVA showed that the MS impaired group felt more pessimistic about the future than either the MS normal or normal control group ($F(2, 266) = 5.43, p < .005$). Tukey's post hoc test indicated that the MS impaired group was significantly more pessimistic than the other two groups, whereas the other two groups were not significantly different from one another. See Table 4.5.

Analysis III

The purpose of the final analysis was to determine whether other symptoms of the disease (for example, depression or physical disability) may also be predictive of the social outcome measures discussed in the Analysis II (employment status, social/recreational activity and pessimism toward the future. Table 4.6 presents the relevant statistical information. Table 4.7 summarizes the predicted and observed outcomes. Table 4.8 shows the percentage of patients who are impaired on a combination of symptoms or having only one symptom or alternately
TABLE 4.6  
VOCATIONAL/RECREATIONAL VARIABLES FOR THE COGNITIVELY IMPAIRED 
MS, COGNITIVELY NORMAL MS, DEPRESSED MS, NON-DEPRESSED MS, 
PHYSICALLY DISABLED MS, AND NON-PHYSICALLY DISABLED MS. 
ANALYSIS III  

GROUP MEMBERSHIP

<table>
<thead>
<tr>
<th></th>
<th>IMPAIRED</th>
<th>NORMAL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGNITION</td>
<td>37</td>
<td>144</td>
<td>181</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>38</td>
<td>143</td>
<td>181</td>
</tr>
<tr>
<td>PHYSICAL DISABILITY</td>
<td>34</td>
<td>147</td>
<td>181</td>
</tr>
</tbody>
</table>

EMPLOYMENT STATUS

<table>
<thead>
<tr>
<th></th>
<th>IMPAIRED</th>
<th>NORMAL</th>
<th>$x^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGNITION</td>
<td>60/40*</td>
<td>78/22</td>
<td>4.23</td>
<td>.034</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>58/42</td>
<td>78/22</td>
<td>5.50</td>
<td>.019</td>
</tr>
<tr>
<td>PHYSICAL DISABILITY</td>
<td>62/38</td>
<td>77/23</td>
<td>2.54</td>
<td>NS</td>
</tr>
</tbody>
</table>

*(WORKING/NON-WORKING)

LEISURE ACTIVITIES

<table>
<thead>
<tr>
<th></th>
<th>IMPAIRED</th>
<th>NORMAL</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGNITION</td>
<td>1.97</td>
<td>2.33</td>
<td>-2.69</td>
<td>.004</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>2.05</td>
<td>2.31</td>
<td>-1.94</td>
<td>.027</td>
</tr>
<tr>
<td>PHYSICAL DISABILITY</td>
<td>2.06</td>
<td>2.30</td>
<td>-1.65</td>
<td>NS</td>
</tr>
</tbody>
</table>

OUTLOOK FOR THE FUTURE

<table>
<thead>
<tr>
<th></th>
<th>IMPAIRED</th>
<th>NORMAL</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGNITION</td>
<td>0.16</td>
<td>0.03</td>
<td>2.01</td>
<td>.026</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>0.13</td>
<td>0.04</td>
<td>1.54</td>
<td>NS</td>
</tr>
<tr>
<td>PHYSICAL DISABILITY</td>
<td>0.11</td>
<td>0.04</td>
<td>1.19</td>
<td>NS</td>
</tr>
</tbody>
</table>
### TABLE 4.7
PREDICTED AND OBSERVED RESULTS OF THE EFFECTS OF COGNITIVE IMPAIRMENT, DEPRESSION AND PHYSICAL DISABILITY ON VOCATIONAL AND RECREATIONAL ACTIVITIES
ANALYSIS III

<table>
<thead>
<tr>
<th>INDEPENDENT MEASURES</th>
<th>COGNITIVE IMPAIRMENT</th>
<th>PHYSICAL DISABILITY (EDSS)</th>
<th>DEPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPLOYMENT STATUS</td>
<td>+/+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>LEISURE ACTIVITIES</td>
<td>+/+</td>
<td>-/-</td>
<td>-/+</td>
</tr>
<tr>
<td>OUTLOOK FOR FUTURE</td>
<td>+/+</td>
<td>-/-</td>
<td>+/-</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3/3 \ 3/3</td>
<td>1/3 \ 0/3</td>
<td>2/3 \ 2/3</td>
</tr>
</tbody>
</table>

( + = Effect)
( - = No Effect)

(Expected / Observed)
<table>
<thead>
<tr>
<th>EXTENT</th>
<th>TOTAL</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL</td>
<td>2</td>
<td>1.1%</td>
</tr>
<tr>
<td>COGNITION &amp; DEPRESSION</td>
<td>6</td>
<td>3.3%</td>
</tr>
<tr>
<td>COGNITION &amp; PHYSICAL DISABILITY</td>
<td>6</td>
<td>3.3%</td>
</tr>
<tr>
<td>DEPRESSION &amp; PHYSICAL DISABILITY</td>
<td>6</td>
<td>3.3%</td>
</tr>
<tr>
<td>PHYSICAL DISABILITY</td>
<td>20</td>
<td>11.0%</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>24</td>
<td>13.3%</td>
</tr>
<tr>
<td>COGNITION</td>
<td>23</td>
<td>12.7%</td>
</tr>
<tr>
<td>NO IMPAIRMENT</td>
<td>94</td>
<td>51.9%</td>
</tr>
</tbody>
</table>
not being in the impaired range on any of the symptoms.

The percentage of the MS group who fell in the depressed range according to the 95th percentile criterion was established as was the percentage falling beyond the 90th percentile on the EDSS. Thirty eight of the 181 MS patients were shown to be in the depressed range using the 95th percentile procedure on the scores of the Beck Depression Inventory. The cutting score was found to be 11. A score of this magnitude would be indicative of moderate depression (Beck et al., 1961). Any MS patient who obtained a score of 12 or greater on the BDI was placed in the "depressed" group. The BDI scores for the depressed group ranged from 12 to a maximum of 36. A chi square statistic determined that the number of MS patients in the depressed range was unlikely to have occurred by chance alone ($\chi^2 (1)=10.94, p<.001$). Thirty four (19%) of the 181 MS patients were found to be in the physically disabled range, which was determined by having an EDSS of greater than 3.5. The EDSS scores for the physically disabled group ranged from 3.5 to 6.0. As no data were available for the normals on the EDSS, a similar check to see whether more MS patients fell in this group than would be expected by chance, could not be done. Table 4.9 gives the mean scores on criterion measures for the three impaired groups and the normal controls.

For each symptom of MS (cognition, depression and physical disability), the impaired and the normal MS groups were compared
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Word Fluency Test</th>
<th>Beck Depression Inventory</th>
<th>Kurtzke EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Impairment</strong></td>
<td>37</td>
<td>21.8(4.5)</td>
<td>7.9(7.9)</td>
<td>2.3(1.5)</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>38</td>
<td>36.8(11.7)</td>
<td>16.2(4.9)</td>
<td>2.3(1.1)</td>
</tr>
<tr>
<td><strong>Physical Disability</strong></td>
<td>34</td>
<td>34.4(11.9)</td>
<td>8.9(7.6)</td>
<td>3.9(0.7)</td>
</tr>
<tr>
<td><strong>Total MS Group</strong></td>
<td>181</td>
<td>37.1(11.9)</td>
<td>7.5(5.8)</td>
<td>2.0(1.2)</td>
</tr>
<tr>
<td><strong>Normal Controls</strong></td>
<td>90</td>
<td>41.8(10.4)</td>
<td>3.5(3.7)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
on employment status and the data are presented in Table 4.6. It was predicted that each symptom should have an effect on the employment status. Chi square statistics showed that cognitive impairment and depression both had an effect ($X^2(1) = 4.23, p < .040$ for cognition; $X^2(1) = 5.50, p < .019$ for depression) while physical disability had no effect ($X^2(1) = 2.54, p > .05$).

The same procedure for social/recreational activities (soc/rec) was done for each of the three symptoms of MS. The predicted outcome was that only impaired cognition should have an effect on soc/rec. However, these predictions were not entirely supported with a t-test for independent groups. Since a predictive model was used, a one-tailed t-test was employed. For cognition, a significant result was found using a t-test for independent groups ($t_{(179)} = -2.69, p = .004$). Therefore, cognitive impairment does affect the total number of leisure activities a person undertakes. Depression also had an effect: $t_{(179)} = -1.94, p = .027$. A trend towards significance was found for physical disability in terms of the number of soc/rec an MS patient undertakes ($t_{(179)} = -1.65, p > .05$).

As previously stated, another purpose of this analysis was to determine which of the MS symptoms were more likely to lead to a pessimistic outlook for the future. It was predicted that both depression and cognition would have an effect on the patient's outlook for the future. However, this analysis showed that while cognitive impairment impacts on a person’s outlook,
depression and physical disability do not: (Cognition: $t(40.57) = 2.01, p = .026$; Depression: $t(44) = 1.54, p > .05$; Physical disability: $t(39.75) = 1.19, p > .05$). A one-tailed t-test was again employed.

By adding up the number of positive effects for each symptom, a rough estimate can be made as to which symptom is most socially disabling for the MS patient. As can be seen from Table 4.7, impaired cognition results in all three measures of social disability (3/3) being affected, while physical disability leads to no effect (0/0) and depression leads to two of the three (2/3) measures being affected.

The final analysis attempted to determine whether these symptoms can occur separately, or in any combination. The results, found in Table 4.8, show that more than half the MS patients (51.9%) did not fall in the impaired range for any of the symptoms. Roughly one percent of the MS sample can be classified as globally impaired (in the impaired range in all three symptoms) and a relatively equal percentage are only impaired on one symptom (12.7, 13.3 and 11.0% respectively for cognition, depression and physical disability). Eighteen of the 181 (9.9%) MS patients fell in the impaired range in a combination of two symptoms. Three and one third percent (3.3%) were in the impaired range for cognition and depression, the same percentage were in the impaired range for depression and physical
disability and a further 3.3% were in the impaired range for cognition and physical disability.

Phi coefficients were computed for each combination of symptoms. A Phi coefficient is a measure of association performed on two dichotomous variables and thus is similar to a Pearson correlation (Howell, 1987). The observed coefficients were: cognition and depression: .01; cognition and physical disability: .04; and depression and physical disability: .03.
Precautions Interpreting the Results of This Study

Before discussing the results of this study, a number of methodological issues should be addressed. The first issue is sampling and subsequent generalization. When designing the current study, specific criteria were used so that any found differences could be attributed to the effects of MS, not other potentially confounding variables. Only patients diagnosed with clinically definite MS with a R/R disease course and mild physical disability were accepted into the study. To ensure a high degree of diagnostic certainty, the Poser et al. (1983) criteria were used for diagnosis. In addition, only patients who were diagnosed before the age of 40 were included, to further reduce the possibility of including patients with atypical MS. To avoid confusing the effects of active disease progression and relapse-related variables such as anxiety or depression, patients were tested in remission. Furthermore, only patients with mild MS (EDSS \( \leq 6.0 \)) were chosen to limit the motor/sensory problems which might interfere with cognitive test performance. Finally, all patients were less than 50 years old upon entry into the study to minimize the effects of aging.

Exclusion criteria were also strictly enforced so to minimize confounds. No patient was accepted into the study with
any medical problems concurrent with MS. This criteria ensured that other problems could not be used as explanations for any observed results. Another exclusion criteria stated that a patient with a psychiatric problem predating their diagnosis was not included. This restriction ensured that if a subject had a psychiatric diagnosis, it may have been a result of MS. In addition, no subject took part in the study if they were currently on any prescribed medication that had any potential central nervous system effects. Some MS therapies can have a potentiating effects on mood or cognition. If it were deemed appropriate, patients medicated with certain drugs were permitted in the study after a one week wash out period. In addition, no subject took part in the study who had a history of excessive recreational drug use (more than once a week). Finally, if a potential subject had had any previous neuropsychological assessment, the patient was not included. When applicable, the normal controls had to meet these criteria. Hence, any observed differences between this sample of MS patients and the control group are most likely due to MS.

The resulting sample had relatively benign physical disability while potential confounding variables were minimized. However, by employing strict sampling criteria, the deleterious effects of MS may be underestimated. For example, those patients who are in the midst of a relapse might likely be more depressed (Cleeland et al., 1970) and may be less likely to be doing social and recreational activities. In addition, by excluding patients
who had psychiatric disorders predating the onset of the disease, patients where the first manifestations of the disease were considered as psychiatric problems would be excluded. This group, in all probability, would have been impaired on measures of social activity. Hence, any differences that are found in the mild, stable form of the disease can only be assumed to underestimate the effect size for the MS patients.

Related to the sampling and generalization issue is the potential problem of whether the population from which the sample was drawn is representative of the population of MS patients in general. In their paper on external validity of experiment, Bracht and Glass (1968) discuss the difference between the experimentally accessible population versus the target population. They define the experimentally accessible population as the population of subjects available to the experimenter and the target population as the population of subjects about whom the experimenter is interested to generalize the findings. The current study uses a clinic based sample. The use of this type of sample may be biased in terms of a different type of patient selection. For example patients who are aware of their problems and see the need for treatment may be more likely to use the MS clinic. Rao et al. (1991a) have suggested that a sample drawn from a local MS society may be more representative of the entire MS population. Nelson, Franklin, Botelier, Baum and Burks (1988) have also suggested that University based samples may under represent those patients who experience a milder course.
However, they found that there were no differences in employment status between a clinic based sample and the "general population" of MS patients. Hence, although the experimentally accessible population used in this investigation may not be representative of the entire MS population, the bias, if present, in all probability underestimates the degree of social disability.

The second issue of concern is whether the control group was suitable for the research question. Clearly in a static group design there is no perfect control group. The "normal" control is often used in MS research but lacks the elements of medication effects, hospitalization and the effects of having a chronic, disabling disease (Rao, 1986). Other control groups have been used such as patients with Huntington's disease (Caine et al., 1986), chronic pain (Rao & Hammeke, 1984), Muscular dystrophy (Jambor, 1969) and brain damaged (Ross & Reitan, 1955). Each type of control group has its own strengths and drawbacks for potential research strategies depending on the hypothesis in question. The control group used in this study was selected for minimal confounds. Since the MS patients provided their own controls (each patient was asked to recruit a person who was comparable in background), the two groups were similar in demographic variables. As the research question was to what extent MS was interfering with the lives of the patients, not whether the effects of MS are different from other neurological disorders, a normal control group was appropriate.
The third issue to be addressed are the potentially confounding variables of instrumentation and fatigue. First, the MS patient and his or her control were tested on the same day, throughout the four years of the study. Therefore if any of the testing instruments changed over time (i.e. deterioration of the tape recording instruments, sensitivity of the interviewer), both groups should have been affected equally. Secondly, fatigue has been suggested as a possible reason for lower scores on neuropsychological tests. This potential confound was controlled by varying the order of presentation of tests and having predetermined rest breaks for all subjects. Furthermore, MS patients perform as well as normals on certain ability tests such as verbally mediated material but do considerably worse on other tests (i.e. memory and constructional functions). If fatigue were the underlying reason for cognitive problems in MS, then deficits should be observed on all tests. Hence, it is unlikely that either fatigue or instrumentation problems could explain the deficits on neuropsychological or social activity measures.

A fourth precaution in the interpretation of the results of this study is the issue the overall type I or experiment wide error rate. Any time a large number of significance tests are performed, the probability of finding one or more significant effects just by chance is increased. The major question in this experiment was to what extent each of the symptoms of MS were affecting the social life of the patient and a total of nine
significance tests were done to address this question. All other tests of significance were performed to validate the appropriateness of the grouping procedures. Hence, when calculating the experiment wise error rate, only the crucial nine tests of significance were included with p=.05 as the contrast-wise error rate. The overall alpha was calculated as .37 using the Tukey's method (Howell, 1987).

A related question is whether in this study it is more detrimental to make a type I error (finding a significant effect when none exists) or a type II error (failing to find an effect when one does exist). In a study such as this, it would be worse to make a type II error and, for example, conclude that cognitive impairment has no effect on social enjoyment and employment status. One way of counteracting a high false positive rate is to decrease the per comparison alphas. However, by doing this procedure, the type II error rate increases. Furthermore, by examining the group by group effects found in the current study, it is fairly unlikely that both depression effects occurred just by chance and even more unlikely that all three cognition effects were artifacts. Therefore, the experiment wise error rate may be indicative of one or more false positive results, however, a type I error is preferable in this type of research.
The final issue to be discussed is the definition of depression. In the current study, depression was defined as an elevation of self reported depressive symptoms on the Beck Depression Inventory (BDI) relative to the normal controls. Those MS patients who scored in the high end of the BDI scale were labelled "depressed". The mean score for the depressed group is 16.2 which is in strong contrast to the non-depressed group who had an average of 5.1 and the normal controls with a mean score of 3.5. According to the guidelines set by the instrument (Beck et al., 1961), a score of 16 would be indicative of moderately severe depression. Although the definition of depression used in the current study is not equivalent to the psychiatric diagnosis of depression, it is consistent with depressed mood.

Significance

Findings

The purpose of the first analysis was to determine whether a group of MS patients who were cognitively impaired could be identified. The results of this analysis suggest that there exists a subsample of mild, R/R MS patients who are cognitively impaired. The impairment experienced by these people is a wide ranging deficit, affecting many different functions including memory, abstraction ability, reasoning, general intelligence, visuomotor tracking and information processing efficiency. The
results of the first analysis also suggest that neither demographic factors nor neurological factors could account for the cognitive impairment in this group. These results are consistent with the more recent literature on the subject of cognitive loss in early MS. Cognitive deficits have been reported in early MS (van den Burg et al., 1987; Beatty et al., 1989) and in patients with R/R disease course (Heaton et al., 1985; Klonoff et al., 1991).

The results also suggest that cognitive impairment may be an independent phenomenon from physical disability and motor/sensory losses. Specifically, even in the absence of severe physical disability (the MS impaired group had an average EDSS score of 2.2 while the normal MS group's mean was 2.0), impairments in cognitive functioning were found. Nor does performance on motor/sensory tasks seem to be predictive of cognitive functioning. Inconsistent results have been reported in the literature regarding the relationship between cognitive impairment and extent of physical disability. Some researchers have found a weak correlation between the two (Beatty & Gange, 1977; Surridge, 1969; Stenager et al., 1989), while others have found no relation (Franklin et al. 1989; van den Burg et al., 1987; Rao et al., 1984; Lyon-Caen et al., 1986). The results of this study support the latter finding of no strong relation between cognitive impairment and physical disability.
The mathematical reasons for the inconsistencies in the literature regarding the relation between severity of illness and status of cognitive functioning have been discussed in chapter 2. A more common sense explanation for these discrepancies may be found by examining lesion distribution. Given the nature of the disease, lesions may occur at any given site. Depending on the location and size of the lesion, different patterns of deficits may occur. For example, a MS patient with lesions only in the spinal cord may have severe physical disability, but since the cortex is spared, the disease may have no impact on his/her cognitive functioning. Similarly, a patient without lesions in the motor/sensory areas, but with lesions in other areas of the cortex may have the opposite pattern of deficits. Although the above assertion has not been formally tested in the literature, there is some evidence to suggest that a subsample of patients may have predominantly spinal cord lesions early in the disease course.

The two MS groups did not differ from one another on the "mentation" functional scale (a measure of cognitive dysfunction), an outcome which was not consistent with the results of the neuropsychological investigation. The mentation score is graded on a continuum from 0 (normal) to 5 (dementia or chronic brain syndrome). The cognitively impaired group had an average score of 0.11 while the cognitively normal MS group had an mean score of 0.03, both scores translating into essentially normal mental status (a score of 1 is given when there is
evidence of mild alteration of mood). Scores on the mentation scale were not significantly different between the two MS subgroups. However, using a more comprehensive examination, one group would be categorized as having problems in cognition. Hence, using more sensitive techniques to assess the presence or absence of impaired cognition, a higher, and possibly more accurate, estimate of the status of cognitive functioning is found than with the mentation score. These results are in agreement with those of Peyser et al. (1980) who reported more patients with cognitive impairment were found with a comprehensive neuropsychological battery than with a standard neurological exam.

The purpose of the second analysis was to determine whether being cognitively impaired lead to a decrease in psychosocial functioning. The results of this analysis suggest that cognitive impairment is related to a decrease in social, vocational and recreational activities relative to a group of MS patients who are not cognitively impaired and a group of normal controls. The findings indicate those patients who are experiencing cognitive problems are more likely to be unemployed or working part time, less likely to be engaging in social or recreational activities and more likely to be pessimistic about the future. However, there does not seem to be an effect on the kinds of social and recreational activities undertaken by members this group relative to the other groups. These findings suggest that
cognitive impairment may be interfering with MS patients' ability to carry on normal life activities.

In their small sample of minimally physically impaired MS patients, Franklin et al. (1989) found that two thirds were cognitively impaired to such a degree that these people were significantly functionally disabled at work or at home. Rao et al. (1991b) found that being cognitively impaired was most disabling in terms of remaining employed and socially and recreationally active. The above findings are reinforced by the results of the current study.

The third analysis was performed to determine whether cognitive impairment, depression, or physical disability was more predictive of social disability. Cognitive impairment was found to be the most handicapping for these MS patient, leading to a significant decline in the ability to remain in the work force, more problems maintaining the same level of social and recreational activities and a reduction of the level of optimism towards the future. These results are consistent with the findings of Rao et al. (1991b) and Franklin et al. (1989).

The results of the current study found that being depressed was detrimental to the ability to remain active in the work force and to the number of leisure activities undertaken. The findings of the current study also indicate that physical disability did not lead to a decrease in any of the social outcome measures.
The average EDSS for the physically disabled group was 3.9, which translates into being fully ambulatory without aid with one functional system a grade 4 (Kurtzke, 1983). Therefore, in the mild stages of MS, physical disability per se does not appear to be as disabling as cognitive impairment and depression. However, as physical disability increases, the associated negative effects would likely become more apparent.

The results of the Analysis III also suggest that, due to the nominal Phi coefficients that were observed, impairment in each of the symptoms can be independent. Although there was some overlap in terms of group membership, the majority of subjects were either unimpaired (51.9%) or impaired on only one symptom (37%). This finding is consonant the more recent literature on the relationship among cognitive impairment, depression, and physical disability (Rao et al., 1991a; Minden, Orav & Reicht, 1989).

Cardinal Findings

The cardinal findings of this study are three-fold. First, a group of MS patients who were cognitively impaired relative to the normal sample were found. Similarly, a group of patients who were depressed were also identified. These two groups were found even though the sample was comprised of young, early, mild, R/R MS patients. A third group was defined based on the degree of physical disability. Second, the three symptoms seem to be
relatively independent. Third, cognitive impairment seemed to be most debilitating in terms of maintaining employment and remaining socially and recreationally active. Depression seems to be the next most disabling followed by physical disability which, at this mild stage, did not seem to have any palpable effects on vocational and recreational activity.

Implications

There are three main themes of this project which have implications for clinical use. First, because estimates of cognitive and affective functioning are needed to plan realistic life goals for the patient and family, all patients should undergo a comprehensive neuropsychological examination (as opposed to a brief mental status exam or neurological assessment of cognitive function) as well as an assessment for the level of depression early in the course of the disease. Second, since cognitive impairment, depression and physical disability can be independent phenomena in mild R/R MS, successful treatment of one symptom (i.e. depression) does not necessarily lead to a decrease in other areas (i.e. cognition). Finally, each of the three symptoms of MS can contribute to social disability, however, some appear to be more handicapping than others.
The first clinical implication to be discussed is the need for the MS patient to undergo an in-depth neuropsychological assessment, including a determination of their level of depression. Hashimoto and Paty (1986) discuss the ethical dilemma involved in discussing the potential problems of MS when speaking to patients about their diagnosis. They state that there has been a tendency in medicine to "protect" the patient from the harsh realities of the disease. In some cases, the patient's neuropsychological status is a sensitive issue, and some patients may not wish to know their status. Furthermore, the clinician who focuses on cognitive and affective problems may create an unwarranted anxiety for the patient and family. However, if the potential problems associated with MS are not addressed, the patient's family, employer, or others may inappropriately attribute the patient's forgetfulness or inability to make decisions as an attempt for attention or sympathy rather than to the disease. Hence, an accurate assessment of cognitive functioning is crucial to supply potentially valuable information for patients and others to plan realistic life goals.

Complete neuropsychological assessment can be time consuming, expensive and tiring. Neurological examinations of mental processes, on the other hand, are quick, easy to administer and relatively inexpensive. However, the current
study indicated that mental status examinations may not be sensitive enough to detect the cognitive problems experienced by the MS patient, a conclusion that others have drawn as well (Peyser et al., 1980). Hence, for adequate knowledge of how MS is affecting the patient, neuropsychological assessment with an extensive battery of cognitive tests is crucial.

In addition to neuropsychological assessment, determining the level of depression in the mild MS patient can provide information for patients, family members and others with respect to the emotional changes that may be occurring. A quick self report measure may be all that is needed. However, some of the popular depression inventories contain items which are indicative of somatic body complaints common in MS and could be mistaken for symptoms of depression. Therefore, care should be taken in the choice of such measures and in the analysis of the final result. Nevertheless, assessment of the level of depression is critical for understanding how the disease is affecting the individual MS patient.

Depending upon the results of the assessment of cognitive impairment or depression, the choice of treatments will be influenced. Some MS treatments are known to cause mood and cognition related side effects. For example, methyl prednisone, an anti inflammatory drug used to control acute exacerbations, is more likely to cause euphoric side effects (Williams, 1981). However, in severe cases or upon withdrawal of the drug,
depression has been noted (Williams, 1981) and a clinician may decide not to treat a depressed patient with this drug. In addition, both Baclophen (anti-spastic) and ditropan (anticholinergic for bladder control), two drugs commonly used in MS, have been reported to induce cognitive side effects (Canadian Pharmaceutical Association, 1989). The potential for reduced alertness may be even more problematic for the MS patient currently experiencing cognitive problems. Therefore, it is important to assess cognitive and affective functioning and to incorporate these results into the determination of a treatment plan.

Independence of Phenomena

The second implication of this study is related to the finding of the relative independence of the three symptoms: cognitive impairment, depression and physical disability. Although these symptoms can exist together in the same patient, the current study suggests that they are not causally related. The implication that follows is that impairment in one symptom, does not necessarily predict impairments in other symptoms.

The independence of the three symptoms is an important factor to consider when establishing rehabilitative programs for the MS patient. For example, if a patient with both depressed mood and cognitive problems is seen by a therapist, the clinician may assume that the cognitive problems are a result of the
depression, and thus, can be alleviated by treating the depression. However, by merely treating the depressed mood, the problems in cognition may not be helped. Similarly, depression in MS has been suggested as a reaction to the loss of physical function and is frequently left untreated. Antidepressant therapy (the treatment of choice for endogenous depression) however, has been found to be beneficial for the depressed MS patient. Therefore, by recognizing that all three problems are not likely causally related, each of the symptoms can be treated individually and the MS patient may benefit optimally from his/her rehabilitative program.

**Differential Effects on Social Ability**

The final implication of this study relates to the differential effects of each of the three symptoms on psychosocial functioning. The results of this study should make those associated with MS patients aware of the potential psychosocial adaptation problems which can be related to symptomatological impairments outlined above. The MS literature dealing with the effects of impaired cognition, depression and physical disability on social and vocational handicap is limited to studies concerning the effects of one symptom without adequately investigating the relative effects of each. Hence, the current study makes an important contribution to the field.
Clearly, the symptoms focussed on in the present study contribute in varying degrees to the social disability experienced by the patient. It is therefore critical for the clinician to acknowledge the existence of and potential problems associated with each symptom. Instead of prescribing treatment plans based on physical problems, rehabilitative energy should be spent on problems associated with cognitive and affective changes. For example, the effect size of cognitive impairment on vocational status could be decreased by teaching cognitive retraining techniques (i.e. memory enhancement). Whether the patient can remain employed, but by taking on a less mentally challenging position, is an alternative that could be investigated. In terms of leisure activities, life-style changes could be made to lessen the impact of cognitive impairment on ultimate life satisfaction. If the patient is depressed, antidepressant therapy has been shown to have modest beneficial effects in MS (Schiffer & Wineman, 1990) and may therefore be successful in maintaining premorbid levels of social and recreational activity as well as employment status.

Ideas for future research

The results of this study suggest that cognitive impairment may be the most disabling aspect of the disease in the early stages. Longitudinal assessment of these MS patients can give very important information about the disease progression. One question that could be asked is whether cognitive functions in
the identified group of cognitively impaired MS patients continue to decline with disease progression. For those patients who are depressed early in the disease, does their depression tend to get worse later in the disease or can their depression lessen? With respect to social outcome measures, later in the disease, is cognitive dysfunction the most handicapping of the symptoms of MS? Can the phenomena (cognitive impairment, depression and physical disability) still be independent later in the disease course? All these questions could be addressed using a longitudinal approach.

The results of this study suggest that perhaps measures of social disability could provide an informative benchmark in order to measure treatment effectiveness. For example a hypothetical case study could be as follows. A moderately depressed patient is tried on an antidepressant medication. After a period of time, this person's progress is monitored. A decrease of 4 points is seen on the BDI (which brings her score from 19 to 15, still in the moderately depressed range). However, before beginning the treatment, this person was only working part time. After treatment, this person has increased her work load to three quarter time and is beginning to regain previous levels of social functioning. The social outcome measure is much more interesting and informative in terms of therapeutic success than the 4 point drop on the BDI. A future study might use social outcome measures as an estimate of the successfulness of a particular therapy. For example by teaching cognitive coping
skills (i.e. memory enhancement techniques) to a group of MS patients who are cognitively impaired, an assessment of the therapeutic intervention could be made in terms of the certain specific social outcome measures.

Another interesting question to ask is whether there is a common underlying lesion or lesion pattern for each of the symptom groups. For instance, does the cognitively impaired group have a different layout of lesions than does the depressed group or the physically disabled group? Do any of the groups have more lesions than the other groups? Lesion pattern analyses have been performed, correlating ventricle-brain ratios (VBR) (Rao, Haughton, St. Aubin-Faubert, & Bernardin 1989a), size of the corpus collosum (Rao, et al. 1989a), total lesion area (Rao et al. 1989a) and atrophy of the corpus collosum (Rao, Bernardin, Leo, Ellington, Ryan & Burks. 1989b) with other disease related variables or cognitive functioning. However, Only two attempts have been made relating site of lesion with psychiatric (Honer, Hurwitz, Li, Palmer, & Paty, 1989) or psychological variables (Boyle, 1992; unpublished doctoral dissertation).
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