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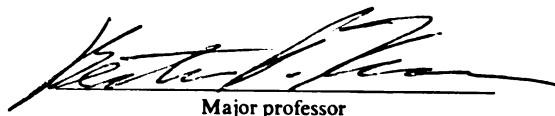
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ALTERNATIVE EXPLANATIONS FOR NEUROPSYCHOLOGICAL IMPAIRMENT
IN MULTIPLE SCLEROSIS PATIENTS

By

Robert Wallace Hill

A DISSERTATION

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ABSTRACT

ALTERNATIVE EXPLANATIONS FOR NEUROPSYCHOLOGICAL IMPAIRMENT IN MULTIPLE SCLEROSIS PATIENTS

By

Robert W. Hill

Multiple Sclerosis (MS) is a disabling neurological condition of unknown cause that affects the central nervous system white matter fiber tracts in the brain and spinal cord. MS is associated with a range of neuropsychological problems including specific deficits with sensorimotor, attention, memory and conceptual problem-solving abilities.

This investigation utilized both neuropsychological measures and magnetic resonance imaging (MRI) of the brain to assess 41 MS patients. The MRI data was scored for location and size of MS lesions by three trained raters independently. The relationship between the location and quantity of central nervous system deterioration observed through MRI and performance on a battery of neuropsychological measures was investigated. Analyses revealed that MS lesions were dispersed in different regions of the brain for each patient rather than a more focal distribution in only one region of the brain. Lesions occurred predominantly in white matter tissue in several areas of the brain, typically adjacent to the ventricles. Discrete relationships between lesion location and specific neuropsychological deficits were not detectable due to the diffuse distribution of lesions. Individual variability in

the effects of MS on the brain and on neuropsychological performance was considerable.

Confirmatory factor analyses revealed two clusters of neuropsychological functions related to MS lesions that formed second order factors. One second order factor, composed of measures that involved sensorimotor, symbol substitution, visuospatial and verbal fluency abilities, was sensitive to MS lesions. The other second order factor, composed of measures that involved memory, conceptual problem-solving, digit span and an auditory serial addition task, was somewhat less sensitive to MS lesions. A cluster of measures hypothesized to involve processing speed was not supported by the data as a unidimensional factor.

Path analyses produced a causal model in which the second order factor of neuropsychological functions more sensitive to MS lesions, that involved sensorimotor, perceptual organizational and timed abilities, accounted for variance before the second order factor that was less sensitive to MS lesions, that involved working memory, abstract reasoning, verbal comprehension and an auditory addition task.

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INTRODUCTION

Multiple Sclerosis (MS) is a disabling neurological condition of unknown cause and a variable prognosis with a prevalence of approximately 30-60 cases per 100,000, depending upon geographic region (Baum & Rothchild, 1981). The disease affects the central nervous system white matter fiber tracts in the brain and spinal cord, producing lesions that appear to attack the myelin sheath exclusively, generally sparing the axons and neurons. Clinical symptoms characteristic of MS include extremity weakness, optic neuritis and sensory disturbances (McAlpine, Compston, & Lumsden, 1955). MS may also be associated with a range of neurocognitive deficiencies including declines in general intellectual functioning as well as specific deficits in attention, memory and conceptual problem-solving (Petersen & Kokmen, 1989; Rao, 1986). The neurocognitive consequences of MS have been relatively neglected until recently and have yet to be fully defined (Peyser & Poser, 1986).

The relatively recent technology available through magnetic resonance imaging (MRI) provides the best available in vivo opportunity to detect demyelinating lesions associated with MS (Young et al., 1981; Ormerod et al.,

1987). MRI data in conjunction with neuropsychological test data provide a means to detect specific relationships between lesion location and cognitive deficits.

The neuropsychological deficits associated with MS may be explained through several different causal paradigms. One approach to explaining these deficits is to document a relationship between the location of specific lesions in the CNS and the specific cognitive deficits suffered by individual patients. Previous research efforts to document this relationship between lesion location and functional deficit have not fared well (Rao, 1986). However, previous investigations have also relied on less sophisticated methods for defining lesion location and size than could be brought to bear on data derived from MRI. The present study employs a comprehensive, multiple-scorer coding protocol for assessing MRI evidence of demyelinating lesions that furnishes more specific data for lesion location and size than previous investigations have provided. Expected relationships between the location and size of discrete lesions and specific neuropsychological deficits are examined in this study, consistent with the neuropsychological literature on the relationship between localized brain damage and cognitive impairments.

A second paradigm for understanding the relationship between MS lesions and cognitive deficiencies has been suggested in which deficits are understood to be a

consequence of a general decline in information processing speed due the disruption of white matter conducting pathways (Litvan, et al., 1988; Rao et al., 1989). Specific neuropsychological deficits are suggested to be the consequence of general information processing deficiencies associated with disruption of major white matter tracts rather than the result of specifically localized discrete lesions. This study investigates predictions derived from this model such as the relationship between deficiencies in information processing and corpus callosum atrophy.

A synthesis of the above models suggests that some of the neuropsychological deficits experienced by MS patients might be explained through the discrete location of certain lesions depending on how specific neural pathways are affected for those functions, while other functional deficits involving more complex neural pathways might be affected by general white fiber tract interference. This investigation seeks to apply neuropsychological and MRI data to evaluate these different explanations of deficits experienced by MS patients.

REVIEW OF LITERATURE

This review will examine the current state of knowledge regarding neuropsychological consequences of multiple sclerosis. After an overview of the clinical manifestations, prevalence, and diagnosis of MS, the literature regarding cognitive deficits will be examined. Next, literature suggesting that MS deficits are the consequence of slowed information processing speed, consistent with a pattern of deterioration labeled subcortical dementia, is presented. Additionally, the application of magnetic resonance imaging technology to understanding MS will be examined to provide background for the methods employed in the present investigation.

Multiple Sclerosis

Clinical Manifestation. MS is a disease that affects the white matter of the central nervous system producing lesions known as plaques that appear to attack the myelin sheath exclusively, most often sparing the axons and neurons (Peyser & Poser, 1986). Lesions do occasionally affect grey matter. The disease is a chronic, sometimes disabling, neurological condition with a highly variable course, and a typical age of onset between 15 and 45. The disease

produces successive exacerbations and remissions in approximately 90% of patients in the early stages (Matthews, et al., 1985; Rao, 1986; Silberberg, 1977). The remaining 10% experience a chronic progressive course without remission, usually with age of onset after 40. The disease may become progressive at any point in time after onset, and estimates of the percentage of cases that become progressive vary widely due to differing samples of patients and protocols for classifying stages (Matthews et al., 1985). Some 5-15% of patients experience a mild manifestation of the disease in which successive attacks may be separated in time by 20 or more years (Rao, 1986). The disease does not shorten life appreciably (Confayreux, Aimard, & Devic, 1980) but does cause impairment and medical expenses comparable to other more fatal conditions such as heart disease and respiratory conditions (Inman, 1983, cited in Rao, 1986).

The signs and symptoms of MS vary considerably among patients. The most common initial symptoms include: extremity weakness (40%), optic neuritis (22%), sensory symptoms (21%), double vision (13%), vestibular symptoms (7%), urinary symptoms (4%), and hemiplegia, trigeminal neuralgia or facial palsy (3%) (McAlpine, Compston & Lumsden, 1955). The most generally prevalent symptoms, occurring in more than 75% of patients at some time, include: ocular disturbances, muscle weakness, spasticity and hyperflexia, Babinski's sign, absent abdominal reflexes,

dysmetria or intention tremor and bladder disturbance. Other symptoms that occur in approximately 50-75% of cases include: nystagmus (rapid, involuntary oscillation of the eyeballs), gait ataxia, dysarthria or scanning speech, paresthesia, and objective alterations of vibratory and position senses (Peyser & Poser, 1986).

In addition to motor and sensory disturbances, lesions in the cerebral white and grey matter can cause cognitive deficits, mood disturbance, personality change, and infrequently, psychosis (Peyser & Poser, 1986). Such neuropsychological correlates of MS have been relatively neglected until recently and will be reviewed further below.

Onset of MS is usually involves an acute manifestation of several symptoms with the subsequent disease course characterized by exacerbation and remission of symptoms. Complete remission of the first symptoms occurs frequently but in subsequent attacks remission may not occur or may be incomplete (Peyser & Poser, 1986). The course of the illness typically extends for one or more decades with variable severity in symptoms. A number of individuals appear to develop a pattern of symptoms that remains static over time suggesting that the disease is arrested (Peyser & Poser, 1986).

The clinical manifestation of MS symptoms are believed to be the consequence of plaques disturbing the central nervous system. However, there is not a one to one

correspondence between plaques and symptoms. Autopsy studies have shown that the number of plaques discovered is often much greater than suspected on the basis of clinical signs and symptoms (Namerow & Thompson, 1969). Research data suggest a lack of correspondence between the course of the disease and the manifestation of symptoms. Exacerbation of symptoms is believed to occur as a result of existing plaques through physical alterations as well as from the production of new plaques (Peyser & Poser, 1986). In a study of 105 attacks experienced by 60 MS patients Thygesen (1953) observed new symptoms suggestive of new plaque occurred in only 19% of attacks. Attacks often involve a previously damaged site in the central nervous system indicated by the replication of previously remitted symptoms.

Several factors have been established as significant to the onset of symptoms, either new symptoms or recurring symptoms. Heat is the best recognized factor leading to the onset of MS symptoms (Peyser & Poser, 1986). Apparently, nerve fibers that have suffered loss of part or all of the myelin sheath are impaired further by even slight rises in body temperature in the conducting of neural impulses. Other factors include changes in calcium concentration, dehydration and intercurrent infection, particularly of the bladder (Peyser & Poser, 1986). Emotional stress and physical trauma can also bring on exacerbation of the

disease. Poser (1979) observes that stress has not been proven to cause new plaques to develop, but stress has been established as a factor leading to the development of new symptoms or exacerbation of pre-existing symptoms which sometimes remain permanent.

Etiology. While the cause of MS remains unknown, there are two schools of thought regarding the cause of the illness (Poser, 1978). One suggests that MS is caused by a slow-acting virus with a long incubation period of years duration. It is believed that the disease is acquired sometime in childhood even though symptoms do not typically appear until patients are in their 30's. Numerous searches for a virus have failed (Peyser & Poser, 1986). MS patients have been found to have higher levels of antibodies against measles than does the rest of the population. However non-affected siblings of MS patients have also been shown to have high levels of antibodies to measles (Brody, Sever & Hanson, 1971).

The other major theory suggests that MS results from some alteration in the body's immune system, perhaps triggered by a wide variety of viral infections (Poser, 1978). Studies have focused on whether the immune system is too active or too deficient but conclusive findings are yet to come (Peyser & Poser, 1986).

Poser (1980) has suggested that the MS disease process involves an alteration in the normally impermeable blood-

brain barrier. "This rekindles a very old theory that the plaques of MS invariably arise around a small blood vessel and result from the destruction of the myelin by some substance that passes from these blood vessels into the substance of the brain" (Peyser & Poser, 1986). This theory has yet to be substantiated.

Epidemiology. The prevalence (cases present at one time per unit population) of MS varies notably by geographic location. The highest prevalence rates occur at latitudes furthest from the equator, in both the northern and southern hemispheres. Kurtzke (1983a) estimates the prevalence of MS in latitudes above the 37th parallel in the United States and northern Europe to be higher than 30 per 100,000, with variation by local geographic region. Baum and Rothchild (1981) estimate the prevalence in the United States above the 37th parallel to be 69 per 100,000. Kurtzke observes that latitudes that bound the high prevalence regions have a more modest ratio of approximately 10-20 per 100,000. Baum and Rothchild (1981) estimate prevalence at 35 per 100,000 in the United States below the 37th parallel. The mean age of onset is 33 years, with the average age of onset for females being two to three years earlier than for males, and MS affects females 1.7 times more often than males (Baum & Rothchild (1981). In a longitudinal study of 150 MS patients, Sibley, Bamford and Clark (1984) found a female to male ratio of 1.4:1. (Kurtzke (1983a) reports that all

world wide geographic regions where a high or medium prevalence rate for MS is reported are predominately white populations. In America, blacks, and Asians and possibly Indians have much lower rates of MS than do whites. There have been no reports of MS among African blacks (Peyser & Poser, 1986).

Kurtzke (1983a) reports provoking findings regarding migration studies of MS patients with implications for the etiology of the disease. On the whole, individuals retain the risk of their birthplace if they migrate after age 15. If they migrate before age 15 they acquire the risk of their new residence. Kurtzke (1983a) suggests that this migration data in addition to observable geographic clustering demonstrates that MS is likely an acquired, exogenous environmental disease. Kurtzke (1983a) also marshals further epidemiological data in support of this conclusion in reporting data on two "epidemics" of MS in Iceland and the Faroe Islands. Both regions experienced a distinctly low prevalence of MS prior to the advent of World War II, and then a high prevalence after the war. Both regions also were subjected to large occupation populations of allied soldiers during the war years which Kurtzke suggests were responsible for transmitting the disease to the local populations.

MS has also been shown to occur in patients with other family members experiencing the disease in approximately 10%

(Peyser & Poser, 1986) or 17% (Sibley, Bamford & Clark, 1984) of cases. The role of a genetic factor in MS has been investigated in numerous studies of families with more than one blood-related member with the disease but have failed to demonstrate, in most instances, any genetic concordance (Ebers, et al., 1982).

Diagnosis. There is no single diagnostic test for MS. Diagnosis is made using a number of methods to ascertain the presence of more than one lesion involving the white matter of the central nervous system. Diagnostic efforts to identify CNS lesions include: a history, neurological exam, analysis of cerebral spinal fluid components, multi-sensory evoked potentials and radiologic procedures such as computerized tomography (CT) and magnetic resonance imaging.

One of the best known diagnostic schemes, developed by Schumacher and others (1965), requires: (1) objective abnormalities on neurologic examination attributable to dysfunction of the CNS; (2) evidence of involvement of two or more parts of the CNS by neurologic examination or by history; (3) the objective neurologic evidence of CNS disease must reflect predominantly white matter involvement (ie. fiber tract damage); (4) the development of neurological symptoms must have occurred temporally in one of the following patterns: (a) in two or more periods of worsening separated by a period of one month or more, each episode lasting at least 24 hours, or (b) in a slow

progression of signs and symptoms over a period of at least six months; (5) the age of the patient at onset of the disease must be in the range of 10-50 years; and (6) the patient's signs and symptoms can not be explained better by some other disease process.

MS is difficult to detect in the early stages, especially if the symptoms could be explained by a single lesion in the cerebrum, cerebellum, brain stem or spinal cord (Rao, 1986). Another problem in the diagnosis of MS is that the symptoms are often transient, lasting only a few hours or minutes, and are often of the type associated with hysterical conversion reactions. If the symptom onset closely follows a stressful event or if there is psychological elaboration of a genuine symptom, the diagnosis of MS is difficult (Peyser & Poser, 1986; Poser et al., 1984).

A number of additional diagnostic techniques have been developed that can be helpful in diagnosing MS. A simple, harmless and inexpensive ancillary test for MS is the hot bath test, which can produce abnormal neurologic signs in MS patients by inducing hyperthermia (Malhotra & Goren, 1981). The measurement of evoked potentials while stimulating visual, auditory and somatosensory pathways has proved useful in detecting lesions suspected on the basis of symptom report, and in revealing lesions that were asymptomatic (Deltenre, et al., 1979; Chiappa, 1980).

Peyser and Poser (1986) also report that refinements in the measurement of the protein components of cerebral spinal fluid (CSF) have led to the identification of special types of immunoglobulin G, termed oligoclonal bands, in over 90% of MS patients (Ebers & Paty, 1980). None of these ancillary tests for MS provide definitive evidence for the diagnosis by themselves, but can contribute converging evidence (Poser et al., 1984).

The diagnosis of MS has been considerably assisted with the advent of CT and MRI images. CT scans have proved useful in identifying scattered lesions, including the classical periventricular lesions, as well as detecting cerebral atrophy (Ebers, Paty & Sears, 1984). Lesions detected through CT scans in patients with acute symptoms have been shown to be active plaques and may also be a consequence of increased water content in the affected area (Ebers, Paty & Sears, 1984). MS lesions typically occur around the ventricles. Less lesions are detected through CT scan as compared to MRI. Lesions detected through CT scan can be enhanced by administering a high dose of iodine-containing contrast material intravenously and delaying the procedure to allow the contrast material to penetrate the blood-brain barrier in areas made permeable by the disease process (Ebers, Paty & Sears, 1984). Evidence for cerebral atrophy commonly found in MS patients through CT scans is enlargement of the ventricles, sulci, cisterns and fissures

(Gyldensted, 1976; Ebers, Paty & Sears, 1984). Evidence of atrophy is believed to be a consequence of shrinkage in surrounding neural mass due to the loss of myelin.

The application of MRI to the detection of MS in the CNS provides finer resolution images than CT and has enabled the detection of more lesions (Ebers, Paty & Sears, 1984; Lukes, et al., 1983). MRI also is a safer procedure, providing images without exposure to radiation and without the need to inject potentially harmful contrast material to enhance diagnostic yield. Disease processes other than MS can give a similar impression, such as vascular diseases and metastatic tumors, so brain imaging alone can not be used to make a diagnosis (Peyser & Poser, 1986).

Because of the many ancillary procedures useful in making a diagnosis of MS, clinical research criteria have been established with guidelines to classify patients with probable or definite manifestations of the disease. Earlier guidelines established by Schumacher and others (1965) have been revised to incorporate newer technology and research data pertinent to the diagnosis of MS. Guidelines established by Poser, Paty and others (1984) incorporate the previously described imaging technology, evoked response studies, measures of cerebral spinal fluid and neuropsychological evaluation to describe specific diagnostic criteria necessary for research studies and useful for clinical practice (Peyser & Poser, 1986; Rao,

1986). The criteria suggested by Poser and others (1984) suggest classifying the diagnosis of MS as either definite or probable, with two subgroups: clinically supported and laboratory supported, depending upon the nature and strength of diagnostic evidence.

In an effort to classify MS patients according to disease severity, Kurtzke (1970) developed a 10-point global disability rating scale, called the Disability Status Score. This scale ranged from 0 (no obvious symptoms) to 9 (bedridden due to MS), with differentiation based predominately on ambulatory skills. Kurtzke (1983b) subsequently revised the scale to include 20 points to improve sensitivity in the middle range. This scale has been frequently used in studies involving the diagnosis and treatment of MS but has been criticized for its insensitivity to disease-related changes involving the cerebrum (Rao & Hammeke, 1984a; Rao et al., 1985). Physical disability is not necessarily related to the degree of neurologic involvement or to the extent to the disease process (Franklin et al., 1989; Peyser & Poser, 1986).

Neuropsychological Deficits Associated With Multiple Sclerosis

History. Cognitive deficits experienced by MS patients were initially reported by Charcot in 1877 with descriptions of symptoms and pathology and observations such as: "marked enfeeblement of memory; conceptualizations are formed slowly; the intellectual and emotional faculties are blunted" (p. 160). Other early (1891-1929) case studies, published in the French and German medical literature, reporting varying intellectual, emotional and psychotic disturbances due to MS, are cited in Peyser & Poser (1986). Early case reports that included dementia as a consequence of MS were published in the United States (Hunt, 1903; Ross, 1917).

One of the first comprehensive accounts including mental disturbance associated with MS was published by Brown and Davis (1922). They noted mental alterations in 90% of their MS cases including changes in mood, inconsistency between mood and the severity of physical symptoms and emotional lability. They reported ambiguous findings of intellectual decline, suspecting cognitive deficits in the majority of cases but observing that patients were typically unaware of their deterioration.

An early influential study of MS involving 100 patients with varied disease duration, focused primarily on affective

symptoms through the use of a psychiatric interview which asked about emotions, thoughts, bodily feelings and affective expression (Cottrell & Wilson, 1926). Cognitive functioning was not reviewed in any detail and only two cases of intellectual deterioration were reported.

In contrast, Peyser and Poser (1986) review the work of the French investigator Ombredane (1929), who was primarily interested in the cognitive deficits of MS, as they were frequently reported in European literature. Ombredane assessed attention, memory, manipulation of spatial and temporal relationships, comprehension, imagination, calculation and judgement. Of 50 randomly selected MS patients, he reported 36 with definite intellectual difficulty. Of those 36, 6 were described as globally demented and the remaining 30 had selected deficits or a partial dementia. Ombredane (1929) observed that the 30 partially demented MS patients could pass a casual mental status exam but displayed cognitive deficits during intellectual tasks. This type of partial cognitive disturbance, not easily detected by routine observation, has proven to be a characteristic pattern of cognitive disturbance in MS (Franklin et al., 1989; Peyser & Poser, 1986; Rao, 1986).

Ombredane's approach of measuring specific cognitive abilities anticipated the methods of current neuropsychological research investigations of MS. However,

Ombredane's (1929) work was not readily available in English, and early and mid-twentieth-century views of the cognitive consequences of MS were influenced more by Cottrell and Wilson's (1926) work and also by a report by the 1921 meeting of the Association for Research in Nervous and Mental Diseases which suggested, with insufficient data, that intellectual impairment was not an important symptom of MS (Peyser & Poser, 1986). The main body of neurological literature on MS has neglected cognitive deficits associated with the disease until relatively recently.

Divergent findings and opinions regarding the prevalence of neuropsychological deficits in MS patients before the 1950's was partly a consequence of the disparate populations sampled by different investigators. Samples were derived from psychiatric institutions and from different neurologic patient populations providing differing symptoms and organic involvement (Trimble & Grant, 1982). Also, prior to the 1950's, there were no well standardized and validated measures of neuropsychological functioning available.

One study utilizing an early standardized measure of cognitive abilities, the Army General Classification Test (AGCT), reported longitudinal data MS patients (Canter, 1951). A group of 23 World War II veterans who had been administered the AGCT upon entry to the service were diagnosed with MS several years later and readministered the

AGCT. A significant drop in AGCT scores was reported, with the greatest drop occurring in patients diagnosed with "severe" neurological symptoms. Canter (1951) also administered the Weschler-Bellevue to a group of 47 MS patients and 38 controls on two occasions separated by a six-month interval. As expected, the scores of the 38 controls were higher on the second administration due to the practice effect, while scores of the MS group declined.

Some earlier investigations that involved assessment protocols using the Rorschach did find evidence of organic brain damage (Scheinberg, Blackburn, Kaim & Stenger, 1953; Ross & Reitan, 1955). Peyser and Poser (1986) also observe that contradictory results using the Rorschach on MS patients that did not show evidence of organicity were based on a sample of MS patients that was biased by the exclusion of any subject with an IQ below the average range (Harrower, 1950; Harrower & Kraus, 1951).

More research involving more sophisticated cognitive measures has been conducted in recent years on MS patients. Of particular interest to this investigation is literature pertinent to disturbances in: sensorimotor abilities, attention and concentration, conceptual and abstract reasoning, memory, and visuospatial processes. Research pertinent to the experience of each of these functions in MS patients will be reviewed.

Sensorimotor Disturbances. Difficulties with sensorimotor abilities are of concern for any formal assessment of MS patients because sensorimotor problems can influence scores on some typical measures used in intelligence and neuropsychological batteries (Peyser & Poser, 1986; Rao, 1986). Several performance subscales of the Weschler Adult Intelligence Scales (WAIS) and the Halstead-Reitan battery, for instance, involve the speed and accuracy of upper-extremity motor responses or require good visual, tactile, or auditory sensory acuity (Rao, 1986). Because some of the more prevalent symptoms of MS involve sensorimotor difficulties, deficits on measures attributable to sensorimotor problems are common. Separating sensorimotor deficits from other more purely cognitive deficits in tasks which might require some combination of sensory, motor and cognitive skills is an important methodological concern in investigating MS (Peyser & Poser, 1986; Peyser, Rao, LaRocca & Kaplan, 1990; Rao, 1986).

One neuropsychological study with findings relevant to sensorimotor deficits compared 30 MS patients diagnosed by the Shumacher (1965) criteria to brain damaged control subjects using the Halsted-Reitan and other measures of motor abilities (Matthews, Cleeland & Hopper, 1970). Each MS patient was matched for age, sex, education and WAIS Full-Scale IQ with a control subject diagnosed with a CNS disorder other than MS. The MS group scored significantly

lower than the control group on measures requiring motor speed, coordination, and steadiness, including grooved pegboard performance and finger tapping rate, and on a test of tactile form discrimination skills.

In another study conducted by Reitan, Reed and Dyken (1971) the Halstead-Reitan Battery was administered to 30 subjects with a confident diagnosis of MS, and 30 control subjects who were matched for age, sex and education. The disease duration for the MS sample varied from 1 to 10 years. Significant differences were observed on almost all tasks with the exception of measures of general information, comprehension and verbal communication skills. The largest differences were seen on measures involving coordinated motor performance.

A study using neuropsychological measures to compare a sample of 20 MS patients with 20 brain damaged patients and 20 psychiatric patients, found that MS patients performed significantly worse on the grooved pegboard task and on finger tapping rate (Goldstein & Shelly, 1974). No significant differences were found for other cognitive measures.

Another study comparing 26 MS patients with 26 control subjects matched for age, sex and education used a battery designed to assess motor and intellectual functioning (Beatty & Gange, 1977). The MS subjects scored significantly less well than control subjects on the grooved

pegboard, finger tapping, static steadiness and trail-making, all of which involve sensorimotor abilities. MS subjects also performed significantly less well than controls on tasks involving short-term verbal memory, and logical and numerical reasoning. Beatty and Gange (1977) reported analyses indicating a correlational relationship between performance on motor and memory tasks for the MS patients.

Ivnik (1978) also compared a group of 14 MS patients with the same number of controls matched for age, sex and education on a battery of neuropsychological measures. The MS patients received significantly lower scores on tasks requiring motor proficiency or complex sensory discriminations, including Trails-Making and grooved pegboard tests. MS patients also performed significantly less well on some pure cognitive measures, including the Categories Test.

In a study comparing relapsing-remitting MS patients (n=57) with chronic-progressive MS patients (n=43) using an extensive neuropsychological battery, all MS patients were found to perform significantly worse than did age and education matched controls (n=100) on pure sensorimotor measures including: finger tapping, grip strength and grooved pegboard (Heaton et al., 1985). The chronic-progressive group was significantly worse than the relapsing-remitting group on the finger tapping and grooved

pegboard tasks.

Impaired sensorimotor performance by MS patients on neuropsychological measures is consistent. Such deficits have been attributed to the effect of lesions in the cerebellum, brainstem and spinal cord which can interrupt sensorimotor conducting pathways without necessarily affecting higher cognitive functions (Peyser & Poser, 1986; Rao, 1986). Peyser and Poser (1986) report a high correlation between ratings of cerebellar disturbance and grooved pegboard performance, but they also caution against attempts to make one-to-one correlations between neuropsychological deficits and anatomic lesions in MS given the typical multiplicity of lesions.

Intelligence. Findings of intellectual deficits in MS patients in MS patients have been somewhat equivocal. Most studies administering intelligence tests to samples of MS patients have found impairment while some have not.

In an investigation to assess intellectual performance in MS patients, De Smedt and colleagues (1984) administered the WAIS (not the WAIS-R) to 46 MS patients (26 men and 20 women) with a mean age of 31 years and a wide range of disease duration. MS patients achieved a mean Full Scale IQ of 84.1, a mean Verbal Scale IQ of 90.73, and a mean Performance Scale IQ of 76.45. The lowest subtest scores were achieved on the Digit Symbol and Object Assembly

subtests. No relationship was found between age, age of onset, or duration of illness and intellectual impairment.

Callanan and others (1989) administered 4 verbal subtests (Vocabulary, Arithmetic, Digit Span and Similarities), and 3 performance subtests (Picture Completion, Picture Arrangement and Block Design) of the WAIS to 48 MS patients and 46 impaired patients with an unimpaired CNS. The investigators used these seven WAIS subtests to estimate the Full Scale IQ for all subjects, and also administered two reading tests to calculate an estimate of premorbid IQ. The WAIS Full Scale IQ estimate was subtracted from the premorbid IQ estimate to produce an IQ deficit score, which was found to be significantly greater for MS patients than for normals.

Other studies using the WAIS to compare MS patients to various control groups, including normals (Jambor, 1969; Reitan, Reed & Dyken, 1971), brain damaged patients (Goldstein & Shelly, 1974; Ivnik, 1978; Jambor, 1969) and psychiatric patients (Goldstein & Shelly, 1974; Jambor, 1969) have not found significantly lower scores for MS patients.

A decline in intellectual functioning over time has been reported by some investigators. Canter (1951) administered the Weschler-Bellvue Intelligence Scale to 47 MS patients and 38 sex and age matched controls on two occasions separated by a six month interval. The MS

patients scored significantly lower than the controls on both Verbal Scale IQ and Performance Scale IQ. The greatest differences were observed for the Comprehension and Arithmetic verbal subtests and the Block Design, Object Assembly and Digit Symbol performance subtests.

Ivnik (1978) administered the WAIS twice to 14 MS patients and 14 sex and age matched brain damaged controls with an interval of three years. The MS patients scored 3-4 points lower on Verbal Scale IQ, Performance Scale IQ and Full Scale IQ, while the control subjects showed 1-3 point improvements.

Another study comparing 100 heterogenous MS patients with 100 normal controls found significantly lower scores on both the WAIS Verbal Scale IQ and Performance Scale IQ for MS patients (Heaton et al, 1985). Patients classified as chronic-progressive scored significantly lower than patients classified as relapsing-remitting on Performance Scale IQ.

Different results were reported by Fink and Houser (1966) who administered only the verbal subtests of the WAIS to a sample of 44 recent onset (less than 5 years) MS patients with a mean age of 45. After one year, a significant four point increase was observed on the Verbal Scale IQ (106 to 110). The sample was unusual in being constituted of only older and recent onset patients and thus could not be considered representative of the general MS population.

Fink and Houser (1966) also found a significant negative correlation between WAIS Verbal Scale IQ and a measure of disability. However, other studies have not found a relationship between intelligence and disability (Marsh, 1980; Rao et al., 1985). Studies have also failed to find a relationship between intellectual impairment and duration of illness (Marsh, 1980; Rao et al., 1985; De Smedt et al., 1984).

One finding regarding the intellectual impairment of MS patients detected by the WAIS that has seen robust replication is a lower Performance Scale IQ than Verbal Scale IQ. Performance Scale IQ has been found repeatedly to be 7 to 14 points lower than Verbal Scale IQ for MS patients (Cantor, 1951; Matthews, Cleeland & Hopper, 1970; Reitan, Reed & Dyken 1971; Goldstein & Shelly, 1974; Ivnik, 1978; Marsh, 1980; Heaton et al., 1985). Lower Performance Scale scores might suggest that MS interferes with tasks requiring complex visuospatial information processing. However, as mentioned earlier, Performance subtests also involve the speed and accuracy of upper-extremity motor responses or require good visual, tactile, or auditory sensory acuity (Rao, 1986). Sensorimotor disabilities can impair scores in Performance subtests and be difficult to distinguish from other abilities. The lowest Performance subtest score typically received by MS patients is Digit Symbol, which is highly susceptible to motor dysfunction, while the highest

Performance scores are achieved on Picture Completion, which is not at all affected by motor functioning.

To summarize research on intellectual impairment in MS, there is some evidence of a slight decrement in intelligence scores over time. There is evidence of an interference in visuospatial processing which can be contaminated by impairment in sensorimotor functioning. Verbal processes appear to be considerably less affected by the disease process than visuospatial and sensorimotor processes. MS patients also show larger standard deviations in intelligence subtests than controls, providing further evidence for considerable individual variability in the disease process.

Memory. MS patients have been found to have learning and memory deficits in numerous investigations (Beatty & Gange, 1977; Caine, Bamford, Schiffer, Shoulson, & Levy, 1986; Grant, McDonald, Trimble, Smith, & Reed, 1984; Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Jambor, 1969; Rao, Hammeke, McQuillen, Kharti & Lloyd, 1984b; Rao, Leo, & St. Aubin-Faubert, 1989c). These reports of memory deficits have been derived from a number of instruments assessing various dimensions of memory including: short vs. long term memory, verbal vs. visual memory, immediate vs. delayed recall, multi-trial vs. single-trial learning and recall vs. recognition memory. While MS patients show considerable

variability in memory deficits, as with most other deficits, short-term memory capacity and recognition memory appear to remain relatively unimpaired, while retrieval strategies for short and long-term memory are impaired.

Short-term memory of MS patients, as assessed using a digit span test, has been found comparable to controls (Grant et al., 1984; Heaton et al., 1985; Rao et al., 1984b; Rao et al., 1989c). When delayed recall is assessed in MS patients, typically after a 30 minute interval, scores are significantly worse than controls with verbal or visual stimuli (Caine et al., 1986; Grant et al., 1984; Litvan et al., 1988; Jambor, 1969; Rao et al., 1984b; Rao et al., 1989c). MS patients do not appear to have difficulty with memory tasks that assess recognition rather than recall abilities (Rao, 1986; Rao et al., 1989c).

The memory impairment experienced by MS patients has been reported to be unrelated to the influences of: duration of illness and degree of physical disability (Rao et al., 1984b; Rao et al., 1989c; Vowels, 1979), psychoactive medication (Grant et al., 1984; Heaton, et al., 1985; Rao et al., 1984b), and mood disturbance (Rao, 1986; Rao et al., 1989c). Rao and colleagues (1984b) found highly variable memory performance among a sample of 44 chronic-progressive MS patients, with 16 (36%) showing no impairment, 19 (43%) experiencing mild memory problems and 9 (21%) experiencing severe disruption of memory functions.

Some of the neuroanatomical implications of the effects of MS on memory performance have been suggested. Because evidence of impaired retrieval occurs for both verbal and visual stimuli cerebral lesions are likely to be bilateral rather than lateralized (Rao, 1986). MS patients who display more severe memory impairment also exhibit a flat learning curve (Rao et al., 1984b) which has been associated with prefrontal lobe lesions (Luria, 1966; Rao, 1986). Some investigators have observed that the pattern of memory impairment displayed by MS patients, where retrieval ability and verbal fluency are affected but not recognition ability, is also observed in patients with Huntington's disease (Caine et al., 1986; Rao et al., 1989c). Huntington's disease has been found to affect the neurons in the basal ganglia and prefrontal cortex (Butters, 1984).

In summary, memory disturbance in MS patients is highly variable, does not appear to follow a distinct progression, but does appear to affect retrieval abilities associated with long-term, and sometimes short-term memory while leaving recognition ability intact. This pattern of impairment has been associated with bilateral lesions in the frontal and limbic regions of the brain.

Conceptual Problem Solving. MS patients report difficulties with conceptual judgement and the planning and organization of behavior. Cognitive tests indicate that MS

patients have difficulty forming concepts, and switching concepts in response to feedback (Rao, 1986; Rao et al., 1984a; Rao et al., 1987).

Among the cognitive measures frequently administered to MS patients, the Category Test (Halstead, 1947) has frequently demonstrated impairment in conceptual problem solving (Heaton et al., 1985; Peyser et al., 1980; Reitan et al., 1971). The Category Test is a relatively complex task that involves a variety of cognitive, mnemonic, attentional and perceptual skills but yields only one score (number of errors) (Rao et al., 1987). The Category Test does not supply data to discriminate the specific kind of deficits that might lead to the low scores MS patients often obtain on this task.

A study conducted by Rao and Hammeke (1984a) assessed concept formation in 38 chronic-progressive MS patients and found that 33 of the patients could generate hypotheses and the 5 who could not were more globally impaired on other cognitive measures. The remaining 33 MS patients were found to make more errors than control subjects because of an inability to eliminate irrelevant hypotheses. MS patients tended to persevere with incorrect strategies despite negative feedback. Rao (1986) observed that similar perseverative tendencies are noted in patients with unilateral frontal tumors.

Another task of conceptual problem solving, the

Wisconsin Card Sort (Grant & Berg, 1948; Heaton, 1981) yields scores that provide information about a person's ability to generate concepts, to switch concepts in response to verbal feedback, to maintain a conceptual set, and to develop more efficient problem-solving strategies as the test progresses (Rao et al., 1987). The first study to use this test on samples of 57 relapsing-remitting and 43 chronic-progressive MS patients and 100 normal controls found that both groups of MS patients performed worse than controls on perseverative responses (Heaton et al., 1985). No significant difference was found between the relapsing-remitting and chronic-progressive patients. Other error patterns can not be analyzed because only perseverative error scores were reported.

Callanan, Logsdail, Ron and Warrington (1989) administered a shortened version of the Wisconsin Card Sort to a group of 48 MS patients and a group of neurologically impaired controls. Because they used a non-standard version of the Wisconsin Card Sort, and did not report overall differences between MS patients and controls, their results are not clear with respect to this test.

Rao, Hammeke and Speech (1987) also administered the Wisconsin Card Sort to relapsing-remitting (n=36) and chronic-progressive (n=33) MS patients, and an age and education-matched control group of chronic back pain patients. The chronic-progressive group made more

perseverative responses than controls due to an impaired ability to shift cognitive sets in response to negative feedback. The relapsing-remitting group was unimpaired relative to the control group on the Wisconsin Card Sort. The investigators recommended that future investigations attempt to correlate perseverative tendencies with MRI evidence of diffuse or focal prefrontal brain damage.

In summary, MS patients do display some deficits in conceptual problem-solving, particularly a perseverative tendency in spite of negative environmental feedback. This cognitive disturbance does not appear to be related to attention, memory, motivational factors or disease duration, but is affected by clinical course (Heaton et al., 1985; Rao, 1986; Rao et al., 1987). Such deficits have been associated with prefrontal lesions, particularly in the right hemisphere (Lezak, 1983).

Attention and Concentration. Attention, concentration and vigilance are functions utilized for many if not all neuropsychological tasks. Because these functions are significant to cognitive operations, research has focused on attentional deficits experienced by MS patients.

In a study to assess the reaction time of 50 MS patients compared to 105 non-brain damaged controls, MS patients were found to have significantly delayed reaction times (Elsass & Zeeberg, 1983). Reaction time was

correlated with degree of disability and chronic-progressive patients were slower than relapsing-remitting patients. However, no effort was made to distinguish impaired motor functioning from reaction time.

In a study looking at memory functioning and information processing speed in a sample of 38 chronic-progressive MS patients compared to 26 age- and education-matched controls, MS patients performed significantly worse on tasks of verbal fluency, and the Symbol Digit Modalities Test, as well as some memory tasks (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988). Verbal fluency tasks have been suggested to involve both retrieval and attention (Petersen & Kokemen, 1989), while the Symbol Digit Modalities Test requires attention, concentration and visuomotor coordination.

Another study compared 40 Dutch MS patients to 40 age-, sex- and education-matched controls on a battery of neurological tests, including attentional measures (van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). MS patients were found to have significantly lower scores on verbal fluency tasks, and on both parts A and B of the Trail Making Test, which involves both attentional and motor performance. When the investigators partialled out variance due to intelligence, verbal fluency scores were no longer significantly different between the MS and control groups. No clear rationale was provided for removing the variance

due to intelligence from verbal fluency scores. The investigators also partialled out variance due to motor functioning from Trail Making Test, and scores were no longer significantly different between groups.

Other investigators have reported significantly lower scores for MS patients on measures involving attention, including Symbol Digit Modalities (Beatty et al., 1988; Franklin et al., 1988), verbal fluency tasks (Beatty et al., 1988; Caine et al., 1986; Heaton et al., 1985; Huber et al., 1987; Rao, Leo, St. Aubin-Faubert, 1989c), the Trails Making Test (Beatty & Gange, 1977; Caine et al., 1986; Franklin et al., 1988; Grant et al., 1983; Heaton et al., 1985; Ivnik, 1978), the Paced Auditory Serial Addition Task (Litvan et al., 1988), and other measures of visual and auditory attention (Callanan, Logsdail & Warrington, 1989; Franklin et al., 1988).

Impairment on measures involving attention has been reported by a number of investigators. Because tasks assessing attention also involve other cognitive functions, separating out a specific attention deficit is difficult. Nevertheless, impairment on tasks involving attention has led to the suggestion that the MS disease process interferes with attention, perhaps by slowing down general cognitive processing speed (Beatty et al., 1988; Litvan, et al., 1988; Rao, St. Aubin-Faubert & Leo, 1989b). The demyelinating plaques attributed to MS appear predominately in white-

matter conducting pathways, possibly interfering with the efficiency of neural transmissions and slowing down cognitive processing speed. This slowed cognitive processing could explain the impairment demonstrated by MS patients on tasks involving attention.

Visuospatial Abilities. Very few investigations have directly assessed complex visuospatial processing abilities in MS patients (Rao, 1986). As noted in the intelligence section, MS patients frequently show impairment on Performance subtests of the WAIS. However, impairment on most Performance subtests could be due to problems with visuospatial functions or to more common sensorimotor deficits. Rao (1986) suggests that future research attempt to address visuospatial functioning in MS patients while avoiding the confound of sensorimotor involvement.

Visuospatial processes have been primarily associated with right hemisphere functioning, with some exceptions (Lezak, 1983). Patients with right hemisphere cerebral damage often have trouble with ordering or organizing complex stimuli, with discriminating patterns or faces, with spatial orientation and visuospatial memory (Lezak, 1983). Tasks that assess visuospatial abilities include: the Hooper Visual Organization Test, Line Orientation Test, facial recognition tests, and several performance subtests from the WAIS (particularly Block Design and Object Assembly).

Some investigations have reported little or no

impairment for MS patients on visuospatial tasks, including Block Design (Goldstein & Shelly, 1974; Jambor, 1969), and Object Assembly (Goldstein & Shelly, 1974). Other investigations have reported significant impairment for MS patients on visuospatial tasks including Block Design (Heaton et al., 1985), Object Assembly (de Semdt et al., 1984; Heaton et al., 1985), figure copying tasks (Caine et al., 1986; Franklin et al., 1988), a pathfinding task (Beatty et al., 1988) and Ravens Progressive Matrices (Huber et al., 1987).

These divergent findings on visuospatial functioning likely reflect differing MS samples, differing disease course and the highly variable individual differences in symptoms and cognitive impairment seen in MS patients. MS patients who do exhibit visuospatial deficits might be expected to have lesions affecting right hemisphere cortical functioning, or the MS disease process may be interfering with the conducting pathways necessary to integrate visuospatial perceptual and constructional functions. Either specific right hemisphere lesions or generalized white matter demyelination might explain visuospatial impairment.

Information Processing Speed and Subcortical Dementia

The pattern of cognitive deficits experienced by MS patients has led to the suggestion that the neurological impairment has the consequence of reduced cognitive processing speed. Physical evidence of the MS disease process show evidence of subcortical white-matter involvement but infrequent involvement of cerebral cortex (Lukes et al., 1983). Past investigations of patients with subcortical lesions have observed slowness of thought on tasks that require verbal or perceptual-motor processing (Albert, Feldman & Willis, 1974). Benson (1983) observed that patients with subcortical dementia experienced slowness in both motor and mental processes, which he termed psychomotor retardation. Recently, several investigators have suggested that neurological impairment due to MS might be viewed as subcortical dementia (Beatty et al., 1988; Caine et al., 1986; Litvan et al., 1988; Rao, St. Aubin-Faubert & Leo, 1989b).

Subcortical dementia has been associated with a syndrome of intellectual impairment that includes: slowing of mental processes, forgetfulness, impaired ability to manipulate acquired knowledge, impaired use of stored information, impaired use of problem-solving strategies and personality and affective changes (Albert et al., 1974; Cummings & Benson, 1984). These symptoms are distinct from

those experienced as a consequence of cerebral cortex dysfunctions including: aphasia, amnesia, agnosia and more severe intellectual impairment. Subcortical dementia is a label for the clinical syndrome in which pathological changes involve primarily, but not exclusively, the basal ganglia, the thalamus, and related brain-stem nuclei (Cummings & Benson, 1984).

Some anatomic and neuropsychological relationships have been reported pertinent to subcortical dementia. In animals, lesions in the caudate have been associated with disruptions in spatial tasks, difficulty in shifting responses and perseveration (Cummings & Benson, 1984). These kind of cognitive disturbances resemble those occurring in frontal lobe dysfunctions and the caudate does have major connections with the frontal lobes as well as the limbic system (Cummings & Benson, 1984). The thalamus has been associated with a number of cognitive functions in humans, including: attention, arousal, mood, memory, language and abstraction. Lesions in the thalamus have impaired memory functions, verbal fluency, and conceptual problem solving (Cummings & Benson, 1984). Language tests have shown deficits in verbal fluency but not aphasia in patients with subcortical conditions (Cummings & Benson, 1984). Memory problems associated with subcortical dementia are with encoding and retrieval and are less severe than the problems associated with cortical dementias such as aphasia,

amnesia, agnosia and apraxia seen in Alzheimer's Disease (Cummings & Benson, 1984).

There has been some criticism of separating subcortical from cortical conditions, suggesting that the distinction is oversimplified in most degenerative disorders (Mayeux, Stern, Rosen & Benson, 1983). Investigators do observe that some cortical lesion involvement is not uncommon in MS, particularly adjacent to the ventricles, but the majority of lesions are found to affect subcortical structures (Peyser & Poser, 1986; Rao, 1986).

Several studies have examined cognitive processing speed and symptom patterns reflecting subcortical dementia in MS patients. Memory impairment and speed of information processing speed was examined in 16 MS patients and 16 age-, sex- and education-matched controls (Litvan, Grafman, Vendrell & Martinez, 1988). MS patients had significantly impaired long-term verbal memory impairment, and significantly impaired processing speed for the two highest rates of presentation on the Paced Auditory Serial Addition Test. The authors suggested that slowed information processing is a deficit that contributes to long-term memory impairment in MS.

Another study compared 38 chronic-progressive MS patients with 28 age- and education-matched controls on tests of information-processing speed, verbal fluency, naming and memory (Beatty, Goodkin, Monson, Beatty &

Hertsgaard, 1988). MS patients were significantly impaired on verbal fluency measures, memory and the Symbol Digit Modalities Test (presented orally), which the investigators believed reflected speed of processing of novel information. The authors suggested that this pattern of symptoms was consistent with those observed in subcortical dementias such as Huntington's disease.

Another study compared 30 MS patients to 30 Huntington's disease patients and 15 matched controls on verbal fluency, memory and motor tasks (Caine, Bamford, Schiffer, Shoulson & Levy, 1986). The MS and Huntington's disease patients had a similar overall pattern of impairment, consistent with subcortical dysfunctions, although the Huntington's patients had greater verbal and non-verbal memory deficits, dyscalculia and language problems.

In one recent assessment MS patients relative to the subcortical syndrome, 36 MS patients were compared to 26 normal controls of equivalent age, education and verbal intelligence on a measure of information processing speed (Rao, St. Aubin-Faubert & Leo, 1989b). These investigators used the Sternberg memory scanning test in which subjects are asked to memorize a set of 1, 2, or 4 digits, and then for each trial, are asked if a digit shown on a CRT screen matches one held in memory. MS patients had a significantly slower overall reaction time than controls, and their

scanning rate, a measure of cognitive speed was also significantly slower.

These findings of reduced information processing speed in MS patients are offered as evidence that subcortical lesions are interfering with conducting pathways and reducing cognitive efficiency. This reduced efficiency in the transmission of neural impulses could contribute to impaired performance on many neuropsychological tests and might explain deficits that might otherwise be attributed to focal cerebral lesions.

In summary, reduced information processing speed, which is consistent with interference in primarily subcortical areas, might explain the cause of neuropsychological deficits typically exhibited by MS patients. Disruption in subcortical structures can produce disturbances in cognitive processing speed, arousal, attention, mood, motivation, language, memory, abstraction and visuospatial skills. MS does also sometimes penetrate cortical areas and thus may also impair cognitive performance through the location of specific lesions.

Magnetic Resonance Imaging and MS

Magnetic resonance imaging (MRI) has been described as the most sensitive means available of studying lesions due to MS (Lukes et al., 1983; Young et al., 1981). Previously,

computed tomography (CT) was the best radiological technology for investigating demyelinating plaques, but the introduction of MRI has provided images of superior quality and sensitivity (Jacobs, Kinkel, Polachini & Kinkel, 1986; Lukes et al., 1983).

About MRI. MRI takes advantage of the fact that magnetic forces naturally occur in the body. As the nuclei of atoms spin they produce a small magnetic field. Some nuclei with an odd number of spinning protons, such as hydrogen (present in water), carbon, sodium, phosphorus and potassium, have individual magnetic properties. Most MRI relies on the distribution of hydrogen nuclei of water in tissue. MRI employs a powerful superconducting magnet which generates a strong magnetic field. When a person is placed in this magnetic field the individual spinning nuclei within the body become aligned with the field. Once the nuclei are aligned, a radio frequency pulse is applied to the field which tilts the resonant atoms at various angles. The body's nuclei spin on an axis tilted with respect to the externally generated magnetic field. When the radio frequency energy is switched off, the body's nuclei revert to their own specific radio frequency signals. Magnetic resonance images are pictorial representations of the radio frequency signals emitted by the body's atomic nuclei (Ebers, Paty & Sears, 1984; Frumkin, Potchen, Aniskiewicz, Moore & Cooke, 1989).

The appearance of anatomic structures in a magnetic resonance image is based on three parameters: (1) the density of spinning nuclei under scrutiny, (2) the time it takes the atomic nuclei to revert back from their tilts to realign with the external magnetic field after the external radio frequency is turned off (T1), (3) the time it takes for the nuclei to dephase or lose their coherence with each other (T2). Differences in these three factors allow for the contrast between different kinds of body tissues, and between normal and abnormal tissue that has made MRI so valuable.

The MRI parameters can be adjusted to gain different types of information dependent upon what is of interest in the image. Images can be adjusted or "weighted" by varying the pattern and timing of the magnetic impulses applied to the body part under scrutiny. The sequencing of magnetic pulses can be adjusted to provide different amounts of density, T1, or T2 information. T1 weighted images provide good anatomical delineation, while T2 weighted images provide good delineation for various body fluids (like cerebral spinal fluid) and pathology (Frumkin et al., 1989). The identification of MS plaques is optimized by a specific protocol of imaging parameters which has been commented upon in some detail (Fazekas et al., 1988; Lukes et al., 1983; Omerod et al., 1987; Reider-Groswasser et al., 1988; Van de Vyver et al., 1989).

MRI and MS. Characteristic evidence of demyelinating lesions due to MS seen via MRI includes: abnormal signal intensities surrounding and extending from the ventricles (particularly the lateral ventricles), and abnormal signal intensities in the white matter of the cerebrum, and in the cerebellum, brainstem, basal ganglia, internal capsule and corpus callosum (Baumhefner et al., 1990; Brainin et al., 1988; Edwards, Farlow & Stevens, 1986; Litvan et al., 1988; Maravilla, 1988; Omerod et al., 1987; Stevens et al., 1986). The abnormal MRI signal intensity has been demonstrated to be associated with the presence of MS plaques in autopsy studies (McDonald, 1988; Maravilla, 1988). MRI evidence of MS also includes corpus callosum atrophy and ventricular enlargement, assumed to be a consequence of the demyelination of corpus callosum neurons and of the neuronal tracts surrounding the ventricles (Brainin et al., 1988; Huber et al., 1987; Maravilla, 1988; Rao et al., 1989a).

Problems with MRI. While MRI does provide the best available evidence for neural damage done by the MS disease process (Lukes et al., 1983; Omerod et al., 1987), the procedure does have some shortcomings. While the images derived through MRI are have considerably finer resolution than CT images, they still are somewhat grainy and some aspects of the images require interpretation based on sometimes scant validity evidence. Neural damage due to MS, and in fact many abnormalities are detected by the

observation of high signal intensity (light colored) areas on the image. MRI literature indicates that a number of factors can produce high signal intensity areas including abnormal tissue, such as that caused by a cancerous tumor, or water, which might be due to edema. The demyelinating process of MS is believed not to cause high signal intensity simply due to the loss of myelin, but is suggested to cause a proportion of neural tissue to be occupied by water molecules which generates the abnormal signal in affected areas (Omerod et al., 1987).

Literature describing the pattern of MRI findings for MS patients clearly warns that MRI should not be the sole diagnostic procedure for MS because other conditions can produce similar patterns of MRI abnormality (Omerod et al., 1987; McDonald, 1988; Van de Vyver et al., 1989). Other demyelinating diseases, cerebrovascular diseases and other degenerative conditions can produce MRI evidence similar to that seen MS patients. One of the consequences of the lack of specificity of abnormal MRI signal for MS demyelinating lesions is that abnormal signal may be recorded for factors that are not a consequence of MS. Abnormal MRI signals seen for a patient could be the result of some unrelated edema or vascular condition and not necessarily MS. In support of MRI, the abnormal signal associated with the MS process has been shown to correspond with plaques found in brains of MS patients after death through autopsy (McDonald, 1988; Omerod

et al., 1987).

Another problem with MRI evidence of MS is the objective coding for the location of lesions. The location of abnormal signal is often obvious on an MRI image as many of the brains anatomical parts are readily identified through contrast with neighboring anatomy. For example, the ventricle areas, the cerebellum, the brain stem, and the cerebral hemispheres are all readily identified. However, other anatomical areas are more difficult to distinguish from neighboring areas. The internal capsule is difficult to distinguish from the thalamus and the caudate for instance, and the parietal lobe region might be difficult to define with respect to the temporal region. Defining the anatomical location of abnormal MRI signal can be a difficult judgement depending on the region of the brain affected. Therefore, specificity regarding location of lesions is limited for some brain regions, the subcortical structures in particular.

MRI, Neuropsychological Measures and MS. While many investigations of MS have been conducted utilizing MRI, only a limited number have combined neuropsychological assessment with MRI in assessing MS. One of the first studies to assess the relationship between cognitive measures and MRI data was conducted on a sample of 33 Dutch patients diagnosed with laboratory-definite MS according to Poser (1984) criteria (Medaer, Nelissen, Appel, Swerts, Geutjens &

Callaert, 1987). The patients ranged in age from 30 to 65 (mean 46.4, SD 7.4), had an average illness duration of 14.6 years (range 2-28) and had a mean Kurtzke disability status of 6.7 (range 3-8.5). The patients were arranged into three different groups, of 11 members each, depending upon their scores on neuropsychological measures indicating: no cognitive impairment, moderate impairment or severe cognitive impairment. The cognitive measures employed included: the WAIS, Raven's Progressive Matrices (assessing analytical, visuospatial reasoning), a verbal-auditory memory task, the Benton Visual Retention Test (a visuospatial memory task), and a test of attention and concentration. The MRI examinations of the patients were summarized in a simple 5 point rating-scale, where 1 was small periventricular lesions, and 5 was broad periventricular lesions with confluent lesions, enlarged ventricles and one or more satellite lesions. Results indicated significantly different MRI scores for the three MS groups who were differentiated according to level of cognitive impairment, except between the moderately and severely impaired groups. While this study did find a relationship between cognitive impairment and MRI evidence of lesions, only gross measures of cognitive functioning and MRI lesions were employed in the analysis of data.

Another study used MRI for an assessment of the memory functioning of 20 Austrian MS patients (Brainin, Goldenberg,

Ahlers, Reisner, Neuhold & Deecke, 1988). These investigators administered a number of subtests from both the WAIS and Weschler Memory Scale (WMS) in order to rate patients memory functions as severely impaired (n=5), moderately impaired (n=10) or no impairment (n=5). These investigators did not apply any means to objectively quantify MRI findings, but instead reported that all 5 patients with severely impaired memory functions showed bilateral lesions in the medial temporal lobe. Of the 10 patients with moderate impairment, 1 showed bilateral medial temporal lobed lesions, 5 showed unilateral medial temporal lesions on the right side and 1 showed left side medial temporal lesions. The 5 patients with no memory impairment showed no medial temporal lesions. The investigators also noted thinning and lining of the corpus callosum and some frontal white matter lesions irrespective of memory impairment. These investigators' findings were more observational than statistical as they did not provide any quantitative assessment of lesion size, or number.

A study conducted by Huber and others (1987) assessed 32 patients diagnosed with clinically definite MS by Poser (1984) criteria with a mean age of 40 years (range, 20 to 65), a mean education of 13.94 years (range, 9 to 19), and a mean Kurtzke Disability Status Score of 5.31 (range, 1 to 9). Patients were administered a variety of neuropsychological measures and MRI was performed using

sagittal only slices and two raters whose interobserver interpretations were averaged. MRI images were scored for total number and size of lesions. Size of lesions was rated on a 1 to 5 scale, where 1= plaque size less than 0.5 cm. and 5= plaque size greater than 2 cm. The MRI data for each patient was also subjectively rated for general cerebral atrophy on a scale of 1 to 5, without measurement. Another rating for corpus callosum atrophy was scored using a 5 point scale where 1= corpus callosum thickness of 10 to 7 mm. and 0 to 3 lesions, and 5= corpus callosum thickness of 2 to 0 mm. and 5 or more lesions. The last rating of MRI data was for severity of periventricular lesions on a scale of 1 to 5 where higher scores were indicative of increased periventricular demyelination.

Huber and colleagues (1987) divided their MS sample into three groups on the basis of neuropsychological test scores: one group with minimal impairment (n=12), a second group with moderate impairment (n=11), and a third group with severe impairment (n=9). The MRI findings were reported with respect to how well the evidence of lesions differentiated these three groups. Neither total number and size of lesions, degree of cerebral atrophy, or periventricular involvement varied significantly with severity of intellectual impairment. However, the degree of corpus callosum atrophy did significantly differentiate the severely impaired group from the moderately or minimally

impaired. No more specific relationship between MRI evidence of plaques and cognitive deficits were reported.

An investigation by Heaton and others (1988) assessed 60 patients diagnosed with clinically definite chronic-progressive MS by Schumacher (1965) criteria, with a mean age of 37, mean education of 14-6 years, mean disease duration of 6 years and mean expanded Kurtzke disability status of 5.3. Patients (and a sex-, age- and education matched control group) were administered a battery of neuropsychological measures including: the Symbol Digit Modalities Test, Trails Making A and B, a test of visual attention, tests of learning and memory for verbal and non-verbal materials, a test of visuospatial construction, a test of verbal fluency, and several tests of language abilities. MRI evidence (on patients only) was quantified using a rating scale of lesion size from 1 to 3, where 1= 0.5 to 1 cm., 2= 1 to 2 cm., and 3= > 2 cm. The number of lesions rated for size were recorded for the anterior and posterior cerebral regions of each hemisphere using contiguous axial and coronal slices. Analyses reported were whole-brain lesion score correlations with specific neuropsychological subtests. The measures and deficits significantly correlated with total-brain lesion included: Symbol Digit Modalities, Trails Making A and B, verbal learning and memory tasks, nonverbal learning, visual naming, visuospatial constructional ability, psychomotor

speed and tests of attention/concentration. Subtests of expressive and receptive language did not correlate significantly with total lesion scores. More specific correlation between left and right hemispheres, and anterior and posterior regions, and cognitive measures were not reported.

Another study using MRI and neuropsychological data was conducted on a sample of 48 MS patients diagnosed by Poser criteria (1984) with a mean age of 36.4 years (range, 20 to 61) with other pertinent characteristics not reported (Callanan, Logsdail & Warrington, 1989). Neuropsychological assessment included measures of: intelligence (WAIS), verbal and visual memory, conceptual problem solving (Wisconsin Card Sort), visual and auditory attention, and naming ability. The MRI evidence was acquired from primarily axial images, with the occasional supplement of sagittal and coronal images. Lesion size was scored on a scale from 0 to 3, where 0 = 2 mm. and 3 = 10 mm. Lesion scores were obtained separately for the periventricular, frontal, and temporal areas, and added together for a total lesion score for each patient. Significant correlations were reported between MRI total lesion score and conceptual problem-solving on the Wisconsin Card Sort and auditory attention. No other cognitive functions were correlated with total lesion area and there were no significant correlations between periventricular, frontal and temporal scores and cognitive

functions.

Another group of investigators reported on 62 patients diagnosed as clinically definite, chronic-progressive MS, with a mean age of 43.5 years (range, 23 to 56), mean duration of disease of 13 years (range, 2 to 37), and a mean Kurtzke EDSS of 5.5 (range, 2.5 to 7; Baumhefner et al., 1990). Patients were administered a variety of physiological measures pertinent to the diagnosis of MS and the Symbol Digit Modalities Test as well as undergoing MRI. The MRI protocol utilized contiguous axial and coronal slices. The cerebral regions were scored for lesions on a 5 point scale, according to the number, size and location of lesions. A second method of assessing lesion area was accomplished by using a computerized image analysis system that involved tracing each lesion on a CRT with a cursor. Software calculated the total lesion area for the cerebrum, cerebellum, brain stem and upper cervical cord for the axial plane and sagittal plane images separately. Results indicated a significant correlation between performance on the Symbol Digit Modalities Test and total lesion area in both the cerebrum and brain stem for axial and coronal planes. Symbol Digit Modalities performance was also correlated with total lesion area in the cerebellum for the coronal but not the axial plane. The investigators were interested in the relative sensitivity of axial versus coronal MRI protocols for detecting MS plaques. They

reported a correlation between axial versus coronal planes for the total cerebral lesion area to be .92 ($P<.0001$), for total cerebellar lesion to be .63 ($P<.0001$), and for total brain stem lesion area to be .39 ($P<.01$). They found coronal images to be less sensitive to brain stem lesions than axial images.

No relationship was found between MRI abnormalities and MS patients' age, gender, illness duration or age of MS onset (Baumhefner et al., 1990; Rao et al., 1989a). A relationship between physical disability and total brain stem lesions area was reported (Baumhafner et al., 1990) and between physical disability and both corpus callosum atrophy and periventricular lesions (Huber et al., 1988). However, no relationship between physical disability and lesion area was found by Franklin and colleagues (1988).

The most comprehensive assessment of the relationship between neuropsychological measures and MRI data was conducted by Rao, Leo, Haughton, St Aubin-Farbert and Bernardin (1989a). These investigators used Poser (1984) criteria to diagnose 53 randomly selected MS patients with a mean age of 43.9 years (range, 27-61), a mean education of 13.6 years (range, 8-20), a mean illness duration of 7.8 (range, 1-28), and a mean disability status (Kurtzke EDSS) of 3.8 (range, 0-8). The patients were administered a battery of neuropsychological measures and were assessed with MRI. The MRI protocol consisted of both axial and

sagittal slices to determine three measures: total lesion area, size of corpus callosum and ventricular-brain ratio. Measures of dimension were obtained by using a computerized imaging system to trace the outline of anatomical structures and lesions using a cursor and a CRT, with software calculating and widths and area. Total lesions area was calculated by summing the area for all lesions, size of corpus callosum was the area from the mid-sagittal slice, and ventricular-brain ratio was the sum of the dimensions of the third and lateral ventricles divided by an axial measure of the total area of the brain.

To summarize the results provided by the numerous cognitive measures and the three MRI variables used by Rao and colleagues, total lesion area was a significant predictor of test scores measuring: recent memory, abstract and conceptual reasoning (including the Wisconsin Card Sort), language (including category fluency) and visuospatial problem-solving (including the Hooper Visual Organization Test and Line Orientation Test). The size (or atrophy) of the corpus callosum was a significant predictor of tests scores measuring: information processing speed (including the Paced Serial Addition Task), sustained attention, rapid problem solving and mental arithmetic. Ventricular brain ratio was not a useful predictor.

Rao and colleagues (1989a) observed that measures of recent memory and abstract/conceptual reasoning are

frequently found to be impaired in MS patients and MRI abnormalities were strong predictors of these deficits. MRI abnormalities also proved good predictors of problems with rapid and sustained problem solving, language and visuospatial tasks, suggesting that cerebral demyelination may be associated with impairment in these cognitive functions. They also observed the relationship between corpus callosum atrophy and performance on tasks requiring sustained attention and rapid problem solving. This data suggests that rapid and precise interhemispheric communication is involved in these tasks and is interrupted by demyelinated callosal fiber tracts.

To summarize the findings of studies that have employed both MRI and neuropsychological measures: gross indices of cognitive impairment have been correlated with gross indices of MRI abnormality (Medaer et al., 1987); memory impairment was observationally associated with medial temporal lobe lesions (Brainin et al., 1988); a combined index of cognitive impairment was correlated with degree of corpus callosum atrophy but not total lesion area or periventricular involvement (Huber et al., 1987); total lesion area but not more discretely localized lesions was correlated with numerous cognitive indices (Heaton et al., 1988); total lesion area was correlated with conceptual problem-solving ability and auditory attention but not other cognitive functions (Callanan, Logsdail & Warrington, 1989);

Symbol Digit Modalities performance was correlated with total lesion area in the cerebrum, cerebellum and brain stem (Baumhefner et al., 1990); and total lesion area predicted numerous cognitive indices and corpus callosum atrophy predicted information processing speed and sustained attention (Rao et al., 1989a).

Most of these investigations utilizing MRI technology employed relatively gross strategies for calculating lesion size and specifying brain locations. Most studies used a 3 to 5 point rating scale to assess lesions size, restricting the range of the data analyzed. Two studies used a cursor tracing combined with computer software to more accurately calculate lesion size (Baumhefner et al., 1990; Rao et al., 1989a). Most studies reported no within brain differentiations, and so recorded only total brain lesion area. Others provided only gross differentiations to identify the area of the brain in which lesions were found, such as left versus right hemisphere or cerebrum versus cerebellum. Recording more specific anatomical locations of lesions within the brain seen through MRI is time consuming and difficult. There is no standardized coding scheme for identifying MRI abnormalities in specific anatomical regions within the brain. While some investigators have reported little success with efforts to correlate specific lesion locations and cognitive deficits (Peyser & Poser, 1986; Rao, 1986), previous investigations have not reported any efforts

to do this with MRI data.

Summary

Numerous neuropsychological deficits have been associated with MS, including disturbance in: sensorimotor abilities, intelligence, memory, conceptual problem-solving, attention and concentration, visuospatial abilities and cognitive processing speed. MS affects primarily the neurons in white-matter regions, particularly subcortical regions and the fibers that make up conducting pathways, but does occasionally involve cortical grey matter. Evidence of CNS degeneration due to MS, including the location and size of lesions, can be detected through MRI. MRI evidence combined with data from standard neuropsychological measures can be applied toward understanding the anatomical cause of neurocognitive deficits suffered by MS patients. Evidence offered by past clinical neuropsychological research might explain some MS cognitive deficits due to the location of specific lesions within the brain. However, because of the pervasive role of white matter conducting pathways in cognitive processing, a general decline in information processing speed has been suggested as an explanation for some MS deficits. This information processing deficit, due to white-matter tract deterioration, might explain deficits in cognitive processes involving more complex neural

pathways. Some MS deficits might be explained as a consequence of discrete lesions affecting functions associated with their locations, while other deficits might be explained as a consequence of the interference in white matter pathways and the transmission of impulses between regions required for cognitive operations.

Hypotheses

1) Sensorimotor abilities. For MS patients, MRI evidence of lesions in the cerebellum and brain stem regions of the brain will predict deficits on sensorimotor tasks as measured by the Purdue Pegboard, Trails Making Tests A and B, fingertip number writing and finger localization.

2) Memory. For MS patients, MRI evidence of lesions in the frontal and medial temporal regions of the brain will predict deficits in retrieval memory as measured by the Weschler Memory Scale (Delayed Recall), and the California Verbal Learning Test (CVLT). The most sensitive CVLT indices for this hypothesis will be Recall Errors, and Recognition Discriminability versus Long-Delay Free Recall.

3) Conceptual problem-solving. MRI evidence of lesions in the frontal region of the brain will predict deficits in conceptual problem-solving as measured by perseverative errors on the Wisconsin Card Sort.

4) Visuospatial abilities. MRI evidence of lesions in the cerebrum of the right hemisphere will predict deficits in tasks involving visuospatial abilities as measured by the

Hooper Visual Orientation Test, the Line Orientation test, and the Face Recognition test.

5) Processing speed, attention, verbal fluency. MRI evidence of lesions in white matter conducting pathways, including the corpus callosum, internal capsule, and subcortical structures, will predict deficits in processing speed, attention and concentration, and verbal fluency. These deficits will be measured by the Paced Auditory Serial Addition Task, the Symbol Digit Modalities Test, the Digit Span subtest from the WAIS-R, the Oral Word Association (CFL) test and the Animal Naming test.

6) Processing speed mediation in other cognitive abilities. Processing speed, as measured by the Paced Auditory Serial Addition Task, Symbol Digit Modalities, the Oral Word Association test (CFL), and the Animal Naming test, will also predict performance on tasks involving sensorimotor abilities, memory, conceptual problem-solving and visuospatial abilities.

METHOD

Subjects

Forty one patients with MS, 10 men and 31 women, agreed to participate in this investigation. The patients were recruited from a local Multiple Sclerosis Society and volunteered their time, with an agreement that they would receive feedback regarding their condition free of charge. Their mean age is 45.56 (range: 30-64; SD=8.17), and the mean years of education is 13.61 (range: 9-19; SD=2.2). All of the patients were screened for their MS symptoms and 40 were diagnosed as having clinically definite MS using criteria suggested by Poser and others (1984). One patient was diagnosed as having clinically probable MS. The mean number of years of disease duration is 13.0 (range: 2-35; SD=8.4) and the mean number of years since disease diagnosis is 7.29 (range: 1-33; SD=6.81).

Selection of Measures

The selection of measures for this investigation was governed by a number of factors pertinent to the research hypotheses. First, previous research investigations of cognitive deficits in MS indicated the type of deficits

typically encountered and specific measures sensitive to those deficits. Recent reviews of the neuropsychological deficits associated with MS have delineated functional problems with sensorimotor, memory, conceptual problem-solving, visuospatial, and attentional abilities (Peterson & Kokmen, 1989; Rao, 1986).

Measures with demonstrated sensitivity to sensorimotor problems (Purdue Pegboard, the Trails Making Test, Fingertip Number Writing and Finger Localization) were included to assess the degree of sensorimotor impairment, which has been a frequently documented symptom of MS and could be attributed to lesions in the brain stem and cerebellum. Two of the most well established measures of memory functioning and learning were selected (the Wechsler Memory Scale - Revised and the California Verbal Learning Test) because MS patients have been reported to have some subtle problems with memory, particularly with retrieval. A measure of conceptual problem solving (the Wisconsin Card Sort) was selected because other investigations of MS have reported perseverative errors on tasks involving abstract reasoning. Measures sensitive to visuospatial abilities (Hooper Visual Orientation Test, Benton's Line Orientation and Facial Recognition Tasks) were selected because previous investigations have reported MS patients to have some visuospatial problems, and the frequently reported relationship between right hemisphere lesions and such

deficits can be assessed in this investigation. Measures with a demonstrated sensitivity to deficits in attention and concentration, verbal fluency and processing speed were included (the Paced Auditory Serial Addition Task, the Symbol Digit Modalities Test, the Digit Span and Digit Symbol subtests from the WAIS-R, the Controlled Word Association Task (CFL) and the Animal Naming Test). These are known deficit areas for MS patients, and these tests have been reported as sensitive to these deficits, and these functions are particularly important to the hypotheses examining information processing speed.

Aside from considering the literature on specific deficits experienced by MS patients, administration time was a consideration for selecting measures. The total battery was designed to be administered in 3-4 hours, thereby making it possible to complete both MRI and neuropsychological assessment in one day.

Soon after measures were selected, a set of guidelines for neuropsychological research in multiple sclerosis was published (Peyser, Rao, La Rocca & Kaplan, 1990) with the support of the National Multiple Sclerosis Society. These investigators made suggestions for methodological standards for MS studies so that results from different investigations might be compared more easily and a large body of data might accumulate. These investigators suggested a core battery of neuropsychological measures using a rationale similar to the

strategy described above. Many of the measures suggested by Peyser, Rao, La Rocca and Kaplan (1990) were also selected for this investigation including: the Symbol Digit Modalities Test, the Paced Auditory Serial Addition Task, the Wechsler Memory Scale - Revised, the California Verbal Learning Test, the Controlled Oral Word Association test (CFL), the Hooper Visual Organization Test and the Wisconsin Card Sorting Test. These investigators also observed that the normative data available on these measures may be substituted for a control group in some studies, partly as a response to the difficulty in defining a control sample comparable to multiple sclerosis patients.

Measures

Purdue Pegboard Test. This test assesses manipulative dexterity of the hands and fingers. A subject is required to insert pins into a line of holes as quickly as possible with a 30 second time limit. The test includes one trial for each hand, and a trial for both hands simultaneously.

Norms are provided for a number of different unimpaired occupational groups by gender (Tiffin, 1968). Retest reliability coefficients are also available for a number of different occupational groups and range from .67 to .79 depending on the subtest. Validity information is available regarding the relationship between pegboard performance and

scores on several other measures of finger dexterity pertinent to occupations such as: machinists, seed analysts, pilots and electric shaver repairmen (Tiffin, 1968).

Trail Making Test. This procedure, a subtest on the Halstead-Reitan Neuropsychological Battery (Reitan & Wolfson, 1985), is an easily administered test of visual, conceptual, and visuomotor tracking. It consists of two parts, A and B, which involve connecting 25 circles randomly placed on a sheet of paper (Part A), and connecting in alternating sequence numbers and letters, that is 1-A-2-B-3-C, etcetera (Part B). During the timed test any mistakes are immediately corrected by the examiner. Delays become part of the final score, which is number of seconds to complete the task. Reitan (1958) demonstrated significant differences in the performance of heterogenous brain damaged subjects matched to a group of controls. Norms provided by Reitan and Wolfson (1985) suggest that any times longer than 72 seconds on Trails B be considered in the impaired range. While psychometric information is not reported on this test individually, both parts require fine motor speed and coordination, visual scanning and the ability to progress in sequence. Trails B requires the additional ability to maintain and integrate two simultaneous sets of symbols. The test is also an index of attention and information processing speed (Stuss, Stethem & Poirier, 1987).

Finger Localization. The ability to name fingers upon tactile stimulation has long been established as an indicator of brain pathology (Benton, Hamsher, Varney & Spreen, 1983) and is part of the Halstead-Reitan Neuropsychological Test Battery (Reitan & Wolfson, 1985). Impairment on this task is termed finger agnosia. The test requires a subject to report which fingers are being touched by an examiner's stylus, with the hand visible, and with the hand hidden from view. Trials are conducted for each hand, and for localization of pairs of fingers on both hands touched by the examiner. The order of finger touching is standardized. Norms are available for a sample of 104 normal patients for different ages, education levels and for left and right hands (Benton, Hamsher, Varney & Spreen, 1983). Reliability data is not reported for this test separately. Validity data regarding the performance of patients with various types of brain disease is available (Benton, Hamsher, Varney & Spreen, 1983).

Finger-tip Number Writing Perception. This procedure, a subtest on the Halstead-Reitan Neuropsychological Battery (Reitan & Wolfson, 1985), requires the subject to report numbers written on the fingertips of each hand without the use of vision. The numbers (3, 4, 5, and 6) are written on the fingertips with a blunted pencil in a standard sequence

with a total of four trials for each finger. On the basis of data derived from both normative and brain damaged samples, Reitan and Wolfson (1985) provide ranges of errors to differentiate normal (<7 errors, both hands) from mildly impaired (7-11 errors, both hands) from severely impaired (12+ errors, both hands). Reliability data is not reported for individual subtests. The difference between left and right hand error scores is useful in detecting lateralized brain damage, particularly in the contralateral parietal lobe (Reitan & Wolfson, 1985).

Wechsler Memory Scale-Revised (WMS-R). The WMS-R is an individually administered, clinical instrument for assessing major dimensions of memory (Wechsler, 1987). The test consists of a series of brief subtests measuring different facets of memory. Eight of the subtests measure short-term learning and recall of both verbal and figural material. When all eight have been administered (requiring about 1/2 hour), four of the subtests are readministered to assess delayed retention of both verbal and visual material. The subtests combine to produce a number of composite scores including: Verbal Memory and Visual Memory which are summed for a General Memory score, and separate scores for Attention/Concentration and Delayed Recall.

The reliability data reported by Wechsler (1987) for WMS-R subscales and composite scores includes assessment of

internal consistency and stability. Internal consistency was assessed using split-half and coefficient alpha formulas depending upon the item content of scales. Internal consistency was assessed on samples divided by ages, with ranges from 17 to 74 years. The average reliability coefficients across age groups and for subtests and composite scores ranged from .41 to .90, with a median value of .74.

The temporal stability of the WMS-R was assessed by readministering the test to three different age groups (total n=151, age range: 20-74) with a 4-6 week interval. Stability coefficients, averaged across age groups, for subtests and composite scores ranged from .45 to .93. Scores on the second administration were typically higher as might be expected with a practice effect.

Evidence supporting the validity of the WMS-R includes factor analytic data suggesting that subtests combine to create two general factors: general memory and attention/concentration. The WMS-R does distinguish patients with known memory impairment from normal controls, and scale norms for a number of different clinical groups are published in the test manual, including a group of 29 MS patients. The WMS-R results reported for 29 MS patients (14 males, 15 females) found significantly lower scores than normals on the General Memory, Visual Memory and Delayed Recall Indexes (Wechsler, 1987).

A separate study administered the WMS-R to a sample of 45 MS patients and a group of 25 age-, sex- and education-matched controls and found that MS patients performed significantly more poorly on all five WMS-R indexes, demonstrating the sensitivity of the WMS-R to memory impairment in MS (Fischer, 1988). The average scores of MS patients were, however, in the normal range.

California Verbal Learning Test (CVLT). The CVLT (Dellis, Kramer, Kaplan & Ober, 1987) provides an assessment of multiple strategies involved in learning and remembering verbal material. The CVLT measures both recall and recognition of word lists over a number of trials. Administration begins by evaluating an individual's ability to recall a list of 16 words (four words from each of 4 semantic categories) over five trials. An interference of list of 16 words is then presented for one trial, immediately followed by a free and category-cued recall of the first list. After a 20 minute delay, free recall, cued recall and recognition of the first list are assessed. The CVLT provides a number of different indices of recall measures, learning characteristics, recall errors, recognition measures and between trial contrasts. A number of split-half reliability coefficients were reported from a sample of 133 normal subjects within a narrow age range (Dellis, Kramer, Kaplan & Ober, 1987). Coefficients from .70 to .92 were derived, yielding standard errors of

measure of 5.07 to 2.61, depending upon how the test was split. Retest reliability is reported from a sample of 21 normal adults with a one year interval yielding significant correlations for most of the CVLT indices. Validity information includes factor analytic data supporting the theoretical structure of the test and concurrent validity coefficients demonstrating expected correlations with the Wechsler Memory Scale (Dellis, Kramer, Kaplan & Ober, 1987). Scores on the CVLT are also reported for a number of different clinical groups including a sample of 56 MS patients. The MS patients displayed problems with immediate recall, and an above average number of perseverations and intrusions. Recognition performance (Discriminability Index) was better than long-delay free recall, suggesting more problems with retrieval than encoding. Kessler, Lauer and Kausch (1985) also found that the degree of CVLT recall impairment in MS patients correlated significantly with level of motor dysfunction.

Wisconsin Card Sorting Test (WCST). The WCST assesses abstract abilities and cognitive flexibility. The test appraises learning strategies for color, form and number sorting. Numerous versions of the test have been used which has handicapped the psychometric literature supporting the test. Heaton (1981) summarized many of the variations used for the WCST and also has provided an effort to standardize

the test in conjunction with Psychological Assessment Resources (Odessa, Florida) who market test materials and a manual.

The test consists of 4 stimulus cards arrayed in front of the subject, and 128 response cards divided into two identical decks of 64 cards each. Each card has one to four figures (star, triangle, circle or plus sign), in one of four colors, with a sequence number listed on the back for the examiner's use. The subject is instructed to place each response card in front of a stimulus card they think it matches. The examiner provides no other information except to say "right" or "wrong" for each card placed. The task for the subject is to determine the card sorting principle the examiner is using and sort 10 consecutive cards successfully. The sorting principles used are color, form, and number (repeated in that order). After 10 cards are sorted successfully, a new sorting principle is instituted by the examiner. The subject is never informed of the principle or when it is changed. The test is completed when 6 complete sets of sorts are accomplished or all 128 cards have been exhausted.

The WCST can be scored for many separate indices including: total number of errors, number of correct responses, number of categories completed, and perseverative responses. Perseverative responses are defined as those that would have been correct in the previous stage (Heaton,

1981).

The new WCST manual (Heaton, 1981) provides standardization information on samples of 208 inpatients with brain disorders (half with frontal lesions, half with other lesions) and 150 normal controls. Mean scores on all of the WCST indices are available for these samples, as well as IQ scores and the Halstead-Reitan Impairment Index. Heaton (1981) reports that frontal lesion patients are significantly more impaired than non-frontal lesion patients, even when general neuropsychological impairment was controlled for. The WCST index most sensitive to frontal impairment is perseverative errors (Drewe, 1974; Heaton, 1981). This data, along with other findings relevant to MS patients reviewed earlier (see Conceptual Problem Solving section) constitute the validity information available for the WCST. No specific assessment of reliability is reported (Puente, 1984). Retest reliability would be extremely susceptible to a practice effect, and assessment of internal consistency would not be particularly meaningful. Performance on the WCST is negatively correlated with age for older subjects (Heaton, 1981).

Hooper Visual Organization Test (HVOT). The HVOT is designed to assess the ability to organize visual stimuli (Hooper, 1958; 1983). The test consists of 30 line drawings depicting simple objects which have been cut into pieces and

rearranged in a puzzle-like fashion. The respondent is asked what each object would be if it were put back together, and a total raw score reflects the number of correct responses. Successful performance depends primarily on visual analytic and synthetic abilities (Hooper, 1983).

Norms are available from a variety of different samples of different age ranges, with a mean score of 25.7 (SD=4.78) reported (Hooper, 1983). Scores for adults above age 70 are lower. The test does not correlate significantly with education, sex, or intelligence (Lezak, 1983). The reliability of the HVOT has been assessed on several normal and clinical populations. Hooper (1958) reported a split-half reliability coefficient of .82 on a sample of 166 college students and .78 on a sample of 73 psychiatric patients.

In support of the validity of the HVOT, scores from a number of different clinical groups, both neurological and psychiatric, have been found to be significantly different from normals (Hooper, 1983). Some evidence for the concurrent criterion-related validity of the HVOT is also reported through significant correlations with other visuospatial tests including: Porteus Mazes and Trails Making part B from the Halstead Reitan Battery (Hooper, 1983). Lezak (1983) described an outline for the interpretation of HVOT scores, suggesting that six to ten failures comprise a "borderline" range indicating mild to

moderate brain disorder, and more than 10 failures indicates organic brain pathology.

Judgement of Line Orientation. Disturbances in spatial perception and orientation have proven to be well documented consequences of brain disease (Benton, Hamsher, Varney & Spreen, 1983). The Line Orientation test developed by Benton and colleagues requires the judgement of orientation of 30 sets of partial lines with reference to a set of responses. Subjects must choose the best parallel line among a set of possible responses. Scoring for the test is the total number of correct responses. Norms are available for 137 normal control subjects divided into six age-sex groups (Benton, Hamsher, Varney & Spreen, 1983). The authors provide guidelines for correcting for age (for subjects over 50 years) and sex (women score two points lower than men). Norms are also provided for samples of left and right hemisphere brain damaged subjects. Right hemisphere patients are frequently impaired, while patients with left hemisphere damaged are infrequently impaired. Corrected split-half reliability of .91 is reported on a sample of 164 subjects. Test-retest reliability of .90 was reported using a sample of 37 subjects with an interval of 6 hours to 21 days. Standard error of measure is reported to be 1.8 points (Benton, Hamsher, Varney & Spreen, 1983). The Line Orientation test appears to be sensitive to right

hemisphere lesions, particularly in the right parietal lobe.

Facial Recognition. Impairment in the ability to recognize faces has long been observed as a consequence of brain damage (Benton, Hamsher, Varney & Spreen, 1983). Recognition of familiar faces will often remain intact while recognition of unfamiliar faces will be impaired with right hemisphere brain damage. This deficit can easily go undetected without specific testing. The Facial Recognition test designed by Benton and colleagues consists of three parts, each requiring the recognition of a stimulus photograph from among a display of six alternatives. The three parts of the tests involve increasingly difficult discriminations by using three-quarter-views and different lighting conditions. Scoring involves the sum of correct matches.

Norms are provided for 286 normal control subjects with an age range of 16 to 74 years. Age and education, but not sex are significantly related to performance, with performance declining with age and lower educational levels. Norms are also reported for samples of brain damaged patients revealing significantly greater deficits for patients with unilateral right hemisphere lesions, particularly for posterior lesions (Benton, Hamsher, Varney, & Spreen, 1983).

Paced Auditory Serial-Addition Test (PASAT). The PASAT (Gronwall, 1977) assesses rate of information processing. The test is administered using a prerecorded tape which delivers a random series of numbers from 1 to 9. The subject is instructed to add pairs of numbers such that each number is added to the one that immediately precedes it; the second is added to the first, the third to the second, the fourth to the third and so on. After a practice trial of 10 numbers, a set of 60 numbers are presented in four consecutive trials, with increasing rates of digit presentation (2.4, 2.0, 1.6, 1.2 seconds respectively). The score is the number of correct responses for each of the four rates of presentation.

PASAT norms are reported for 90 normal control subjects ages 14 to 55 years as well as retest scores which do indicate a practice effect (Gronwall, 1977). Additional norms were also reported for a sample of 50 normal controls divided by gender, age and education (Stuth, Stethem & Poirier, 1987). Education was found to be positively correlated with PASAT scores and older subjects tended to perform more poorly than younger subjects. Gronwall (1977) found PASAT scores sensitive to closed head injuries which was attributed to impaired information processing speed. A sample of 16 MS patients compared to 16 age-, sex- and education-matched controls was found to perform significantly worse on the PASAT for the two highest rates

of presentation (Litvan, Grafman, Vendrell & Martinez, 1988). The test involves attention, information processing speed and calculating abilities.

Symbol Digit Modalities Test (SDMT). For the SDMT (Smith, 1976) a subject is required to substitute a number for randomized presentations of geometric figures. The appropriate number is shown in a key presenting numbers from one to nine, each of which is paired with a different geometric symbol. The test preserves the substitution format of Wechsler's Digit Symbol subtest but reverses the presentation of material so that the symbols are printed and the numbers are written in. The subject can respond by writing in the numbers or orally stating the numbers. Ninety seconds are allowed for a maximum of 110 items.

Norms have been published for 420 adults ranging in age from 18 to 74 years, as well as several clinical brain damaged samples (Smith, 1976). The mean score for normals in the 18 to 24 age range is 55 for the written form and 63 for the oral form. For adults in the 65 to 75 age range, the means score is 37 for the written form and 46 for the oral form. When given to 100 patients with "confirmed and chronic" brain lesions, a cutoff point of -1.5 standard deviations below the mean correctly identified 86% of a patient group and 92% of the normal sample (Smith, 1976). Validity of the SDMT is also supported by significantly

different performance on the test between a number of samples of different clinical groups and normal subjects. Smith (1976) also reports assessment of retest reliability on a small sample of aphasic patients (n=15) with less than a one point difference between average scores after a 22 month interval. Scores on the SDMT do correlate positively with education and decrease with age.

Wechsler Adult Intelligence Scale-Revised (WAIS-R)

Subtests. The WAIS-R is a revised version of the Wechsler Adult Intelligence Scale (Wechsler, 1955) with new norms based on a sample of 1,880 adults stratified by a number of demographic variables acquired between 1976 and 1980 (Wechsler, 1981). The scales of interest for the present investigation are the Digit Span and Digit Symbol subtests. These two subtests are unchanged from the 1955 version of the WAIS. WAIS reliability and validity studies have been reviewed extensively by others (Klove, 1974; Matarazzo, 1972) and the Digit Span and Digit Symbol subtests have been found to be among the most sensitive indicators of neurological impairment.

The average retest reliability coefficients for a number of samples of various ages with a 1 to 7 week interval is .83 for Digit Span and .82 for Digit Symbol (Wechsler, 1981). The average standard error of measurement is 1.23 for Digit Span and 1.27 for Digit

Symbol.

The Digit Span subtests requires that a subject retain a string of 3 to 9 random digits in immediate memory long enough to repeat then back to the examiner. In the second half of the test the subject repeats the spoken digits in backward order. This subtest assesses auditory attention and immediate memory, as well as the ability to manipulate mentally the digits in reverse order.

The Digit Symbol subtest is a symbol substitution task consisting of four rows containing a total of 100 blank squares each paired with a randomly assigned number from 1 to 9. At the top of the test sheet is a key that pairs each number with a different symbol. The subject is given 90 seconds to fill in the blank squares the symbol which belongs to the number printed above the squares. This test involves sustained attention, motor speed and visual-motor coordination.

Satz-Mogel Short Form of the WAIS-R. The full WAIS-R takes approximately 1 to 1 and 1/2 hours to administer, so in the interest of conserving time, a short form version was used.

The Satz-Mogel Short Form of the WAIS (Satz & Mogel, 1962) has been modified to use with the WAIS-R (Adams, Smigielski & Jenkins, 1984). The short form involves administering every odd item or every third item, depending upon the

subscale, of the original WAIS-R. The Digit Span and Digit Symbol subscales are given in their entirety. The reliability of the modified Satz-Mogel Short Form WAIS-R has been assessed by simply correlating scores between the short form and the full WAIS-R. The alternate-form correlations from a sample of 107 adults were .98 for Full Scale IQ, .98 for Verbal IQ and .95 for Performance IQ (Adams, Smigielski, & Jenkins, 1984). Because the same items are on both forms the test, the artificially inflated correlations were statistically corrected and the adjusted reliabilities were .90 for Full Scale IQ, .90 for Verbal IQ and .80 for Performance IQ (Adams, Smigielski & Jenkins, 1984). For the purposes of this investigation, this short form of the WAIS-R was chosen to provide an index of IQ.

Verbal Fluency. Two different verbal fluency tasks were used in this investigation, each is a controlled word association task used different aphasia screening batteries. The first task is the Controlled Word Association Task (Form A) from the Multilingual Aphasia Examination (Benton & Hamsher, 1983). This task of oral fluency simply asks a subject to make verbal associations to different letters of the alphabet by saying all the words which he or she can think of beginning with a given letter within a time limit of 60 seconds. Three letters of progressively increasing associative difficulty are presented successively as

stimuli. The letters utilized in this test are C, F and L, and the test is commonly referred to as the CFL test. The score for the CFL test is simply the total number of responses for all three letters. Benton and Hamsher (1983) provide norms derived from a sample of 360 normal subjects ranging in age from 16 to 69 years. They also provide a table of recommended score adjustments for different levels of age and education as CFL performance decreases with age and increases with education. Benton and Hamsher (1983) do not report reliability data for the aphasia tasks separately, but they do report that the CFL test is sensitive to organic impairment, particularly to lesions in the left frontal lobe. The test involves verbal associative and retrieval capacities.

A second verbal fluency task used in this investigation is referred to as Animal Naming, and is part of the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983) and was included in the 3rd revision of the Stanford-Binet Intelligence Scale (Terman & Merrill, 1960). The test asks a subject to say the names of as many animals as possible within 60 seconds. Scoring is simply the number of acceptable responses. Norms are provided from a 1980 sample of 147 normal subjects ranging in age from 25 to 85 years (Goodglass & Kaplan, 1983). The mean for that sample was 22.5 (range: 9-41; SD=6.8), and a score of 12 was recommended as a cutoff score for the diagnosis of aphasia.

Reliability and validity data is not reported for this subtest individually but for clusters of subtests from the aphasia battery (Goodglass & Kaplan, 1983). The performance of brain injured patients can be low on the Animal Naming task due to impaired processing speed, as well as damage to brain areas involved with retrieval and verbal processing.

MRI Parameters

The MRI examinations were performed on a 1.5 Tesla General Electric Signa system. Contiguous slices through the axial and sagittal planes were performed with a 5 mm section thickness and 2.5 mm between slices. Imaging parameters included an acquisition matrix of 256 x 128 with a nexus of 2. T₁-weighted spin echo sequences were obtained in the axial (Tr of 2500, Te of 30 and 90) and sagittal (Tr of 2500, Te of 25, 50, 75, and 100) planes.

Procedure

Forty two patients who volunteered to participate in the research were screened by a clinical neuropsychologist in consultation with a neurologist to confirm diagnoses of MS using criteria suggested by Poser and others (1984). One volunteer was eliminated after finding his symptoms were due to a vascular condition rather than MS. The 41 MS patients were scheduled to undergo neuropsychological assessment and MRI examinations within the same week, and 39 patients received both assessments on the same day. The neuropsychological measures took approximately 3 to 4 hours to administer, with a break provided to relieve any fatigue. The measures were administered by masters level clinical psychologists. The MRI examination was conducted by radiological technicians at the Michigan State University Clinical Center Department of Radiology.

The MRI data was scored for size and location of lesions by two masters level graduate students in clinical psychology, and one doctoral level speech pathologist. Training for scoring MRI images was done in consultation with experienced radiologists. Each patient's MRI images were scored for lesion size and location by all three raters independently. Scoring the MRI data took approximately 1 and 1/2 hours for each patient.

Confirmatory Factor Analysis

Each of the measures that contributes to the model described by the hypotheses was included in a correlation matrix. Next, a confirmatory factor analysis was performed. Each of the measures that was hypothesized to contribute to a specific measurement factor or construct was included in an appropriate cluster of measures as defined by the measurement model. These factors, defined on the basis of content analysis, were analyzed using confirmatory factor analysis of the correlations among the observed variables to test the fit of the measurement model to the data.

The confirmatory factor analysis provided the correlations of each measure with the factor or construct defined by the measurement model, which are referred to as "factor-pattern coefficients." The factor-pattern coefficients are the regression weights of the observed variables (each measure) on the corresponding factors specified by the measurement model (Hunter & Gerbing, 1982). The confirmatory factor analysis also provided the correlations between factors, and the correlations between each measure and each factor, referred to as "factor loadings."

The confirmatory factor analysis was performed with "communalities" in the diagonal to eliminate effects due to error of measurement. When communalities are placed in the diagonal of the correlation matrix, the item-factor

correlations become the estimated correlations between the items and cluster "true" scores (or scores without measurement error). The factor-factor correlations become the estimated correlations between cluster "true" scores. The communalities are calculated by squaring the factor-pattern coefficients. The correlation of each item with its measurement model factor can be considered an observed correlation between an item and another item of the same reliability. Using communalities in the diagonal does have the effect of increasing the effects of sampling error somewhat, and the accuracy of the correlations depends on the fit of the measurement model. The confirmatory factor analyses were performed on an IBM compatible micro-computer using statistical software called Package, originally developed by Hunter and Cohen (1969).

The items or measures that compose each factor of the measurement model not only share a common meaning with respect to content but need to display statistical evidence of unidimensionality. Aside from the quality or comparable degree of correlation of items within a factor and the factor, items that compose factors need to be correlated with outside variables in a parallel way. This criterion of external parallelism for unidimensional factors stipulates that items within a cluster have a similar pattern of correlations with other variables. The measurement model described by the hypotheses was assessed and revised

according to the criteria of unidimensionality and according to the content of the measurement clusters.

RESULTS

Data Preparation

The data derived through MRI regarding the location and size of lesions was collected by recording the lesions observed for each specific anatomical area, for each axial slice. In preparation for analysis, the data for each anatomical region was summed over all of the axial slices for each patient to provide the sum of lesion area for each anatomical region. Similarly, the coding for lesions in the corpus callosum involved three sagittal slices, which were summed to provide the total lesion area for the corpus callosum.

The summed lesion area for each region of the brain was then averaged for the three different raters. The decision to use the average of the three raters was an effort to minimize the impact of rater errors. The means and standard deviations for each of the neuropsychological measures for the MS patients are reported in Table 1. The means and standard deviations for normals, matched by mean age when available, are also reported in Table 1. Several statistics to compare the performance of the MS sample with normative samples are also provided, including the z-ratio (z), an index for size of the difference (D), and an estimated correlation (r). The mean total lesion area observed through MRI for each brain region is reported in Table 2.

Table 1: Performance on Neuropsychological Measures

	<u>MS Patients</u>		<u>Normal Controls</u>				
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	<u>z</u>	<u>D</u>	<u>r</u>
FSIQ	102.44	13.48	100.00	15.00	1.04	0.16	.08
PIQ	100.61	15.78	100.00	15.00	0.26	0.04	.02
VIQ	103.44	12.96	100.00	15.00	1.47	0.23	.11
Pegboard	31.24	12.03	46.76	4.04	-24.58	-3.84	-.89
Trails A'	44.42	25.77	27.58	9.30	-11.59	-1.81	-.67
Trails B'	110.95	65.50	64.10	16.30	-18.40	-2.87	-.82
F.Local	54.05	4.70	57.50	2.70	-8.18	-1.28	-.54
F.Write'	9.78	8.71	2.50	2.50	-18.65	-2.91	-.82
DigFor	7.98	1.78	8.70	1.80	-2.56	-0.40	-.20
DigBack	6.44	2.92	6.80	2.10	-1.10	-0.17	-.09
WLogic2	17.39	8.69	21.90	9.20	-3.14	-0.49	-.24
WVerbal	94.39	16.82	101.10	16.40	-2.62	-0.41	-.20
WVisual	100.56	18.43	99.90	15.90	0.27	0.40	.02
WGeneral	94.68	15.95	101.10	17.70	-2.32	-0.36	-.18
Watten	94.95	15.46	99.70	15.80	-1.93	-0.30	-.15
WDelayed	93.42	16.16	101.60	17.30	-3.03	-0.47	-.23
CRecall	52.63	12.24	52.81	7.20	-0.16	-0.03	-.01
CTrialB	6.85	2.00	6.14	2.40	1.89	0.30	.15
CSTR	10.63	3.09	10.38	2.50	0.64	0.10	.05
CSTCR	11.59	2.82	11.62	2.60	-0.07	-0.01	-.01
CLTR	11.05	2.97	11.05	2.90	0.00	0.00	.00
CLTCR	11.81	2.76	11.71	2.80	0.23	0.04	.02
Discrim	93.85	6.41	94.16	4.50	-0.44	-0.07	-.03
WCSCat	4.51	1.65	5.40	1.30	-4.38	-0.69	-.32
WCSPers'	24.37	19.87	12.60	10.20	-7.39	-1.15	-.50
LineOr	24.76	4.04	25.60	5.70	-0.94	-0.15	-.07
FaceRec	44.81	4.21	45.40	3.96	-0.95	-0.15	-.07
HVOT	26.57	2.49	25.71	4.78	1.15	0.18	.09
PASAT24	30.85	12.80	43.43	10.16	-7.93	-1.24	-.53
PASAT20	26.90	11.45	41.87	10.16	-9.44	-1.47	-.59
PASAT16	25.02	10.03	33.10	12.20	-4.24	-0.66	-.31
PASAT12	17.68	8.82	24.63	10.55	-4.22	-0.66	-.31
DigSymb	8.95	3.35	10.00	3.00	-2.24	-0.35	-.17
SDMT-W	39.54	13.04	49.00	8.50	-7.13	-1.11	-.49
SDMT-O	46.78	14.85	57.00	10.00	-6.54	-1.02	-.46
CFL	36.90	10.43	40.00	10.43 ²	-1.90	-0.30	-.15
Animal	13.39	5.10	22.50	6.80	-8.58	-1.34	-.56

Abbreviations:

z= z-ratio ($|z| > 2.57$ indicates significant difference at $p < .01$, two tailed)

d= size of effect (difference between means divided by SD)

r= estimated correlation between MS and normative samples

FSIQ= Full Scale IQ (WAIS-R, Satz-Mogel Short Form)

VIQ= Verbal Scale IQ (WAIS-R, Satz-Mogel Short Form)

PIQ= Performance Scale IQ (WAIS-R, Satz-Mogel Short Form)

F.Local= Finger Localization

Table 1 (continued)

F.Write= Fingertip Number Writing
 DigFor= Digit Span Forward (from Wechsler Memory Scale-R)
 DigBack= Digit Span Backward (WMS-R)
 WLogic2= WMS Logical Memory Delayed
 CRecall= California Verbal Learning Test (CVLT) Total Recall
 CSTR= CVLT Short Term Recall
 CSTCR= CVLT Short Term Cued Recall
 CLTR= CVLT Long Term Recall
 Discrim= CVLT Discrimination Index
 HVOT= Hooper Visual Organization Test
 PASAT24= Paced Auditory Serial Addition Task (2.4s)
 DigSymb= Digit Symbol Test (WAIS-R)
 SDMT-W= Symbol Digit Modalities Test-Written
 SDMT-O= Symbol Digit Modalities Test-Oral
 CFL= Controlled Oral Word Association Test
 Animal= Animal Naming Test
 1= signs for z, D and r were reversed because these
 variables are scored for errors (higher scores are worse)
 2= normative std. dev. for CFL unavailable, std. dev. for MS
 sample used as an estimate

Table 2: MRI Total Lesion Area by Brain Region (sq. mm)

	<u>mean</u>	<u>std. dev.</u>
Brain Stem	23.82	38.08
Cerebellum	31.26	46.47
Corpus Callosum	121.79	153.32
Basal Ganglia	17.18	24.04
Internal Capsule	13.89	20.18
Right Frontal	325.17	380.62
Left Frontal	277.99	314.58
Right Temporal	420.79	452.47
Left Temporal	450.94	517.40
Right Parietal	366.20	314.44
Left Parietal	337.71	277.97
Total Lesion Area	2315.48	2185.43

Inter-rater Reliability

The correlations between raters for the different regions of the brain scored for lesions were calculated. The average of the three inter-rater correlations for each region were calculated to provide an estimate of single rater reliability. Since this study averaged across three raters, the reliability of the composite rating was computed from the single rater reliability using the Spearman-Brown formula. For each region, the correlations between individual raters, the average of the three inter-rater correlations and the composite reliability are reported in Table 3. The reliabilities ranged from .48 to .92, with a median reliability of .84.

Table 3: Inter-rater Correlations

	GN	GR	NR	AVE	ADJ
Brain Stem	.66	.68	.57	.64	.84
Cerebellum	.62	.65	.32	.53	.77
Corpus Callosum	.16	.78	.02	.32	.57
Basal Ganglia	.36	.18	.17	.24	.48
Internal Capsule	.27	.79	.09	.38	.65
Right Frontal	.69	.85	.66	.73	.89
Left Frontal	.79	.80	.78	.79	.92
Right Temporal	.60	.91	.55	.68	.87
Left Temporal	.51	.89	.52	.64	.84
Right Parietal	.80	.59	.61	.67	.86
Left Parietal	.65	.61	.48	.58	.81
Total Lesion Area	.72	.89	.63	.74	.90

GN - correlations between raters G and N

GR - correlations between raters G and R

NR - correlations between raters N and R

AVE - single rater reliability: average correlation among three raters

ADJ - composite reliability computed using Spearman-Brown formula

Measurement Model

The hypotheses under investigation delineated a measurement model utilizing specific tests to assess the relationship between different constructs. For example, hypothesis one described a factor labeled "sensorimotor abilities" composed of the following neuropsychological measures: Purdue Pegboard, Trails Making A and B, Fingertip Number Writing and Finger Localization. This sensorimotor ability factor composed of the five specified measures, was hypothesized to be affected by lesions in a specific area of the brain, namely the brain stem and cerebellum, which define another composite factor in the measurement model. Hypothesis one suggests that lesions in the brainstem and cerebellar regions will negatively affect sensorimotor abilities. The complete measurement model specified by the research hypotheses is listed below in Table 4.

Table 4: Measurement ModelSensorimotor Ability

Purdue Pegboard
 Trails A and B
 Fingertip Number Writing
 Finger Localization

Memory

Wechsler Memory Scale-Delayed Recall
 California Verbal Learning Test
 (particularly Recall Errors, and Long Delay Free Recall)

Conceptual Problem-Solving

Wisconsin Card Sort (perseverative errors)

Visuospatial Ability

Hooper Visual Organization Test
 Line Orientation Test
 Face Recognition Test

Information Processing Speed, Attention and Fluency

Paced Auditory Serial Addition Task (PASAT)
 Symbol Digit Modalities Test (SDMT)
 Digit Span (WMS-R)
 Digit Symbol (WAIS-R)
 Controlled Oral Word Association (CFL)
 Animal Naming

Brainstem and Cerebellum Lesions

Pons, Medulla, Midbrain, Vermis and Cerebellum lesions

Frontal and Temporal Lobe LesionsFrontal Lobe LesionsRight Hemisphere Lesions

Frontal, Temporal, Parietal lesions on the right side

Subcortical Lesions

Corpus Callosum, Internal Capsule, and Basal Ganglia structure lesions

Revision of the Measurement Model

The fit of the measurement model was assessed by examining the magnitude of the factor-pattern coefficients and the nature of the parallelism among items that composed the factors. The matrix produced by confirmatory factor analysis is presented in Table 5, in the Appendix. Because of the sampling error that is expected with a sample of size of 41, the observed correlations between items and factors must be interpreted with respect to a wide interval of possible error.

The confirmatory factor matrix was examined to assess the unidimensionality of the factors composing the measurement model. Several of the measures were found not to correlate well with their measurement model clusters, and lacked parallelism with other variables. The measurement model factors were therefore revised to better fit the data. The factor revisions were undertaken to both maximize the unidimensionality of the factors and to maintain the meaningful content of the factors.

Sensorimotor and Visuospatial factors. The sensorimotor factor, composed of the Purdue Pegboard, Trails Making A and B, Fingertip Number Writing and Finger Localization, formed a cluster which did satisfy the criteria for unidimensionality. The visuospatial factor, composed of the Hooper Visual Orientation test, Line Orientation and Face Recognition tests, formed a cluster

which was also satisfactorily unidimensional.

Memory factor. The memory factor was originally defined in the measurement model to use tests of delayed memory as the MS literature suggested this was one of the more prominent memory deficits displayed by MS patients. However, the factor composed of the Wechsler Memory Scale Delayed index and the CVLT Discrimination index (an index that accounts for false positive responses in a recognition task) did not show a distinct relationship relative to other factors. Another memory factor consisting only of short term memory indices was correlated .71 with the delayed memory factor, and both memory factors showed parallel correlations with other variables. The data indicated that both memory factors could be combined to form a general memory index, and that more specific distinctions between discrete memory functions were not likely to be detected in the data.

Conceptual Problem-Solving factor. The Wisconsin Card Sort (WCS) - Perseverative Errors was found to correlate well with the score for categories correct, and these two indices showed parallel correlations with other variables. When they were combined to form a factor, they showed equal factor-pattern coefficients (.88). The conceptual problem-solving factor was therefore composed of both the WCS Categories correct and Perseverative errors.

Processing Speed, Attention and Fluency. The many measures that comprise this factor in the measurement model were found to be better defined as separate clusters in the confirmatory factor analysis. A number of different combinations of measures was attempted in an effort to compose a processing speed factor according to the content of the measures. For example, the PASAT trials, Symbol Digit Modalities (Oral), and the Fluency measures were combined to form a cluster of speeded tests that was independent of motor function. However this cluster did not show unidimensionality in the within cluster correlations, nor through external parallelism. The PASAT trials formed an independent cluster, the two fluency tests (CFL and Animal Naming) formed a separate cluster, and Symbol Digit Modalities (Oral and Written) combined with Digit Symbol to form a factor of symbol substitution tasks. These separate factors provided a better fit to the data than the larger, more heterogenous factor described on the basis of content alone by the measurement model.

Brain Region Lesion factors. One cluster was created by combining brainstem (pons, medulla and midbrain) and cerebellum lesions. Another cluster, defined by the information processing speed hypothesis, combined corpus callosum, internal capsule and basal ganglia region lesions to create a subcortical conducting pathways factor. Cortical brain regions were defined simply as right

temporal, left temporal, frontal and parietal regions. These brain region lesion factors were defined through the measurement model and were supported by the confirmatory factor analysis.

One of the more important results of the confirmatory factor analyses was the high correlations among the brain region lesion factors. These correlations are listed in Table 6. Included in this table is the second order factor for total lesions, a composite of all discrete brain region lesions.

Table 6: Correlations Among Brain Region Lesion Factors

		(1)	(2)	(3)	(4)	(5)	(6)	(7)
Sub-Cortical	(1)	1.00	.95	.96	.92	.80	.66	1.00
Right Temporal	(2)	.95	1.00	.94	.87	.79	.60	.98
Left Temporal	(3)	.96	.94	1.00	.89	.71	.50	.95
Frontal	(4)	.92	.87	.89	1.00	.79	.51	.94
Parietal	(5)	.80	.79	.71	.79	1.00	.65	.90
Brainstem+Cereb.	(6)	.66	.60	.50	.51	.65	1.00	.74
Total Lesions	(7)	1.00	.98	.95	.94	.90	.74	1.00

These high correlations among the lesions observed in different regions of the brain indicate that statistical tests designed to detect relationships between neuropsychological measures and discrete brain region lesions are unrealistic. The common variance among the different brain region lesions obscures any more discrete relationships between neuropsychological performance and

specific locations of lesions.

The correlation between lesions observed in the brainstem and cerebellum regions, and to some extent the parietal region, and the other regions of the brain were lower than the correlations between other regions.

Second Order Factors

Global Factors. To help clarify the relationships among measurement model factors, two second order factors were created. One factor was simply the combination of all neuropsychological measures. The second was the combination of all brain region lesions. The factor composed of all of the neuropsychological measures was useful in assessing how specific brain region lesions were related to overall neuropsychological performance. The factor composed of all the different brain region lesions was useful in assessing which neuropsychological measures were more sensitive to total evidence of MRI lesions.

Relationships Among Neuropsychological Performance Factors. The relationship between several specific neuropsychological performance factors were observed to be highly correlated with each other. In an effort to better assess these relationships, a confirmatory factor matrix was created with age of patient partialled out of the correlations. Age is known to be related to performance on

a number of the neuropsychological measures administered in this investigation, so removing the effects of age through partial correlation was an attempt to remove variance due to age that might obscure the relationships among factors. The second order factor matrix with age partialled out is presented in Table 7-B, in the Appendix. The second order factor matrix without age partialled out is presented in Table 7-A.

The confirmatory factor matrix shows that four neuropsychological factors are correlated with each other and show parallel correlations with other factors. These four neuropsychological factors are: Symbol Substitution, Sensorimotor, Visuospatial and Fluency. These four neuropsychological factors are also the most sensitive factors to brain lesions, as indicated by their strong correlations with the total lesion factor.

The remaining four neuropsychological factors: Memory, Conceptual Problem-Solving, Paced Auditory Serial Addition and Digit Span, were also correlated with each other and show parallel correlations with other factors. These four factors were less sensitive to brain lesions as indicated by their weaker correlations with total lesion factor.

Table 7-A: Second Order Factor Matrix

	522	523	524	525	501	505	506	507	512	508	511	515	509	510	514	513	515	516	517	518	519	520	521
522	100	-67	101	110	-39	66	94	90	93	89	100	93	73	78	73	77	93	-41	-62	-56	-57	-64	-71
523	-67	100	-74	-54	8	-25	-64	-48	-83	-72	-60	-59	-37	-35	-36	-39	-59	74	95	98	94	90	100
524	101	-74	100	92	-31	55	94	82	95	94	101	95	61	66	62	65	95	-53	-66	-62	-61	-73	-76
525	110	-54	92	100	-49	78	90	96	85	79	93	85	85	90	85	90	85	-23	-54	-46	-48	-50	-62
501	-39	8	-31	-49	100	-14	-17	-19	-30	-38	-30	-17	-44	-39	-13	-38	-17	-5	13	12	0	13	8
505	66	-25	55	78	-14	100	53	93	44	41	58	62	65	43	46	60	62	-18	-23	-19	-21	-27	-22
506	94	-64	94	90	-17	53	100	100	88	82	97	80	59	65	60	63	80	-49	-59	-51	-52	-53	-72
507	90	-48	82	96	-19	93	100	100	73	68	85	78	70	60	63	70	78	-35	-45	-38	-40	-42	-51
512	93	-83	95	85	-30	44	88	73	100	85	87	81	54	52	62	66	81	-59	-74	-71	-73	-77	-82
508	89	-72	94	79	-38	41	82	68	85	100	89	73	57	53	48	59	73	-51	-67	-66	-56	-69	-70
511	100	-60	101	93	-30	58	97	85	87	89	100	100	63	75	62	56	100	-41	-54	-45	-51	-59	-66
515	93	-59	95	85	-17	62	80	78	81	73	100	100	54	63	57	59	100	-44	-48	-49	-46	-64	-62
509	73	-37	61	85	-44	65	59	70	54	57	63	54	100	46	44	43	54	-20	-42	-31	-27	-44	-33
510	78	-35	66	90	-39	43	65	60	52	53	75	63	46	100	43	58	63	-13	-38	-28	-26	-22	-55
514	73	-36	62	85	-13	46	60	63	62	48	62	57	44	43	100	47	57	-15	-28	-29	-37	-46	-36
513	77	-39	65	90	-38	60	63	70	66	59	56	59	43	58	47	100	59	-15	-41	-37	-42	-26	-47
515	93	-59	95	85	-17	62	80	78	81	73	100	100	54	63	57	59	100	-44	-48	-49	-46	-64	-62
516	-41	74	-53	-23	-5	-18	-49	-35	-59	-51	-41	-44	-20	-13	-15	-15	-44	100	50	60	51	65	66
517	-62	95	-66	-54	13	-23	-59	-45	-74	-67	-54	-48	-42	-38	-28	-41	-48	50	100	94	89	71	96
518	-56	98	-62	-46	12	-19	-51	-38	-71	-66	-45	-49	-31	-28	-29	-37	-49	60	94	100	87	79	95
519	-57	94	-61	-48	0	-21	-52	-40	-73	-56	-51	-46	-27	-26	-37	-42	-46	51	89	87	100	79	92
520	-64	90	-73	-50	13	-27	-53	-42	-77	-69	-59	-64	-44	-22	-46	-26	-64	65	71	79	79	100	80
521	-71	100	-76	-62	8	-22	-72	-51	-82	-70	-66	-62	-33	-55	-36	-47	-62	66	96	95	92	80	100

501-AGE

505-VIQ

506-PIQ

507-FIQ

508-SENSORIMOTOR

509-MEMORY

510-CONCEPTUAL PROBLEM-SOLVING

511-VISUOSPATIAL

512-SYMBOL SUBSTITUTION

513-PASAT

514-DIGIT-SPAN

515-FLUENCY

516-BRAINSTEM-CEREBELLUM

517-L-TEMPORAL

518-R-TEMPORAL

519-FRONTAL

520-PARIETAL

521-SUB-CORTICAL

522-ALL-NEUROPSYCHOLOGICAL FACTORS

523-ALL-LESION REGIONS

524-MORE SENSITIVE NEUROPSYCHOLOGICAL FACTORS

525-LESS SENSITIVE NEUROPSYCHOLOGICAL FACTORS

Intelligence. A short form intelligence measure (WAIS-R) was included as a factor in the confirmatory factor analyses because general intelligence is suggested to explain a considerable proportion of variance assessed in specific cognitive tasks. The separate indices for Performance and Verbal IQ as well as Full Scale IQ were included. Correlations with these three indices of IQ were corrected for attenuation due to error of measurement using their reliabilities. The retest reliabilities reported for the full form WAIS-R are: PIQ $r = .90$, VIQ $r = .97$, and FIQ $r = .96$ (Wechsler, 1981). These reliabilities were adjusted downward using the Spearman-Brown formula for a half-test as an estimate of the diminished reliability due to the short form administration.

IQ was correlated with the All Neuropsychological factor: PIQ $r = .85$, VIQ $r = .64$ and FIQ $r = .90$. IQ was also correlated with the All Lesion factor, with PIQ $r = -.58$, VIQ $r = -.23$, and FIQ $r = -.48$.

Second Order Neuropsychological Factors. A second order confirmatory factor analysis was performed to create two second order factors from the neuropsychological factors. One factor, which might be called the Most Sensitive Four, was composed of the: Symbol Substitution, Sensorimotor, Visuospatial and Fluency factors. The second factor, which might be called the Less Sensitive Four, was composed of the remaining four factors: Memory, Conceptual

Problem-Solving, Paced Auditory Serial Addition, and Digit Span. These factors were created because they fit the data. The explanation of the homogeneity of these factors in terms of their relative content was deferred until further statistical assessment of their fit to the data was performed.

A second order confirmatory factor matrix was computed, presented below in Table 8, with age, the All Lesion factor, the Most Sensitive Four Neuropsychological factor, PIQ, VIQ and the Less Sensitive Four Neuropsychological factor. These factors, and their correlations, provide a composite summary of the relationships between all of the relevant variables under investigation. The measures that contribute to each factor are listed below Table 8.

Table 8: Second Order Factor Matrix

		501	523	524	506	505	525
Age	501	100	8	-31	-17	-14	-49
All Lesions	523	8	100	-74	-64	-25	-54
Most Sensitive Four	524	-31	-74	100	94	55	92
PIQ	506	-17	-64	94	100	53	90
VIQ	505	-14	-25	55	53	100	78
Less Sensitive Four	525	-49	-54	92	90	78	100

Composition of Factors501 Age523 All Lesions: factor with all brain region lesions combined524 Most Sensitive Four:

- (1) Symbol Substitution (SDMT and Digit Symbol)
- (2) Sensorimotor (Pegboard, Trails A +B, Finger Localization and Fingertip Number Writing)
- (3) Visuospatial (HVOT, Face Recognition, Line Orientation)
- (4) Fluency (CFL and Animal Naming)

506 PIQ (Performance IQ)505 VIQ (Verbal IQ)525 Less Sensitive Four:

- (1) Memory (WMS Logical Memory-Delayed, WMS Delayed Index, CVLT: Short-term Recall, Short-term Cued Recall, Long-term Recall, Long-term Cued Recall, Discrimination Index)
- (2) Conceptual Problem-Solving (Wis. Card Sort Categories and Perseverative Errors)
- (3) Digit Span (forward and backward)
- (4) Paced Auditory Serial Addition (all 4 trials)

Path Analyses

The confirmatory factor analyses provided statistical evidence to support hypotheses regarding the casual relationships among factors. Age and brain lesions clearly affected performance on neuropsychological tasks. Age was correlated with the Most Sensitive Four Neuropsychological factor, $r = -.31$, and the Less Sensitive Four Neuropsychological factor, $r = -.49$. Age was only weakly correlated with PIQ, $r = -.17$ and with VIQ, $r = -.14$. The neuropsychological factors were differentially affected by brain lesions. The second order cluster of factors that were Most Sensitive to lesions correlated with the All Lesion factor $r = -.74$, and the cluster of factors that were Less Sensitive to lesions correlated with the All Lesion factor $r = -.54$. Also, Performance IQ was more strongly related to the Most Sensitive Four Neuropsychological factor ($r = .94$) than was Verbal IQ ($r = .55$). These observations suggested a causal ordering among the factors that is presented in Figure 1. This causal model fit the relationships among factors observed in Table 8.

The causal model described in Figure 1 was assessed for fit using path analysis statistics. The resulting path coefficients are noted along the pathways of the model in Figure 1. The path coefficients can be interpreted as regression beta weights. The fit of the model can be assessed by comparing the observed correlations between the

factors, as determined by the confirmatory factor analysis, with the reproduced correlations that are a product of the path model. The difference between the observed and reproduced correlations represents the error or lack of fit of the path model, and should not differ from zero by more than sampling error. These comparisons are shown in Table 9. A chi-square test for the model represented in Figure 1 shows that the differences are not significantly different from zero (Chi-square = 1.23, df=7), suggesting that the model does fit the data.

Figure 1: Path Model

Age			-.24			
-.25	Most Sensitive Cognitive Measures		PIQ		VIQ	
-.72		.94		.53		.40
						Less Sensitive Cognitive Measures
All Lesions				.62		

Most Sensitive Measures: Symbol Substitution, Sensorimotor, Visuospatial, and Fluency

Less Sensitive Measures: Memory, Conceptual Problem-Solving, Digit Span and Pace Auditory Serial Addition

Table 9: Error Analysis of Path ModelObserved correlations:

	Age	AL	MSF	PIQ	VIQ	LSF
Age	100	8	-31	-17	-14	-49
All Lesions	8	100	-74	-64	-25	-54
Most Sensitive Four	-31	-74	100	94	55	92
PIQ	-17	-64	94	100	53	90
VIQ	-14	-25	55	53	100	78
Less Sensitive Four	-49	-54	92	90	78	100

Reproduced correlations:

	Age	AL	MSF	PIQ	VIQ	LSF
Age	100	8	-31	-29	-15	-50
All Lesions	8	100	-74	-70	-37	-63
Most Sensitive Four	-31	-74	100	94	50	90
PIQ	-29	-70	94	100	53	87
VIQ	-15	-37	50	53	100	75
Less Sensitive Four	-50	-63	90	87	75	100

Errors: (Actual - reproduced)

	Age	AL	MSF	PIQ	VIQ	LSF
Age	0	0	0	12	1	1
All Lesions	0	0	0	6	12	9
Most Sensitive Four	0	0	0	0	5	2
PIQ	12	6	0	0	0	3
VIQ	1	12	5	0	0	3
Less Sensitive Four	1	9	2	3	3	0

Other path models were sought in an effort to assess other possible explanations of the relationships between the MS disease process and different neuropsychological abilities. However, any good-fitting model for this data

requires that the cluster of the four most sensitive neuropsychological factors is antecedent to other neuropsychological factors, and PIQ is antecedent to VIQ. VIQ and the less sensitive neuropsychological factors are less affected by the general lesion factor. No better fitting path model could be found.

Summary

The inter-rater reliability of the MRI data varied by lesion area with a median reliability of .84. Several of the neuropsychological factors in the measurement model specified in the hypotheses required revision after examining relationships among tasks using confirmatory factor analysis. The specific brain region lesion factors were unidimensional but they were found to be extremely highly correlated with each other. One of the consequences of the high correlation among the lesions in different brain regions is that specific relationships between lesion location and neuropsychological ability factors cannot be detected. The correlations for lesions observed in the brainstem and cerebellum, and parietal lobes were lower than the correlations among the other brain regions.

Second order factors were created by combining all lesion factors, and by combining four of the neuropsychological ability factors that were: (a) highly correlated with the total lesion factor, and (b) highly

correlated with each other. A second neuropsychological ability factor was created by combining the four neuropsychological factors that were less sensitive to MRI evidence of brain lesions. These four factors were also highly parallel to each other and defined a second order factor. A path model (Figure 1) that included age and brain lesions as exogenous factors, and the most sensitive four neuropsychological factors, PIQ, VIQ and the less sensitive neuropsychological factors, was found to fit the data.

DISCUSSION

This investigation was designed to explore the relationship between the impact of multiple sclerosis on the central nervous system and neuropsychological deficits. The evidence of the pathophysiological impact of MS on the brain was derived through magnetic resonance imaging. The evidence for the cognitive consequences of MS was derived from a battery of neuropsychological measures. This investigation has implications for the use of MRI data, along with neuropsychological data, for understanding the MS disease process.

MRI Data

Coding. The data derived through MRI involved choosing a particular protocol of imaging parameters based on the literature involving MS and MRI, and the recommendations of radiologists. The quantification of the MRI data involved developing a method for coding the location and size of lesions. Because no standard procedure exists for coding MRI data, and previous investigations often reported simple efforts at quantification, one of the unique procedures of this investigation involved a more comprehensive effort to measure the specific location and size of lesions than had previously been reported in the MS literature.

MRI Reliability. After training to achieve agreement on the identification of the signs of MS and on the identification of brain anatomy seen through MRI, three raters independently coded the MRI data. The MRI coding sometimes involved judgments about the identification of MS lesions and the specific location of the lesions. There was sometimes difficulty in determining if the intensity of signal observed on an MR image was high enough to indicate evidence of MS or was instead an artifact independent of MS. There was sometimes difficulty in specifying the anatomical location of a high intensity signal, particularly if the signal appeared at the boundary of two regions such as along the along the internal capsule and thalamus for example.

The inevitable judgement involved in the MRI coding has the consequence of attenuating the reliability of MRI observed MS lesions. This investigation employed three raters which provided both a means of assessing the reliability of MRI as a quantitative measure, and a means of correcting for the error due to rater judgement. While the median composite inter-rater reliability of the MRI coding was a relatively acceptable .84, the range indicated that the composite inter-rater reliability was as low as .48, and the agreement between two individual raters for different brain regions was at times quite low (see Table 3).

The lowest composite inter-rater reliability (.48) was for the basal ganglia structures which was likely due to the

difficulty in distinguishing between the basal ganglia structures and surrounding tissue. Also, coders found that high signal intensity due to MS is difficult to identify independently of high signal intensity normally present in the periphery of basal ganglia structures seen on MRI. The low correlations between raters for the corpus callosum were likely due to one rater interpreting high signal frequently seen at the boundary of the corpus callosum as outside the corpus callosum, while the other two raters scored high signal on the rim of the corpus callosum as inside.

The reliability of the MRI data indicates that coding evidence of MS is difficult to do objectively because some judgement is inevitably required. Judgement is involved regarding what is sufficiently high signal intensity to indicate a lesion, and what is the exact anatomical location of the lesion. While MRI is a useful diagnostic indicator of brain lesions, it has limits as a quantitative measure due to the judgement involved. Previous investigations utilizing MRI have made little effort to correct for the limited reliability of MRI data, which can be accomplished by using multiple raters and by correcting for attenuation. This investigation has demonstrated that MRI data does involve notable error due to rater judgement and ignoring this measurement error could obscure any results obtained through MRI.

Research Hypotheses

Lesion Location and Neuropsychological Performance.

The first five hypotheses under investigation were concerned with relationships between the specific locations of MS lesions observed through MRI and performance on specific neuropsychological measures. None of these specific hypotheses were supported by the data. However, strong relationships between MRI evidence of lesions and neuropsychological performance were found. MRI evidence of brain lesions did prove highly predictive of neuropsychological performance, but specific locations of lesions were not associated with specific neuropsychological deficits.

The manifestation of lesions in different locations within the brain observed through MRI proved to be highly correlated. So, if lesions were observed in any particular region of the brain, they were likely to be found in other areas of the brain as well. This high inter-correlation of lesions in different areas of the brain obscured any specific relationships between discrete locations of lesions and neuropsychological performance. The data indicated no particular focus for the location within the brain of MS lesions. The individual variability in the physical manifestation of the disease is large as indicated by the large standard deviations for lesion area in all regions of

the brain (Table 2).

The research hypotheses initially proposed in this investigation were based partly upon expectations derived from the clinical neuropsychological literature regarding relationships between brain lesions and neuropsychological performance. The clinical literature is based on study of the impact of focal lesions caused by tumors, vascular failure, head trauma and other causes of localized brain damage. The results of this study suggest that the brain damage caused by MS observable through MRI is not localized but diffuse, and that specific neuropsychological consequences are therefore difficult to predict.

Neuropsychological literature on diffuse brain damage caused by traumatic brain injury that has caused minute lesions and lacerations scattered throughout the brain has reported impairment similar to that observed in this sample of MS patients. Traumatic brain injury causing widespread diffuse damage has been reported to compromise mental speed, attentional functions, cognitive efficiency, and when severe, high level concept formation and reasoning abilities (Lezak, 1983). Patients with diffuse damage often experience slowed thinking and reaction times and score significantly lower on timed tasks. Patients with diffuse brain damage also have been reported to perform relatively poorly on tasks requiring concentration and mental tracking such as oral or sequential arithmetic (Lezak, 1983). These

kinds of neuropsychological impairment do resemble the deficits exhibited by the MS patients in this investigation.

The location of MRI lesions for this sample did show a typical periventricular involvement, a tendency for lesions to occur proximate to the lateral ventricles, particularly at the anterior and posterior horns. This pattern of lesions is commonly described in the MS literature, but may not be obvious from the results of this investigation describing the location of lesions.

Periventricular lesions were recorded in the particular lobe in which the ventricle bordered. Periventricular lesions in the anterior horns of the lateral ventricle were recorded in the frontal lobe for example, while periventricular lesions in the posterior horn might be recorded as temporal or parietal lobe lesions (depending upon the axial level). The MS lesions observed in this sample were also predominantly in white matter rather than grey matter tissue, although this distinction at the grey and white matter junctions was difficult to determine from the MRI images.

Processing Speed. Two research hypotheses were based on literature suggesting that the deficits in neuropsychological performance caused by MS could be due to interference in white-matter conducting pathways that resulted in a reduction in information processing speed. These hypotheses were based on the expectation that the demyelination due to MS interferes with the efficiency of

neural transmissions, resulting in a global decline in cognitive processing speed. These information processing speed hypotheses were not supported by the location of MS lesions detected through MRI.

Hypothesis five predicted that evidence of lesions in the principle neural conducting pathways (the corpus callosum, and internal capsule) and basal ganglia structures would predict performance on neuropsychological measures sensitive to processing speed. The MRI data indicated that MS lesions in the conducting pathways were frequently accompanied by lesions in other areas of the brain. No particular brain region proved to be a focus of lesions independently of other regions, and no particular brain region could predict deficits in processing speed better than another region.

Hypothesis six predicted that a cluster of measures thought to be sensitive to processing speed, namely the Paced Auditory Serial Additions Task (PASAT), the Symbol Digit Modalities Task (SDMT), and the Verbal Fluency tasks (CFL and Animal Naming), would predict deficits on all of the other clusters of cognitive measures (sensorimotor, memory, conceptual problem-solving and visuospatial abilities). The data did not support the clustering of these measures into one composite factor. Confirmatory factor analysis indicated that the PASAT, the SDMT and the Verbal Fluency tests formed independent factors, and

attempts to create a factor combining them all were not supported by the data.

An implication of the lack of support for hypothesis five is that MRI evidence of MS does not indicate a focus of MS deterioration in the neural conducting pathways independent of other brain regions. The lack of support for hypothesis six suggests that either processing speed is not a useful construct for explaining MS deficits or the measurement model for processing speed was not a good measure of the construct.

Correlations Among Brain Region Lesion Factors

The correlations between different brain region lesion factors were high as mentioned earlier. However, the correlations between the Brainstem and Cerebellum factor and the other regions were lower (see Table 6). The correlation between the Brainstem and Cerebellum factor and the Total Brain Lesions factor was $r = .74$, while the correlations between the other regions and the Total Lesions factor were all $r = .90$ and above. This difference in the strength of correlation for brainstem and cerebellar lesions may indicate some difference in the MS disease process for this region of the brain.

Previous studies of MS using MRI have found a lower percentage of lesions observed in the brainstem and

cerebellum than in cerebral white matter (Omerod, et al., 1987; Van de Vyver, et al., 1989). One investigation reported a much higher percentage of lesions in the brainstem and cerebellum of MS patients with a clinically definite diagnosis of MS, than patients with a clinically probable diagnosis, although cerebral white matter lesions were also proportionally different (Brainin, Reisner, Neuhold, Omasits, & Wicke, 1987).

An examination of the shape of the distribution of the brainstem and cerebellar lesions observed in this investigation indicated less positive skew than the distributions for the other regions. One explanation for this could be that lesions in the brainstem and cerebellum occur before lesions in other areas of the brain. However, lesions which appear on MRI have been found to disappear at a later point in time, consistent with a patients remitting course of symptoms. The evidence is not conclusive as to the whether brainstem and cerebellar lesions occur temporally prior in the course of the disease process. MS does have a highly variable course of symptoms and causes a highly variable manifestation of lesions.

The brainstem and cerebellum are referred to as infratentorial because they are structurally separated from the cerebrum by the tentorium, a membrane created by a fold in the meninges in the space between the cerebellum and the cerebrum. The anatomical separation between the

infratentorial and supratentorial structures, and possibly the consequent differences in exposure to blood supply and cerebral spinal fluid, might provide some different susceptibility to MS for the brainstem and cerebellum.

However, another factor in the differing manifestations of lesions in the brainstem and cerebellum and other regions of the brain may be that lesions in the brainstem are difficult to detect through MRI. MRI parameters typically used for MS patients are less sensitive to infratentorial lesions than supratentorial lesions (Van de Vyver, et al., 1989). The brainstem area is small and more subject to high signal intensity artifacts than other regions. Thus the detection of lesions in this investigation may have been less sensitive for lesions in the brainstem and cerebellum than for supratentorial structures.

Second Order Neuropsychological Factors

The results indicated relationships among measurement factors that have implications for the assessment of MS using MRI and neuropsychological measures. Confirmatory factor analyses and path analyses yielded support for clustering some of the neuropsychological measures with respect to their sensitivity to MRI evidence of MS and their correlations with each other. These measurement clusters were also ordered causally with respect to Performance IQ

and Verbal IQ in a further effort to identify the nature of the impact of MS, as appreciated through MRI, on neuropsychological performance (see Figure 1, Results section).

Measures Most Sensitive to MS Lesions

The measurement factors created through confirmatory factor analysis that proved most sensitive to MRI evidence of MS lesions were: Symbol Substitution tasks, Sensorimotor tasks, Visuospatial tasks and Verbal Fluency tasks (in that order). These measures, with the exception of visuospatial tasks, have also proved sensitive to MS deficits in other studies.

Symbol Substitution Tasks. The most sensitive factor, Symbol Substitution tasks, correlated with the all lesion factor (total lesions from all different regions of the brain) with an r of $-.83$. This factor consisted of the Symbol Digit Modalities (Written and Oral) and the Digit Symbol from the WAIS-R. Both Symbol Digit Modalities Written and Oral were nearly equally impaired relative to normals ($z = -7.13$ and $z = -6.54$ respectively). This finding suggests that functions other than motor speed were accounting for variance in this cluster of measures. These tests involve visual scanning, perceptual motor speed and are affected by general mental or motor slowing. These

tasks tend to be sensitive to organic dysfunction regardless of the location of damage (Lezak, 1983).

Sensorimotor Tasks. The next most sensitive factor, Sensorimotor tasks, correlated with the all lesions factor with an r of $-.72$. Two of the measures composing this cluster were timed (Purdue Pegboard and Trail Making A and B) and the remaining two measures were not timed (Finger Localization and Fingertip Number Writing). Performance on all of these tasks was significantly lower for MS patients than for normative samples. Sensorimotor performance difficulties are an expected finding for MS patients, and might be viewed as supporting evidence for the construct validity of the composite factor of measures most sensitive to MS. The MS literature consistently indicates that sensorimotor symptoms are the most commonly described consequences of MS.

Visuospatial Tasks. The Visuospatial factor correlated with the all lesion factor with an r of $-.60$. This factor consisted of the Hooper Visual Organization Test, and Benton's Line Orientation and Face Recognition tests. Few investigations have assessed the complex visuospatial abilities of MS patients with tasks that are independent of sensorimotor functions (Rao, 1986). The results from this investigation suggest that visuospatial abilities are related to MRI evidence of MS lesions, although the average performance of this sample of MS patients was not impaired

relative to published norms. These tasks all involve visual scanning in addition to specific abilities including visual-spatial analysis, visual detail analysis, and visual-perceptual integration. This finding suggests that changes in visuospatial functions due to MS deserves further attention.

Verbal Fluency Tasks. The Verbal Fluency tasks correlated with the all lesion factor with an r of $-.59$, and included the CFL and Animal Naming tests. Other investigators have reported lower performance on fluency tasks for MS patients as reviewed earlier. Fluency tasks have been described as involving attention, processing speed, retrieval and as placing particular demands on retrieval organization (Lezak, 1983).

Second Order Factor. These four factors that are sensitive to MRI evidence of MS lesions were very highly correlated with each other and showed parallel correlations with external variables, providing evidence that this reflects a second order factor. This factor was named "Most Sensitive Measures" in comparison to the other neuropsychological factors. The Most Sensitive Measures factor is composed of tasks that involve processing speed, sensorimotor ability, and perceptual organization. The Most Sensitive Measures factor correlated with the all lesion factor with an r of $-.74$.

Measures Less Sensitive to MS Lesions

The results indicated that four measurement factors were less sensitive to MRI evidence of MS lesions and could be placed after the Most Sensitive Measures factor and Performance IQ in the hierarchy of second order measurement factors sensitive to MRI evidence of MS lesions. These four Less Sensitive factors were: Memory, Conceptual Problem-Solving, Digit Span and the Paced Serial Auditory Addition Task (PASAT).

Memory. Memory performance was somewhat less sensitive to MRI evidence of MS lesions than other neuropsychological functions included in the Most Sensitive Measure factor. Previous investigations indicated variable problems with memory for MS patients compared to normal controls, with some convergence on findings that long-term retrieval is typically impaired while short-term memory is relatively preserved. The results of this investigation indicated no appreciable difference between performance on short versus long-term indices of memory performance for MS patients. The correlations between the short-term memory, and long-term memory factors and the all lesion factor were $r = -.45$, and $r = -.36$ respectively. The effects of MS lesions appreciated through MRI appeared to impact short-term memory just as badly as long-term memory. A composite memory factor created from seven different indices of short and

long-term recall and recognition memory correlated $r = -.37$ with the all lesion factor, indicating that memory functions were affected by MS lesions.

Conceptual Problem-Solving. Conceptual problem-solving, as measured by the Wisconsin Card Sort (WCS), was also reported in previous literature to be affected by MS, particularly through perseverative errors. This investigation found similar sensitivity to MRI evidence of MS lesions for WCS categories correct ($r = -.25$) and for WCS perseverative errors ($r = -.35$). Both scores (categories correct and perseverative errors) were combined to create a conceptual problem-solving factor which was correlated with the all lesion factor with an r of $-.34$.

The mean performance of this MS patient sample on the WCS perseverative errors (mean=24.37 errors, sd=19.87) was well below the mean for a normal sample (mean=12.6, sd=10.2; $z = 7.39$, $p < .01$), suggesting that these MS patients did display some impairment with this task. Other investigations have also reported MS patients to make more perseverative type errors on the WCS than normal control subjects.

Digit Span. Digit Span Forward and Backward trials correlated with the MRI all lesion factor with an $r = -.26$, and $r = -.33$ respectively. The average performance of the MS patients on this task was not impaired relative to normals. The Digit Span tasks involve efficiency of

attention and working memory. For the backwards trial, the task places the additional demand on the examinee to reverse the temporal ordering of the orally presented stimuli (Lezak, 1983). This task is included as one of the Verbal scale subtests on the WAIS-R but factor analytic studies of the WAIS and WAIS-R indicate that it loads only weakly on this factor. Instead, Digit Span has been found to create, along with the Arithmetic subtest, a separate (and relatively weak) factor labeled as memory or freedom from distractibility (Cohen, 1957; Parker, 1983; Russell, 1972). Digit Span performance (forward and backward trials combined) does appear to be related to MRI evidence of MS, with an $r = -.36$ with the all lesion factor.

PASAT. The Paced Auditory Serial Addition Task (PASAT) was included in the neuropsychological battery as an index of processing speed. The task appears to involve mental arithmetic, attention, working memory, resistance to interference (from the previous calculation) and information processing speed. The four scores derived from the PASAT were unidimensional. The correlation of the PASAT factor with the all lesion factor was $-.40$. The mean performances of the MS patients on the PASAT were also below normative performances. These results suggest that performance on the PASAT task is affected by MS.

Second Order Factor. The four factors that were less highly correlated with MRI evidence of MS lesions than the

Most Sensitive Measures were also highly correlated with each other and showed parallel correlations with other factors. This evidence of unidimensionality suggested that these factors reflected a second order factor, which was labeled "Less Sensitive Measures." The Less Sensitive Measures factor was correlated with the all lesion factor with an r of $-.54$, while the Most Sensitive Measures correlated with the all lesion factor with an r of $-.74$.

Causal Model

The causal model that fit the data described a hierarchical ordering of the data in which the Most Sensitive Measures factor was followed immediately by Performance IQ, which was in turn followed by the Less Sensitive Measures factor, which was in turn followed by Verbal IQ. This causal order suggest that the variance explained by the Most Sensitive Measures factor is most similar to the variance explained by the measures that constitute the Performance IQ scale ($r = .94$).

Performance IQ. The Performance IQ scale (WAIS-R short form) has been investigated in a number of factor analytic studies of the WAIS reviewed by Matarazzo (1972). Factor analysts have repeatedly derived three factor solutions for the WAIS subscales: (1) a verbal comprehension factor, (2) a perceptual organization factor, and (3) a memory/freedom

from distractibility factor. A second order factor (g) for general intelligence is also reported. The verbal comprehension factor includes all of the subtests in Wechsler's Verbal IQ scale except for low loadings for Digit Span and Arithmetic. The perceptual organization factor includes all of the WAIS Performance scale subtests, although Digit Symbol loads the lowest. However for clinical samples of brain damaged subjects the loading for Digit Symbol on the perceptual organization factor increases considerably (Cohen, 1957; Russell, 1972). The memory/freedom from distractibility factor includes Arithmetic and Digit Span. Factor analyses of the WAIS-R using the published standardization sample data have reported similar three factor solutions, although the stability of the third factor is weak (Parker, 1983; Silverstein, 1982).

The perceptual organization factor identified in factor analytic studies of the WAIS and WAIS-R has been variously identified as: the organization of nonverbal visually perceived material against a time limit; spatial-perceptual; and nonverbal organization. These descriptions overlap with the descriptions that might be used to convey the common content of the Most Sensitive Measures factor derived in this investigation. Also, the findings that the Digit Symbol subtest loads more strongly on this factor for brain damaged samples is consistent with the results from this

investigation of MS patients in which Symbol Substitution tasks are most sensitive to MRI evidence of brain lesions.

Verbal IQ. The four factors that compose the second order factor of measures Less Sensitive to MS lesions were immediately preceded in the causal model by the WAIS-R Verbal IQ scale. This ordering observes the common variance between these two factors ($r = .78$). The common content of these two second order factors involves: working memory, verbal comprehension, sustained attention, and problem-solving (among other functions).

Less Sensitive Measures and MS. The results indicate that the MRI evidence of the MS disease process is not always consistent with neuropsychological evidence of the MS disease process. The MRI evidence of lesions was not as sensitive to performance of the MS patients on the Wisconsin Card Sort (perseverative errors) or to performance on the PASAT as to other neuropsychological measures. Yet the performance of the MS patients on these two measures was distinctly lower than normal healthy individuals. This discrepancy between the MRI and neuropsychological evidence of MS indicates that MRI may be a less comprehensive indicator of the MS disease process than neuropsychological measures. The discrepancy between MRI evidence and neuropsychological measures could also be a consequence of sampling error and the quality of the normative data for the various measures.

Summary of the Factor Clusters. The clusters of measures derived from the data assess or involve some common functions which help explain the content of the factors. The measures that compose the Most Sensitive Measures factor (Symbol Substitution, Sensorimotor, Visuospatial, and Fluency) involve processing speed, visual scanning, sensorimotor ability and perceptual organization, among other functions. The visuospatial tasks do not involve speed, and the fluency tasks do not involve sensorimotor or perceptual abilities. Otherwise, these tasks do involve similar functions which explains the common variance contributing to their clustering together as a factor. The Most Sensitive Measures factor was also highly correlated with the WAIS-R Performance IQ scale which is composed of measures that involve similar neuropsychological functions. The Most Sensitive Measures factor and the Performance IQ scale are both somewhat more sensitive to MRI evidence of MS lesions than the Less Sensitive Measures factor and the WAIS-R Verbal IQ scale.

The measures that compose the Less Sensitive Measures factor (Memory, Conceptual Problem-Solving, Digit Span and the PASAT) all involve working memory. Working memory involves holding stimuli in memory ready for retrieval access. These tasks rely on the ability to hold and manipulate information acquired auditorially. They require concentration and mental tracking. These common functions

provide an explanation for the common variance that led to the clustering of these measures into a factor. These measures also involve more heterogeneous abilities including abstract reasoning and speed and accuracy of mental arithmetic. This cluster of measures, along with the WAIS-R Verbal IQ scale was somewhat less sensitive to MS lesions as detected through MRI than the Most Sensitive Measures cluster and Performance IQ.

Performance of MS Patients Compared to Normals on
Neuropsychological Measures

The performance of the MS patients assessed in this study was not impaired relative to normals on several of the neuropsychological measures that were well correlated with MS lesions as detected through MRI (see Table 1). The MS patient sample assessed in this study may have experienced above average intellectual abilities before the onset of their disease. Their WAIS-R Full Scale IQ scores were above average (mean= 102.4) after the onset of MS, as were their Verbal IQ scores (mean= 103.4). Their WAIS-R Performance IQ score was equivalent to normal (mean= 100.6) even though scores on these tasks, that rely heavily on sensorimotor and perceptual organizational abilities, would be expected to be affected by MS. Performance IQ and the All Lesion factor were correlated $r = -.64$.

The standardization samples for the various neuropsychological measures may not all provide appropriate performance norms to compare to this MS patient sample. The premorbid abilities of this sample were possibly superior to some of the normative samples used to standardize the various neuropsychological measures. This may help explain some of the discrepancies observed between the expected performance of MS patients relative to normals on neuropsychological measures. The lack of impairment shown by the MS sample on measures of visuospatial abilities, memory functions and Performance IQ may to some degree reflect the lack of appropriate normative comparison groups for these measures. The sampling error involved in this group of MS patients also may contribute to the discrepancy from expected findings. The relationship between lesions detected through MRI and neuropsychological measures may be a better indicator of the impact of MS on neuropsychological functions than comparing performance on these measures to various normative groups.

Conclusions

MRI. The MRI coding procedure involved a comprehensive effort to record the size and location of all lesions observed on multiple axial levels, as well as three sagittal slices around the midline for corpus callosum lesions. This

involved a time consuming procedure for multiple raters. This coding procedure was a successful means of recording evidence of CNS deterioration due to MS, and using multiple raters was a necessary method of overcoming the limited reliability that is a consequence of quantifying MRI data. MRI does have limitations in the differentiation of evidence of MS from other causes of high signal intensity, particularly if the lesion is small or of low intensity. MRI also sometimes has limits in the identification of the anatomical region in which lesions are found. The limited reliability of the MRI data is partly a consequence of the limited specificity of the MRI technology in identifying MS deterioration.

Location of MS Lesions and Neuropsychological Performance. Evidence for the location of MS lesions within the brain indicated no particular focus for location. All regions of the brain were affected except outer cortex. The typical periventricular pattern of lesion distribution in predominately white matter tissue was observed, and the distributions of lesions within the brain was highly correlated among regions. This diffuse infiltration of MS deterioration observable through MRI made specific relationships regarding lesion location and cognitive performance undetectable.

The diffuse impact of MS on the brain may be characteristic of the disease. Previous investigations have

reported little or no success in identifying specific relationships between lesion location and cognitive deficits (Peyser & Poser, 1986; Rao, 1986). The results of this investigation and previous studies suggest that the traditional neuropsychological paradigm which attempts to associate specific cognitive deficits with the location of specific lesions may not be appropriate for MS. MS may cause too diffuse deterioration for specific relationships to be observed, or the evidence for location of CNS damage derived through MRI may provide evidence of MS damage too indirectly to appreciate the actual effects on the neural network. Neuropsychological paradigms for evaluating more diffuse rather than focal brain damage are likely more appropriate for MS.

Neuropsychological Functions and MRI Evidence of MS.

The results of this investigation indicate that symbol substitution, sensorimotor, visuospatial, and verbal fluency tasks are most sensitive to MS lesions as detected through MRI. These tasks involve processing speed, sensorimotor abilities, and visual-perceptual organization. These measures been found sensitive to MS in numerous other investigations, although the impact of MS on visuospatial tasks that are independent of motor functions has received little attention in the research literature on MS.

The results of this investigation suggest that functions involving working memory, abstract reasoning and

paced serial addition are less well sensitive to MS lesions appreciated by MRI, although MRI evidence was correlated with performance on these functions. Other research findings have found MS to affect memory, particularly long-term retrieval, abstract reasoning, and performance on the PASAT. This investigation did find these functions affected for some patients, particularly performance on the Wisconsin Card Sort and the PASAT. Most other investigations of cognitive functions affected by MS have been designed to compare the performance of MS patients to normals on cognitive tasks.

Causal Order of MRI Evidence of Neuropsychological Performance. The results of path analyses suggests a causal ordering of the cognitive functions that show MRI evidence of MS. The results indicate that the sensorimotor, speeded and perceptual organizational tasks show more MRI evidence of MS deterioration. MRI evidence of MS deterioration had a slightly weaker relationship to tasks involving working memory, abstract reasoning, verbal comprehension, and a paced auditory addition task.

Generalization. All of the results from this investigation were derived from a sample of 41 MS patients with a broad range of disease duration. While this is a typical sample size for a study of a MS, this is a small sample size on which to base statistical generalizations. The validity of the results from this study, while

convergent in some cases with previous research, will await future research for information regarding the sensitivity of MRI for MS deterioration.

Implications for MS

The results of this investigation have a number of implications for our knowledge of the MS disease process. The MRI data displayed no predictable focus of evidence of MS lesions with respect to the brain regions affected. Lesions did show a pattern of occurring adjacent to the ventricles and in predominantly white matter tissue, but affected all regions of the brain except the outer cortex. The neuropsychological impact of the CNS deterioration due to MS is not likely due to the focal location of specific lesions but more likely a consequence of more dispersed disturbance in neural pathways. While information processing speed is affected by MS, processing speed deterioration alone does not explain deficits in cognitive functions.

The neuropsychological functions most correlated with MRI evidence of the MS disease are tasks that involve sensorimotor abilities, perceptual organization abilities and processing speed. Neuropsychological functions that are somewhat less correlated with MRI evidence of the MS disease process include verbal skills, working memory and abstract

reasoning, and paced auditory addition. Individual variability in the effects of MS on the brain and on cognitive performance is considerable.

Future Research

The results of this investigation suggest that future use of MRI for the study of MS should ideally involve a well defined coding procedure and multiple raters. MRI data inevitably involves judgement and therefore rater error. The results of this investigation, along with previous investigations, suggest that efforts to discover specific relationship between lesions observed through MRI and cognitive deficits are not likely to be successful.

Future research into the nature and order of cognitive impairment that is a consequence of MS could benefit by measuring the performance of a sample of MS patients and a sample of normals using many of the measures employed in this investigation. Measures should be chosen with respect to guidelines available for neuropsychological investigations of MS (Peyser, Rao, LaRocca & Kaplan, 1990), which do overlap considerably with measures employed in this investigation.

If the research community does adhere to a standard battery of measures and procedures for neuropsychological investigations of MS, a large body of data may accumulate

and allow for the assessment of convergent findings.

Because studies of MS are typically limited to smaller samples, the generalization of research results will benefit from a meta-analysis of research findings. A meta-analysis of the cognitive performance literature on MS will be considerably enhanced if standard batteries are employed for future studies.

APPENDIX

Table 5: Confirmatory Factor Matrix

		2	4	5	6	8	9	7	10	11	12	13	14	17	22	27	28	29	30
Age	2	100	-28	62	46	-14	-17	-18	-36	-35	-38	-18	-17	-50	-20	-46	-37	-35	-33
Educ	4	-28	100	-3	-6	48	17	38	8	23	24	21	9	41	27	31	40	40	38
Durat	5	62	-3	100	38	1	-4	-3	-35	-33	-21	5	-1	-31	-8	-16	-6	-12	-1
Type	6	46	-6	38	100	-8	-19	-16	-60	-29	-22	-17	-27	-28	-13	-33	-29	-27	-18
VIQ	8	-14	48	1	-8	100	51	86	25	27	42	39	19	54	52	46	46	54	56
PIQ	9	-17	17	-4	-19	51	100	87	52	62	71	60	34	22	58	44	45	53	45
FIQ	7	-18	38	-3	-16	86	87	100	43	52	64	57	28	45	65	52	52	61	58
Peg	10	-36	8	-35	-60	25	52	43	53	58	53	52	57	16	26	29	36	36	34
TrlsA	11	-35	23	-33	-29	27	62	52	58	64	81	61	38	34	55	52	59	51	42
TrlsB	12	-38	24	-21	-22	42	71	64	53	81	63	62	40	35	58	49	52	50	46
FinLoc	13	-18	21	5	-17	39	60	57	52	61	62	65	63	22	49	39	50	51	51
FinWr	14	-17	9	-1	-27	19	34	28	57	38	40	63	41	10	23	-4	11	11	17
Logic2	17	-50	41	-31	-28	54	22	45	16	34	35	22	10	45	66	54	53	52	58
WDelayed	22	-20	27	-8	-13	52	58	65	26	55	58	49	23	66	40	56	55	53	52
STRecall	27	-46	31	-16	-33	46	44	52	29	52	49	39	-4	54	56	75	87	81	79
STCrecal	28	-37	40	-6	-29	46	45	52	36	59	52	50	11	53	55	87	83	85	89
LTRecall	29	-35	40	-12	-27	54	53	61	36	51	50	51	11	52	53	81	85	84	88
LTCrecal	30	-33	38	-1	-18	56	45	58	34	42	46	51	17	58	52	79	89	88	87
Discrim	31	-23	22	-14	-26	46	27	41	27	19	31	19	13	45	26	49	54	66	66
WCS-Cat	32	-33	16	-26	-22	39	51	52	25	37	44	42	14	21	27	39	33	32	25
Persev	33	-37	9	-13	-15	35	52	50	20	47	59	48	19	21	35	53	47	41	36
LineOr	34	-7	19	-7	-13	52	68	69	33	59	52	53	23	39	53	30	42	45	40
FaceRec	35	-28	5	-15	-18	30	51	46	45	45	52	56	50	1	14	12	19	22	23
Hooper	36	-23	13	-6	-27	27	53	46	28	57	46	43	19	26	46	58	63	54	53
DigSym	41	-12	10	-23	-34	38	77	65	69	63	65	48	36	9	34	36	34	47	37
SDM-W	42	-38	25	-35	-50	38	73	63	74	78	76	52	41	24	41	48	50	50	43
SDM-O	43	-34	21	-37	-35	44	74	68	56	80	76	50	24	30	48	53	54	53	46
PASAT-24	37	-30	34	-28	-17	59	57	67	35	45	60	36	19	35	44	37	30	36	28
PASAT-20	38	-37	27	-17	-18	62	59	70	29	44	58	49	24	44	57	44	39	39	37
PASAT-16	39	-34	24	-22	-18	52	53	62	32	46	54	42	26	43	51	34	29	31	29
PASAT-12	40	-35	9	-32	-19	35	34	41	38	39	45	32	33	34	29	14	8	10	11
DigSpanF	15	-4	4	-17	-10	35	38	44	38	29	35	37	7	6	26	25	29	29	36
DigSpanB	16	-17	-3	-24	-10	38	49	53	34	38	40	38	-2	23	37	35	24	40	32
CFL	44	-1	-2	-5	-9	42	46	51	37	30	35	33	26	18	38	23	23	18	27
Animal	45	-20	8	-11	-38	33	45	43	43	42	45	32	20	18	37	33	39	32	35
Stem+Cer	46	-5	-5	11	22	-17	-44	-34	-45	-45	-42	-26	-34	-1	-21	-15	-16	-29	-23
LTemp	54	13	-5	20	24	-22	-53	-43	-49	-75	-70	-33	-24	-24	-44	-43	-39	-34	-25
RTemp	53	12	4	25	23	-18	-46	-36	-57	-70	-65	-29	-28	-18	-35	-34	-27	-24	-21
RFront	51	0	7	16	20	-19	-47	-38	-50	-61	-59	-20	-22	-9	-28	-26	-29	-25	-19
LFront	52	-1	2	14	16	-19	-46	-37	-44	-64	-57	-16	-20	-10	-29	-27	-26	-21	-14
RPariet	55	11	-5	25	18	-23	-36	-33	-63	-46	-47	-23	-26	-9	-16	-32	-42	-37	-48
LPariet	56	12	5	29	27	-21	-51	-40	-66	-66	-59	-39	-38	-8	-22	-34	-40	-43	-40
BaselG	47	19	1	16	12	-15	-51	-37	-37	-57	-62	-23	-24	-9	-39	-40	-35	-26	-20
CorCal	48	-4	4	12	0	-10	-38	-27	-47	-54	-47	-23	-20	1	-12	-17	-18	-11	-14
CCAtrop	49	18	-17	16	10	-25	-52	-44	-29	-58	-62	-38	-16	-6	-22	-38	-32	-37	-28
IntCap	50	-11	-2	4	8	-12	-49	-34	-38	-52	-45	-19	-16	7	-15	-19	-22	-14	-13

		2	4	5	6	8	9	7	10	11	12	13	14	17	22	27	28	29	30
age	501	100	-28	62	46	-14	-17	-18	-36	-35	-38	-18	-17	-50	-20	-46	-37	-35	-33
educ	502	-28	100	-3	-6	48	17	38	8	23	24	21	9	41	27	31	40	40	38
durat	503	62	-3	100	38	1	-4	-3	-35	-33	-21	5	-1	-31	-8	-16	-6	-12	-1
type	504	46	-6	38	100	-8	-19	-16	-60	-29	-22	-17	-27	-28	-13	-33	-29	-27	-18
VIQ	505	-14	48	1	-8	100	51	86	25	27	42	39	19	54	52	46	46	54	56
PIQ	506	-17	17	-4	-19	51	100	87	52	62	71	60	34	22	58	44	45	53	45
FIQ	507	-18	38	-3	-16	86	87	100	43	52	64	57	28	45	65	52	52	61	58
Motor	508	-38	22	-23	-41	40	74	65	73	80	80	80	64	31	56	44	55	53	51
Memry	509	-44	43	-16	-32	63	53	67	37	56	58	51	15	67	63	87	91	92	93
WCS	510	-39	14	-22	-21	42	59	58	25	48	58	51	19	24	36	52	45	41	35
Visuo	511	-30	19	-15	-29	56	88	82	54	82	76	77	47	33	57	51	63	62	59
Symsub	512	-30	20	-34	-42	43	80	70	71	79	78	53	36	23	44	49	49	54	45
PASAT	513	-38	26	-28	-21	58	57	67	38	49	60	45	29	44	50	36	30	32	30
DigSpem	514	-13	0	-26	-13	45	54	60	45	41	47	46	3	18	39	38	33	43	42
Fluency	515	-17	5	-12	-38	60	72	75	64	58	64	51	36	29	59	45	49	39	48
StemCer	516	-5	-5	11	22	-17	-44	-34	-45	-45	-42	-26	-34	-1	-21	-15	-16	-29	-23
Ltemp	517	13	-5	20	24	-22	-53	-43	-49	-75	-70	-33	-24	-24	-44	-43	-39	-34	-25
Rtemp	518	12	4	25	23	-18	-46	-36	-57	-70	-65	-29	-28	-18	-35	-34	-27	-24	-21
Front	519	0	4	15	18	-20	-47	-38	-48	-64	-59	-18	-22	-10	-29	-27	-28	-24	-17
Pariet	520	13	0	30	25	-25	-48	-40	-71	-62	-58	-34	-35	-10	-21	-36	-45	-44	-48
SubCort	521	8	-5	16	10	-21	-65	-49	-52	-76	-74	-35	-26	-3	-30	-39	-37	-31	-26

	31	32	33	34	35	36	41	42	43	37	38	39	40	15	16	44	45	46
2	-23	-33	-37	-7	-28	-23	-12	-38	-34	-30	-37	-34	-35	-4	-17	-1	-20	-5
4	22	16	9	19	5	13	10	25	21	34	27	24	9	4	-3	-2	8	-5
5	-14	-26	-13	-7	-15	-6	-23	-35	-37	-28	-17	-22	-32	-17	-24	-5	-11	11
6	-26	-22	-15	-13	-18	-27	-34	-50	-35	-17	-18	-18	-19	-10	-10	-9	-38	22
8	46	39	35	52	30	27	38	38	44	59	62	52	35	35	38	42	33	-17
9	27	51	52	68	51	53	77	73	74	57	59	53	34	38	49	46	45	-44
7	41	52	50	69	46	46	65	63	68	67	70	62	41	44	53	51	43	-34
10	27	25	20	33	45	28	69	74	56	35	29	32	38	38	34	37	43	-45
11	19	37	47	59	45	57	63	78	80	45	44	46	39	29	38	30	42	-45
12	31	44	59	52	52	46	65	76	76	60	58	54	45	35	40	35	45	-42
13	19	42	48	53	56	43	48	52	50	36	49	42	32	37	38	33	32	-26
14	13	14	19	23	50	19	36	41	24	19	24	26	33	7	-2	26	20	-34
17	45	21	21	39	1	26	9	24	30	35	44	43	34	6	23	18	18	-1
22	26	27	35	53	14	46	34	41	48	44	57	51	29	26	37	38	37	-21
27	49	39	53	30	12	58	36	48	53	37	44	34	14	25	35	23	33	-15
28	54	33	47	42	19	63	34	50	54	30	39	29	8	29	24	23	39	-16
29	66	32	41	45	22	54	47	50	53	36	39	31	10	29	40	18	32	-29
30	66	25	36	40	23	53	37	43	46	28	37	29	11	36	32	27	35	-23
31	39	9	28	25	7	14	32	33	31	25	21	11	3	25	26	18	18	-8
32	9	79	77	44	51	34	32	41	53	43	59	51	28	30	38	42	29	-12
33	28	77	79	37	51	46	33	44	53	44	60	50	28	21	34	41	27	-10
34	25	44	37	55	43	49	50	56	67	39	50	43	25	40	49	44	46	-18
35	7	51	51	43	33	36	49	52	56	34	49	44	37	43	39	39	33	-31
36	14	34	46	49	36	43	40	50	56	20	35	21	-6	3	22	40	45	-31
41	32	32	33	50	49	40	79	89	80	63	48	44	43	49	52	40	43	-62
42	33	41	44	56	52	50	89	98	91	65	56	50	48	42	42	39	56	-56
43	31	53	53	67	56	56	80	91	83	65	64	59	49	46	52	45	61	-47
37	25	43	44	39	34	20	63	65	65	76	85	78	72	30	49	33	26	-19
38	21	59	60	50	49	35	48	56	64	85	84	89	70	26	44	39	38	-6
39	11	51	50	43	44	21	44	50	59	78	89	92	84	21	43	40	36	-14
40	3	28	28	25	37	-6	43	48	49	72	70	84	68	28	33	31	23	-15
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45	18	29	27	46	33	45	43	56	61	26	38	36	23	20	13	38	42	-37
46	-8	-12	-10	-18	-31	-31	-62	-56	-47	-19	-6	-14	-15	-13	-12	-18	-37	100
54	-21	-28	-39	-41	-21	-46	-64	-72	-69	-44	-34	-36	-31	-12	-33	-36	-24	50
53	-15	-19	-30	-31	-22	-35	-65	-70	-64	-38	-25	-33	-37	-18	-29	-38	-24	60

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52	-12	-17	-26	-40	-25	-29	-64	-68	-63	-46	-30	-36	-41	-22	-30	-37	-15	50
55	-40	-5	-9	-23	-24	-31	-62	-61	-51	-23	-7	-10	-18	-44	-26	-39	-26	52
56	-29	-24	-31	-42	-47	-43	-71	-74	-70	-28	-21	-29	-33	-35	-30	-43	-37	65
47	-10	-39	-53	-23	-21	-39	-49	-59	-57	-49	-42	-46	-34	1	-23	-31	-29	51
48	-10	-17	-26	-28	-27	-25	-59	-55	-49	-32	-17	-25	-32	-30	-30	-48	-4	38
49	-24	-38	-57	-42	-37	-50	-48	-57	-63	-34	-29	-33	-11	-9	-38	-32	-33	37
50	-2	-26	-29	-26	-28	-29	-61	-59	-53	-33	-20	-25	-25	-21	-18	-32	-16	66
501	-23	-33	-37	-7	-28	-23	-12	-38	-34	-30	-37	-34	-35	-4	-17	-1	-20	-5
502	22	16	9	19	5	13	10	25	21	34	27	24	9	4	-3	-2	8	-5
503	-14	-26	-13	-7	-15	-6	-23	-35	-37	-28	-17	-22	-32	-17	-24	-5	-11	11
504	-26	-22	-15	-13	-18	-27	-34	-50	-35	-17	-18	-18	-19	-10	-10	-9	-38	22
505	46	39	35	52	30	27	38	38	44	59	62	52	35	35	38	42	33	-17
506	27	51	52	68	51	53	77	73	74	57	59	53	34	38	49	46	45	-44
507	41	52	50	69	46	46	65	63	68	67	70	62	41	44	53	51	43	-34
508	29	43	51	58	66	51	75	85	76	52	54	53	50	39	39	43	48	-51
509	62	34	47	49	18	56	41	52	57	42	50	41	20	32	39	30	38	-20
510	21	88	88	46	57	45	37	48	60	49	67	57	32	29	41	47	32	-13
511	24	66	68	75	57	65	71	80	91	47	68	55	29	44	56	63	63	-41
512	34	45	47	62	56	52	89	99	91	69	60	55	50	49	52	44	57	-59
513	17	51	51	44	46	20	56	62	66	87	92	96	82	30	47	40	35	-15
514	31	43	34	55	51	16	62	52	60	49	43	40	37	81	81	51	21	-15
515	29	57	54	72	57	68	65	76	85	47	61	60	43	53	39	63	63	-44
516	-8	-12	-10	-18	-31	-31	-62	-56	-47	-19	-6	-14	-15	-13	-12	-18	-37	100
517	-21	-28	-39	-41	-21	-46	-64	-72	-69	-44	-34	-36	-31	-12	-33	-36	-24	50
518	-15	-19	-30	-31	-22	-35	-65	-70	-64	-38	-25	-33	-37	-18	-29	-38	-24	60
519	-16	-18	-28	-41	-28	-31	-68	-71	-65	-46	-30	-34	-41	-28	-32	-40	-17	51
520	-38	-16	-22	-36	-39	-41	-74	-75	-67	-28	-15	-22	-28	-44	-31	-45	-35	65
521	-16	-41	-57	-41	-39	-49	-75	-79	-76	-51	-37	-44	-35	-20	-38	-49	-28	66

	54	53	51	52	55	56	47	48	49	50	501	502	503	504	505	506	507	508
2	13	12	0	-1	11	12	19	-4	18	-11	100	-28	62	46	-14	-17	-18	-38
4	-5	4	7	2	-5	5	1	4	-17	-2	-28	100	-3	-6	48	17	38	22
5	20	25	16	14	25	29	16	12	16	4	62	-3	100	38	1	-4	-3	-23
6	24	23	20	16	18	27	12	0	10	8	46	-6	38	100	-8	-19	-16	-41
8	-22	-18	-19	-19	-23	-21	-15	-10	-25	-12	-14	48	1	-8	100	51	86	40
9	-53	-46	-47	-46	-36	-51	-51	-38	-52	-49	-17	17	-4	-19	51	100	87	74
7	-43	-36	-38	-37	-33	-40	-37	-27	-44	-34	-18	38	-3	-16	86	87	100	65
10	-49	-57	-50	-44	-63	-66	-37	-47	-29	-38	-36	8	-35	-60	25	52	43	73
11	-75	-70	-61	-64	-46	-66	-57	-54	-58	-52	-35	23	-33	-29	27	62	52	80
12	-70	-65	-59	-57	-47	-59	-62	-47	-62	-45	-38	24	-21	-22	42	71	64	80
13	-33	-29	-20	-16	-23	-39	-23	-23	-38	-19	-18	21	5	-17	39	60	57	80
14	-24	-28	-22	-20	-26	-38	-24	-20	-16	-16	-17	9	-1	-27	19	34	28	64
17	-24	-18	-9	-10	-9	-8	-9	1	-6	7	-50	41	-31	-28	54	22	45	31
22	-44	-35	-28	-29	-16	-22	-39	-12	-22	-15	-20	27	-8	-13	52	58	65	56
27	-43	-34	-26	-27	-32	-34	-40	-17	-38	-19	-46	31	-16	-33	46	44	52	44
28	-39	-27	-29	-26	-42	-40	-35	-18	-32	-22	-37	40	-6	-29	46	45	52	55
29	-34	-24	-25	-21	-37	-43	-26	-11	-37	-14	-35	40	-12	-27	54	53	61	53
30	-25	-21	-19	-14	-48	-40	-20	-14	-28	-13	-33	38	-1	-18	56	45	58	51
31	-21	-15	-19	-12	-40	-29	-10	-10	-24	-2	-23	22	-14	-26	46	27	41	29
32	-28	-19	-18	-17	-5	-24	-39	-17	-38	-26	-33	16	-26	-22	39	51	52	43
33	-39	-30	-28	-26	-9	-31	-53	-26	-57	-29	-37	9	-13	-15	35	52	50	51
34	-41	-31	-40	-40	-23	-42	-23	-28	-42	-26	-7	19	-7	-13	52	68	69	58
35	-21	-22	-30	-25	-24	-47	-21	-27	-37	-28	-28	5	-15	-18	30	51	46	66
36	-46	-35	-31	-29	-31	-43	-39	-25	-50	-29	-23	13	-6	-27	27	53	46	51
41	-64	-65	-69	-64	-62	-71	-49	-59	-48	-61	-12	10	-23	-34	38	77	65	75
42	-72	-70	-71	-68	-61	-74	-59	-55	-57	-59	-38	25	-35	-50	38	73	63	85
43	-69	-64	-64	-63	-51	-70	-57	-49	-63	-53	-34	21	-37	-35	44	74	68	76
37	-44	-38	-44	-46	-23	-28	-49	-32	-34	-33	-30	34	-28	-17	59	57	67	52
38	-34	-25	-29	-30	-7	-21	-42	-17	-29	-20	-37	27	-17	-18	62	59	70	54
39	-36	-33	-31	-36	-10	-29	-46	-25	-33	-25	-34	24	-22	-18	52	53	62	53
40	-31	-37	-39	-41	-18	-33	-34	-32	-11	-25	-35	9	-32	-19	35	34	41	50
15	-12	-18	-33	-22	-44	-35	1	-30	-9	-21	-4	4	-17	-10	35	38	44	39

16	-33	-29	-33	-30	-26	-30	-23	-30	-38	-18	-17	-3	-24	-10	38	49	53	39
44	-36	-38	-41	-37	-39	-43	-31	-48	-32	-32	-1	-2	-5	-9	42	46	51	43
45	-24	-24	-19	-15	-26	-37	-29	-4	-33	-16	-20	8	-11	-38	33	45	43	48
46	50	60	50	50	52	65	51	38	37	66	-5	-5	11	22	-17	-44	-34	-51
54	100	94	86	89	55	74	72	79	59	71	13	-5	20	24	-22	-53	-43	-67
53	94	100	83	86	64	79	67	84	52	74	12	4	25	23	-18	-46	-36	-66
51	86	83	96	96	68	80	60	82	38	70	0	7	16	20	-19	-47	-38	-56
52	89	86	96	96	57	75	70	80	45	76	-1	2	14	16	-19	-46	-37	-53
55	55	64	68	57	83	82	38	67	34	45	11	-5	25	18	-23	-36	-33	-54
56	74	79	80	75	82	83	51	73	56	59	12	5	29	27	-21	-51	-40	-71
47	72	67	60	70	38	51	64	44	57	67	19	1	16	12	-15	-51	-37	-54
48	79	84	82	80	67	73	44	50	39	72	-4	4	12	0	-10	-38	-27	-51
49	59	52	38	45	34	56	57	39	32	36	18	-17	16	10	-25	-52	-44	-54
50	71	74	70	76	45	59	67	72	36	70	-11	-2	4	8	-12	-49	-34	-45
501	13	12	0	-1	11	12	19	-4	18	-11	100	-28	62	46	-14	-17	-18	-38
502	-5	4	7	2	-5	5	1	4	-17	-2	-28	100	-3	-6	48	17	38	22
503	20	25	16	14	25	29	16	12	16	4	62	-3	100	38	1	-4	-3	-23
504	24	23	20	16	18	27	12	0	10	8	46	-6	38	100	-8	-19	-16	-41
505	-22	-18	-19	-19	-23	-21	-15	-10	-25	-12	-14	48	1	-8	100	51	86	40
506	-53	-46	-47	-46	-36	-51	-51	-38	-52	-49	-17	17	-4	-19	51	100	87	74
507	-43	-36	-38	-37	-33	-40	-37	-27	-44	-34	-18	38	-3	-16	86	87	100	65
508	-67	-66	-56	-53	-54	-71	-54	-51	-54	-45	-38	22	-23	-41	40	74	65	100
509	-42	-31	-28	-25	-40	-39	-32	-15	-34	-14	-44	43	-16	-32	63	53	67	57
510	-38	-28	-26	-25	-8	-31	-52	-24	-54	-31	-39	14	-22	-21	42	59	58	53
511	-54	-45	-51	-48	-40	-67	-42	-41	-66	-42	-30	19	-15	-29	56	88	82	89
512	-74	-71	-73	-70	-62	-77	-59	-59	-60	-62	-30	20	-34	-42	43	80	70	85
513	-41	-37	-40	-43	-16	-31	-48	-30	-30	-29	-38	26	-28	-21	58	57	67	59
514	-28	-29	-41	-32	-44	-40	-14	-37	-29	-24	-13	0	-26	-13	45	54	60	48
515	-48	-49	-47	-42	-52	-63	-48	-41	-52	-38	-17	5	-12	-38	60	72	75	73
516	50	60	50	50	52	65	51	38	37	66	-5	-5	11	22	-17	-44	-34	-51
517	100	94	86	89	55	74	72	79	59	71	13	-5	20	24	-22	-53	-43	-67
518	94	100	83	86	64	79	67	84	52	74	12	4	25	23	-18	-46	-36	-66
519	89	87	98	98	64	79	67	83	43	74	0	4	15	18	-20	-47	-38	-56
520	71	79	82	73	91	91	49	78	50	58	13	0	30	25	-25	-48	-40	-69
521	96	95	86	93	63	82	80	70	56	84	8	-5	16	10	-21	-65	-49	-70

509 510 511 512 513 514 515 516 517 518 519 520 521

2	-44	-39	-30	-30	-38	-13	-17	-5	13	12	0	13	8
4	43	14	19	20	26	0	5	-5	-5	4	4	0	-5
5	-16	-22	-15	-34	-28	-26	-12	11	20	25	15	30	16
6	-32	-21	-29	-42	-21	-13	-38	22	24	23	18	25	10
8	63	42	56	43	58	45	60	-17	-22	-18	-20	-25	-21
9	53	59	88	80	57	54	72	-44	-53	-46	-47	-48	-65
7	67	58	82	70	67	60	75	-34	-43	-36	-38	-40	-49
10	37	25	54	71	38	45	64	-45	-49	-57	-48	-71	-52
11	56	48	82	79	49	41	58	-45	-75	-70	-64	-62	-76
12	58	58	76	78	60	47	64	-42	-70	-65	-59	-58	-74
13	51	51	77	53	45	46	51	-26	-33	-29	-18	-34	-35
14	15	19	47	36	29	3	36	-34	-24	-28	-22	-35	-26
17	67	24	33	23	44	18	29	-1	-24	-18	-10	-10	-3
22	63	36	57	44	50	39	59	-21	-44	-35	-29	-21	-30
27	87	52	51	49	36	38	45	-15	-43	-34	-27	-36	-39
28	91	45	63	49	30	33	49	-16	-39	-27	-28	-45	-37
29	92	41	62	54	32	43	39	-29	-34	-24	-24	-44	-31
30	93	35	59	45	30	42	48	-23	-25	-21	-17	-48	-26
31	62	21	24	34	17	31	29	-8	-21	-15	-16	-38	-16
32	34	88	66	45	51	43	57	-12	-28	-19	-18	-16	-41
33	47	88	68	47	51	34	54	-10	-39	-30	-28	-22	-57
34	49	46	75	62	44	55	72	-18	-41	-31	-41	-36	-41
35	18	57	57	56	46	51	57	-31	-21	-22	-28	-39	-39
36	56	45	65	52	20	16	68	-31	-46	-35	-31	-41	-49
41	41	37	71	89	56	62	65	-62	-64	-65	-68	-74	-75
42	52	48	80	99	62	52	76	-56	-72	-70	-71	-75	-79
43	57	60	91	91	66	60	85	-47	-69	-64	-65	-67	-76

37	42	49	47	69	87	49	47	-19	-44	-38	-46	-28	-51
38	50	67	68	60	92	43	61	-6	-34	-25	-30	-15	-37
39	41	57	55	55	96	40	60	-14	-36	-33	-34	-22	-44
40	20	32	29	50	82	37	43	-15	-31	-37	-41	-28	-35
15	32	29	44	49	30	81	53	-13	-12	-18	-28	-44	-20
16	39	41	56	52	47	81	39	-12	-33	-29	-32	-31	-38
44	30	47	63	44	40	51	63	-18	-36	-38	-40	-45	-49
45	38	32	63	57	35	21	63	-37	-24	-24	-17	-35	-28
46	-20	-13	-41	-59	-15	-15	-44	100	50	60	51	65	66
54	-42	-38	-54	-74	-41	-28	-48	50	100	94	89	71	96
53	-31	-28	-45	-71	-37	-29	-49	60	94	100	87	79	95
51	-28	-26	-51	-73	-40	-41	-47	50	86	83	98	82	86
52	-25	-25	-48	-70	-43	-32	-42	50	89	86	98	73	93
55	-40	-8	-40	-62	-16	-44	-52	52	55	64	64	91	63
56	-39	-31	-67	-77	-31	-40	-63	65	74	79	79	91	82
47	-32	-52	-42	-59	-48	-14	-48	51	72	67	67	49	80
48	-15	-24	-41	-59	-30	-37	-41	38	79	84	83	78	70
49	-34	-54	-66	-60	-30	-29	-52	37	59	52	43	50	56
50	-14	-31	-42	-62	-29	-24	-38	66	71	74	74	58	84
501	-44	-39	-30	-30	-38	-13	-17	-5	13	12	0	13	8
502	43	14	19	20	26	0	5	-5	-5	4	4	0	-5
503	-16	-22	-15	-34	-28	-26	-12	11	20	25	15	30	16
504	-32	-21	-29	-42	-21	-13	-38	22	24	23	18	25	10
505	63	42	56	43	58	45	60	-17	-22	-18	-20	-25	-21
506	53	59	88	80	57	54	72	-44	-53	-46	-47	-48	-65
507	67	58	82	70	67	60	75	-34	-43	-36	-38	-40	-49
508	57	53	89	85	59	48	73	-51	-67	-66	-56	-69	-70
509	100	46	63	54	43	44	54	-20	-42	-31	-27	-44	-33
510	46	100	75	52	58	43	63	-13	-38	-28	-26	-22	-55
511	63	75	100	87	56	62	100	-41	-54	-45	-51	-59	-66
512	54	52	87	100	66	62	81	-59	-74	-71	-73	-77	-82
513	43	58	56	66	100	47	59	-15	-41	-37	-42	-26	-47
514	44	43	62	62	47	100	57	-15	-28	-29	-37	-46	-36
515	54	63	100	81	59	57	100	-44	-48	-49	-46	-64	-62
516	-20	-13	-41	-59	-15	-15	-44	100	50	60	51	65	66
517	-42	-38	-54	-74	-41	-28	-48	50	100	94	89	71	96
518	-31	-28	-45	-71	-37	-29	-49	60	94	100	87	79	95
519	-27	-26	-51	-73	-42	-37	-46	51	89	87	100	79	92
520	-44	-22	-59	-77	-26	-46	-64	65	71	79	79	100	80
521	-33	-55	-66	-82	-47	-36	-62	66	96	95	92	80	100

Brain region lesion factors:

508-SENSORIMOTOR(10-14)
 509-MEMORY(17,22,27-31)
 510-CONCEPTUAL(32-33)
 511-VISUOSPAT(34-36)
 512-SYMBSUB(41-43)
 513-PASAT(37-40)
 514-DIGIT SPAN(15,16)
 515-FLUENCY(44,45)
 516-STEM-CERE(46)
 517-L-TEMP(54)
 518-R-TEMP(53)
 519-FRONTAL(51,52)
 520-PARIETAL(55,56)
 521-SUB-CORT(47-50)

Table 7-B: Second Order Factor Matrix With Age Partialled

	522	523	524	525	505	506	507	512	508	511	515	509	510	514	513	515	516	517	518	519	520	521
522	100	-70	102	113	67	97	91	93	87	101	95	67	74	75	73	95	-47	-63	-57	-62	-65	-75
523	-70	100	-75	-58	-24	-64	-47	-84	-75	-61	-59	-38	-34	-36	-40	-59	75	95	98	95	90	100
524	102	-75	100	93	54	94	82	95	93	102	96	56	61	61	60	96	-57	-65	-62	-64	-73	-77
525	113	-58	93	100	82	95	101	85	75	95	89	81	88	91	89	89	-29	-55	-46	-55	-51	-67
505	67	-24	54	82	100	52	93	42	39	57	61	66	41	45	60	61	-19	-22	-18	-21	-26	-21
506	97	-64	94	95	52	100	100	88	83	98	79	58	64	59	62	79	-51	-58	-50	-53	-52	-72
507	91	-47	82	101	93	100	100	72	67	85	77	70	58	62	69	77	-37	-44	-37	-41	-41	-51
512	93	-84	95	85	42	88	72	100	83	86	81	48	46	61	62	81	-64	-74	-71	-77	-77	-84
508	87	-75	93	75	39	83	67	83	100	88	73	48	45	47	52	73	-57	-68	-67	-61	-70	-73
511	101	-61	102	95	57	98	85	86	88	100	101	58	72	61	51	101	-45	-53	-44	-53	-58	-67
515	95	-59	96	89	61	79	77	81	73	101	100	53	62	56	58	100	-46	-47	-48	-47	-63	-62
509	67	-38	56	81	66	58	70	48	48	58	53	100	35	43	32	53	-25	-41	-29	-30	-43	-33
510	74	-34	61	88	41	64	58	46	45	72	62	35	100	42	51	62	-16	-36	-26	-28	-19	-57
514	75	-36	61	91	45	59	62	61	47	61	56	43	42	100	46	56	-16	-27	-28	-37	-45	-35
513	73	-40	60	89	60	62	69	62	52	51	58	32	51	46	100	58	-18	-39	-35	-45	-23	-48
515	95	-59	96	89	61	79	77	81	73	101	100	53	62	56	58	100	-46	-47	-48	-47	-63	-62
516	-47	75	-57	-29	-19	-51	-37	-64	-57	-45	-46	-25	-16	-16	-18	-46	100	51	61	51	66	67
517	-63	95	-65	-55	-22	-58	-44	-74	-68	-53	-47	-41	-36	-27	-39	-47	51	100	94	90	71	96
518	-57	98	-62	-46	-18	-50	-37	-71	-67	-44	-48	-29	-26	-28	-35	-48	61	94	100	88	79	95
519	-62	95	-64	-55	-21	-53	-41	-77	-61	-53	-47	-30	-28	-37	-45	-47	51	90	88	100	80	92
520	-65	90	-73	-51	-26	-52	-41	-77	-70	-58	-63	-43	-19	-45	-23	-63	66	71	79	80	100	80
521	-75	100	-77	-67	-21	-72	-51	-84	-73	-67	-62	-33	-57	-35	-48	-62	67	96	95	92	80	100

505-VIQ

506-PIQ

507-FIQ

508-SENSORIMOTOR

509-MEMORY

510-CONCEPTUAL PROBLEM-SOLVING

511-VISUOSPATIAL

512-SYMBOL SUBSTITUTION

513-PASAT

514-DIGIT-SPAN

515-FLUENCY

516-BRAINSTEM-CEREBELLUM

517-L-TEMPORAL

518-R-TEMPORAL

519-FRONTAL

520-PARIETAL

521-SUB-CORTICAL

522-ALL-NEUROPSYCHOLOGICAL FACTORS

523-ALL-LESION REGIONS

524-MORE SENSITIVE NEUROPSYCHOLOGICAL FACTORS

525-LESS SENSITIVE NEUROPSYCHOLOGICAL FACTORS

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