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RELATIONSHIPS BETWEEN MRI-OBSERVED PLAQUE AND MEMORY FUNCTIONING IN MULTIPLE SCLEROSIS

By

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ABSTRACT

RELATIONSHIPS BETWEEN MRI-OBSERVED PLAQUE AND MEMORY FUNCTIONING IN MULTIPLE SCLEROSIS

By

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Memory deficits are fairly common in MS, but like motor and sensory impairments, relatively little is know about the the pathological processes responsible for the marked inter- and intra-patient variations in functioning. Magnetic resonance imaging (MRI) provides the first reliable method of observing MS plaque in vivo, but reports of the relationship between MRI-visualized lesion burden and impairment have been disappointing. However, these generally negative findings may have resulted from insensitive MRI and deficit measures, especially in studies of memory. This investigation compared several MRI indices to identify which lesion burden markers are most predictive of memory dysfunction. Forty-one clinically-definite MS patients of varying disease and demographic characteristics were administered the Wechsler Memory Scale - Revised and California Verbal Learning Test. MRI's were scored for whole brain, cerebral, and uni-hemisphere lesion area as well as corpus collosal (CC) and periventricular involvement. Correlations between lesion burden and memory measures were relatively small, but comparable to those reported previously. Contrary to prediction, cerebral lesion area was not more sensitive to memory test performance than the other lesion burden indices excepting CC lesion area. The absolute and relative degree of

association between lesion and memory appeared similar across primary versus secondary and verbal versus visual memory measures, disease course and duration, and one estimate of premorbid cognitive functioning. The failure of cerebral lesion area to outperform other plaque measures is attributed partly to a possible nonlinear relationship between function and acute plaque fluctuation. MRI insensitivity to histological-level changes, lesion dissemination characteristics, diffferences between direct versus representational lesion indices, and restriction of memory test performance range also are offered as factors contributing to the results.

In memory of Dane Francis Martin

and

to my parents for their love

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurologic disease noted for its extremely varied symptoms and course, but also for its consistently similar pathological changes to CNS myelin. These changes are characterized by glial plaques disseminated in time and space. Identification of etiological and pathogenic factors continues to frustrate the scientific community; thus, much of what is known about MS concerns its clinical and pathophysiological features (Matthews, Acheson, Batchelor, & Weller, 1985).

Physical manisfestations associated with MS are fairly well-documented, whereas investigations of cognitive dysfunctions have followed more slowly (Grant, 1986). Paralleling deficits in motor and sensory functions, deteriorations in mentation vary widely among patients although some degree of memory decline is relatively common (Rao, 1986).

Memory impairments were included in the earliest descriptions of MS (e.g., Charcot, 1877). Yet, delineation of all cognition in MS lagged until the mid-1900's with the advent of modern, empirically-based testing. Until the last decade, however, the evaluation of memory has not been a major focus. These later efforts have been primarily concerned with the description of memory impairments within the patient population. Very little data exist on the relationship between pathological changes in the CNS and memory decline. In great part, this paucity reflects the

fact that the field lacked reliable methods for identifying MS plaque in-vivo until recently. Current breakthroughs in nuclear magnetic resonance imaging (MRI) may offer the technology needed for such essential, but neglected, research.

At this point, a general description of MS would be useful before proceeding with a review of the literature on memory functioning in MS.

General Description of MS

MS was identified as a clinical entity through the work of Jean-Martin Charcot in mid-nineteenth century Paris (Charcot, 1877). Parceling together earlier, but incomplete, descriptions by Cruveilhier, and his own clinical experiences, Charcot identified distinguishing characteristics needed for accurate course description and differential diagnosis (Compsten, 1988). More importantly, Charcot made the fundamental connection between clinical course and the morphological changes (i.e., plaque-like lesions) seen at autopsy. By the turn of the century, a large body of knowledge had been compiled about the course, clinical features, and pathophysiology of MS (e.g., Meuller, 1904) and much of this data remains accurate by modern standards (see Brain, 1930; Dejong, 1970; McAlpine, 1955 and 1972 for more detailed treatment).

Current research in the United States suggests that, aside from traumatic injury, MS is the most common neurological disorder of people under 60 years of age (Johnson, Katzman, McGreer, Price, Shooter, & Silberberg, 1979), yet it is relatively rare, with an annual incidence

of less than 5 per 100,000 (Baum & Rothschild, 1981). Incidence rates are typically higher in women than for men at a ratio of approximately 1.8 : 1 (Kurtzke, Beebe, & Norman, 1979). MS rarely appears before adolescence; rates increase greatly through the early 40's and decrease markedly after the sixth decade (Visscher, Clark, Detels, Malmgren, Valdiviezo, & Dudley, 1981). Blacks apppear to have a lower predilection for MS than whites, although both races have similar age and geographic distributions (Acheson, 1985).

An especially enigmatic feature of MS is its lack of uniform geographical distribution as identified in even the earliest epidemiological studies (e.g., Steiner, 1938; Limburg, 1950). A direct and positive relationship between the distance from the equator and the rate of incidence is consistently apparent (e.g., Gonzalez-Scarno, Spielman, & Nathanson, 1986). Furthermore, the "risk factor" associated with residence appears to be mutable. Acheson (1985) reviewed a number of epidemiological studies collected throughout the world. From this, he presented evidence suggesting that a person migrating to a different latitude before the age of 15 "acquires" approximately the same probability of developing the disease as his/her new neighbors. Moves after the age of 15 result in no shift in the "risk factor" and a person retains approximately the same probability of acquiring MS as his/her homelanders. Numerous theories were unsuccesfully applied to explain this relationship between geography and incidence. Familial and racial genetics, climate (e.g., amount of sunshine), type of dwelling, and diet were proposed to act as the "trigger" for

MS -- in conjunction with hypothesized viral agents or other causal processes.

Other etiological models have faired just as poorly. Pathogens secondary to primary agents such as cholera overexertion, congenital disposition (especially through familial inheritance), primary viral infection, venal thrombosis, and various exogenous (e.g., heavy metals) and endogenous toxins (e.g., lypolytic enzymes), all have enjoyed attention as a possible "cause" of MS but have received little or no empirical support (Dejong, 1970).

More current models suffer from a similar lack of confirming evidence. One of the most popular and long-standing family of theories posits long-latency, viral infectious agents as responsible for onset of demyelination. Bolstered by epidemiological data consistent with a viral etiology, by commonalities with disorders occurring from microvirii (e.g., poliomyelitis), and by the lack of other viable theories, viral infection models have remained in the literature even though no viral agent(s) specific to MS have been identified. Similarly, hypotheses that MS is an anaphylactic or auto-immune disorder received support from years of animal research on EAE (experimental allergic encephalomyelitis), without the identification of responsible antigens (Field, 1988). Increased incidence and prevalence rates found amoung certain ethnic groups (e.g., Scandinavians) (Kurtske, 1986) and families (Field, 1984) have pointed to possible idiopathic mechanisms. In fact, some polygenic inheritance models using HLA (histocompatability) sites on the 6th and 14th chromosomes have drawn support as possible markers of inherent

susceptability to MS (Compston, 1986). Still, substantiation of responsible pathogenic mechanism(s) remains frustratingly absent. Investigations of pathogenic models based on the production and maintenance of healthy myelin are promising new areas of exploration. Chief among these are the search for genetic lipid abnormalities and polyunsaturated fatty-acid involvement to affirm MS as an abiotrophic disorder (Field, 1988). It is still not clear, however, that the morphological changes seen in MS result from a fundamental weakness in the development of myelin.

Poor understanding of the processes responsible for demyelination has hampered the development of effective treaments. The number and type of therapies that have been investigated are surprising and include variations on immunotherapy, plasmapheresis, anti-bacterial and anti-viral drugs, diet, and snake venom. Current treatment relies on exercise and drug regimens, often corticosteroids. These have had disappointing results at best (see Tourelette, Baumhefner, Potvin, Potvin, & Poser, 1983, or Matthews, 1985 for more extended reviews). The stunted progress of effective therapy also is attributable to problems associated with the high frequency of spontaneous remission in MS. Clinical trials are exquisitely difficult to evaluate with such an elevated rate of untreated improvement. Given the state of present etiological models, it may be that identification of an effective curative or even preventative agent will occur before an understanding of how the agent works -- as has happened in the past with some frequency (e.g., cholera). Until then, management will be limited to the secondary care of complications, symptoms,

and signs.

The two most distinguishing characteristics of MS are symptom dissemination in space and in time (e.g., McAlpine, Compsten, & Lumsdun, 1955). The extreme variability of symptom type across patients presumably reflects the fact that numerous locations in the CNS can host MS plaques. McAlpine's (1972) review of more recent patient series provides a list of typical presenting symptoms: weakness of one or more limbs (40%), optic neuritis (22%), parathesiae (21%), diplopia (12%), vertigo (5%), and disturbance of micturation (5%). Increased spinal reflexes, cerebellar involvement, ataxia, and losses of sensory perception and sphincter control are commonly seen later in the course (Poser, Wikstrom, & Bauer, 1979). However, many other symptoms have been reliably attributed to initial and later stages of MS: prodromal and paroxymal symptoms, Lhermitte's sign, dysphagia, tonic seizures, facial mykomia, limb weakness and spasticity, and muscle wasting (Matthews, 1985). Changes in mentation also occur, including generalized intellectual deterioration, memory and attention deficits, and impairments in abstract reasoning and information processing speed (e.g., Grant, 1986; Hill, 1990; Peyser, Edwards, Poser, & Filskov, 1980).

Temporal factors also vary widely across patients. Symptoms and signs can appear and disappear within a short time (e.g., days) and the latency between bouts can vary from days to years (Hallpike, 1983). Researchers disagree about possible course differences; however, most agree that there are at least benign, relapsing-remitting, and chronic-progressive subtypes (Matthews, 1985). These categories

reflect the wide range of temporal changes seen in clinical manifestations, ranging from negligible (constantly declining or no change) to marked (highly variable patterns of relapse and remission). Some researchers also include a malignant (or acute) variety to mark the three (Poser, Wikstrom, & Bauer, 1979) to 12 percent (Bauer, Firnhaber, & Winkler, 1965) who die and/or deteriorate significantly within the fifth year of diagnosis. Difficulties in gathering accurate diagnosis and relapse data make clinical course distinctions difficult to validate. In fact, Hallpike (1983) has argued that MS is an essentially chronic-progressive disease whose clinical picture is blurred by the randomness of lesion location and the severity of its effects on functioning. He suggests that it is in the later stages of MS that a more consistent pattern emerges when the effects of lesion dissemination accumulate and remission frequency and intensity lessen. At this time, it is not clear whether different course designations represent actual differences in disease parameters (e.g., variations in pathological changes/rates) or that different courses are merely spurious artifacts of happenstance lesion distribution as offered by Hallpike.

Disagreements over course notwithstanding, Hallpike (1983) and others do agree that the "Kurtzke 5-year rule" is a better indicator of long-term disability prognosis than is course. Based on Kurtzke, Beebe, Nagler, Kurland, and Auth's (1970) study using the Kurtzke disability scale (Kurtzke, 1965), the authors found a highly significant and positive correlation between ratings at 5 years and those at 10 and 15 years. This relationship between first and later

half-decade disability also compares more favorably than relapse rate, duration, and initial symptoms in predicting clinical disability (Matthews, 1985).

Mortality prognosis is more difficult to ascertain after the first five years (pre-fifth year mortality reflecting a malignant/acute course) because of the long interval between diagnosis and death where parcelling out effects unrelated to MS becomes critical (e.g., aging). Nevertheless, many surveys indicate that a majority of patients live 25 to 35 years (e.g., Kurtzke, Beebe, Nagler, Nefzger, Auth, & Kurland, 1970; Confavreaux, Aimard, & Devic, 1980) with a range of days to 60 years (Matthews, 1985). Few patients die directly of MS, but rather succumb to secondary causes such as pneumonia (Leibowitz, Kahana, Jacobsen, & Alter, 1972).

The diagnosis of MS is difficult owing to the appearance and disappearance of sometimes subtle and wide-ranging symptoms. And for any given exacerbation, symptoms can mimic and be mimicked by many other pathologies. Our limited understanding of pathogenic and etiologic factors has hampered the development of laboratory tests with sufficient sensitivity and specificity to serve as pathognomonic indicators. Diagnosis was and continues to be essentially a clinical exercise.

Because of this dependence on clinical acumen, diagnostic accuracy suffered until empirically-supported criteria could be developed. Present systems supplement historical clinical data with paraclinical evidence (e.g., evoked responses) and laboratory evidence (e.g., oligoclonal bands in the cerebrospinal fluid) to delimit categories such

as clinically and laboratory-supported definite, probable, and possible MS. The most commonly used nosologies are those by the Schumacher Committee, 1965; McAlpine, 1972; Rose, Ellison, Myers, and Tourtellote, 1976; McDonald and Halliday, 1977, and especially the Boston University Workshop (also known as the Poser criteria) (Poser, Paty, Scheinberg, et al., 1983).

The reliability of these systems depends heavily on the use intended. For example, the Boston University Workshop system has no "possible" category and uses comparatively stringent inclusion criteria to insure low false-positive rates. The cost to this system is an increased false-negative rate, which may hamper, for example, studies focusing on early-case detection. Thus, care must be taken to choose a system appropriate for the task at hand. Although employment of these systems has improved diagnostic reliability and validity, they still rely considerably on clinical judgement and remain susceptible to inter-rater variation. Until true pathognomonic tests are developed, however, little can be done to ameliorate this problem. Finally, recent advances in radiological imaging (MRI) have outpaced revisions of some schemas, although a flurry of work is currently underway to validate MRI techniques for use in diagnostic systems.

Gross pathological examination of MS-involved CNS finds lesions throughout, although some sites are more apt to contain plaque. Periventricular white matter locales are most common, containing as much as 40% of plaque distribution confirmed at autopsy (Brownell & Hughes, 1962).

White matter, in general, is most likely to be affected, although cortex and the junction between the two also can contain plaque (Lumsden, 1970). MS typically appears symmetrically between the cerebral hemispheres and distribution between the four major lobes is relatively similar, although usually with less involvement in the occipital lobe (Brownell & Huges, 1962). Other common sites include the cervical spinal cord and optical tracts (Adams, 1983). Most plaques lie in close proximity to venules or larger veins (Fog, 1965), but the reasons for this association are not known.

Analyses on a histological level have provided possible clues about the relationship between pathological and clinical changes. Microscopic examination indicates that complete axonal and cell body loss occurs infrequently, although histological changes in these structures are seen to some degree in most, but especially chronic cases (Oppenheimer, 1976). Lesion growth fans out from a locus, usually sparing some portion of an axon's myelin (Lumsden, 1970). Grossly, much of the myelin within this sphere appears intact, but on closer examination some signs of deterioration (e.g., thinning) or outright destruction (e.g., microglial phagocytosis and complete absence of myelin) can be seen (Adams, 1983). From this, Adams (1983) concluded that MS lesion distribution is diffuse rather than multifocal. An important implication of this distinction is its impact on functioning and this will be discussed in greater length below.

Several factors have been used to explain why neuronal functioning in affected areas is not completely nor

irrevocably lost. First, demyelination is a gradual process wherein only the final-stage, chronic lesions show total loss of myelin and oligodendroglial cells (Weller, 1985). Some functioning may continue between this and the earliest stages of degeneration where remission, in turn, may further delay the final result (Weller, 1985). A gradual degradation also may allow time for the development of alternative pathways or compensatory functioning. A second factor that may explain why functioning continues in affected areas is the tendency for lesion growth to spread centrifugally (Lumsden, 1970). Localized structures often are spared from complete demyelination, presumably resulting in the preservation of at least limited functioning of the involved tissues. Third, remyelination is thought to occur in and around plaques, although its extent and quality is not completely known (Harrison, McDonald, Ochoa, & Ohlrich, 1972; Blakemore, 1982). Neural transmission may exist in active lesions where a suffient number of oligodendroglial cells remain to allow remyelination. The pathophysiological mechanisms responsible for a remission are not known, but it is probably the case that remyelination is only a small part of the picture. Review of exisiting literature by Matthews (1985) suggests that de novo and early exacerbations are caused as much by edemal and other acute responses to demyelination as the actual destruction of myelin. Thus, remission may simply reflect the ending of the acute response. Continued investigation is needed, however, as the relationship between pathophysiology and clinical changes is poorly understood still.

Our relative ignorance about the pathophysiological mechanisms responsible for deficit is due, in great part, to our almost total dependence on post-mortem examination. Full description of patho-clinical relationships, including the processes responsible for relapse and remission, would be furthered by dynamic, in-vivo examinations. MRI may provide the technology necessary for such investigation.

Before moving to a review of the literature on memory functioning in MS, a brief introduction to memory terminology, theoretical models, and research methodology is provided.

General Description of Memory

Functional Aspects

The study of human memory encompasses a wide range of approaches, with contributions by neuropsychologists, clinical, cognitive, and experimental psychologists, linguists, educators, computer science and artificial intelligence specialists, and neurologists. This introduction is limited to psychological studies of "conscious" memory as they relate most directly to memory research on MS. It excludes attentional mechanisms, executive functions, and other functions that are recognized as essential to intact memory processing. Extensive coverage of these functions and other aspects of memory may be found in texts on cognition and memory (e.g., Ashcraft, 1989; Reynolds & Flagg, 1983; Squire, 1987; Squire & Butters, 1984; Tulving & Donaldson, 1972).

Early research on memory was guided by intuitively important features of memory (e.g., Ebbinghaus, 1885), and

modern models often still rely on fairly common sense distinctions. These include temporary versus more permanent memory systems, the types of information retained in memory, and the way in which memories are used. The distinctions between temporary and permanent systems involve a broad family of concepts and theories that seek to account for temporal gradients in information processing. Most models include at least two tiers beyond the level of the sensory memory registers: one that accounts for immediate and conscious processing demands without regard to permanent information storage and a second system responsible for the storage and recollection of more long-lasting memories. The best known memory function models use the terms primary memory (PM) (James, 1890), short-term memory (STM) (e.g., Miller, 1956), and working memory (e.g., Baddeley & Hitch, 1974) to refer to the system that deals with information in here-and-now. Testable distinctions between the concepts of PM, STM, working memory, attention, and consciousness are quite blurry and each has received at least partial support from over 100 years of empirical study. Even though controversy exists as freely as agreement (e.g., Cermak, 1982), some synthesis and generalization is possible regarding theories of temporary memory. Pioneering work by Miller (1956) and others indicates that the temporary system is limited in capacity by the amount of information that it can handle (i.e., seven bits of information plus or minus two) rather than by a simple decay over time. That is, information in STM is lost more because of competition with other material than because of failure to rehearse or other means of deterioration of the memory trace (Peterson &

Peterson, 1959). The limit in capacity may by overcome by increasing the meaningfulness of the information (e.g., semantic coding and personal attributions) and by the process of "chunking" -- grouping specific bits of material into larger functional units (e.g., grouping a string of random digits as the area code and exchange of a phone number).

The working memory model elaborates the temporary memory system including the presence of a master, "executive control system" (ECS) that oversees memory and other intellectual processes (Baddeley, 1981). Analogous to some conceptualizations of attention and a variety of executive functions, the ECS purportedly initiates and allocates cognitive resources, maintains flow of information to and from memory stores, and otherwise controls decisions. At least two "slave" systems serve the ECS by providing "working space" (hence the term, working memory) for cognitive tasks. The articulatory rehearsal loop handles most verbally-mediated tasks and, within its limits, holds and recycles information for later recall. The "visuo-spatial scratch pad" parallels the articulatory loop but only for visual tasks. A primary tenet of the working memory model is that if the limits of either of the slave systems are reached (i.e., around six bits of information), the efficiency of the ECS begins to decrease with attendant increases in processing time and errors. Although the working memory model does an admirable job of explaining data on immediate memory, many questions are left unanswered, the most puzzling of which may be phrased as "who watches the watcher?" Baddeley has yet to explain how

the ECS makes decisions, for example.

A review on memory functioning and MS requires that we differentiate between temporary and more durable memory, but it is not necessary to understand all of the nuances that distinguish the various models of the temporary memory system. To make thins simpler, PM will be used for all future references to the less permanent memory system unless otherwise specified. This should not be taken to mean that the PM model is most accurate or preferred.

PM is frequently measured by so-called "attention span" tests. Subjects are required to repeat verbal (e.g., digits) or nonverbal (e.g., tapping blocks) bits of information, which are presented in rapid fashion so as to prevent rehearsal or the development of other strategies that could allow storage and recall from secondary memory. However, evidence indicates that digit span tests may be an inadequate measure of PM because the task is well-automaticized in most subjects (Mack, 1986). Another test, originally developed by Brown (1958) and Peterson and Peterson (1959), taps slightly different PM functions than digit span and minimizes the problem of automaticity through the use of a dual task paradigm. Subjects are shown a subspan stimulus (e.g., consonant trigrams), asked to perform some non-automatic distractor task (e.g., counting backwards), and finally asked to recall the original stimulus. This test can provide an estimate of distractability and ability to divide attention. PM integrity also can be inferred from the response pattern on a supraspan immediate recall task. For example, subjects are asked to recall a list of words (usually 12 or more)

immediately after their presentation. (Because the amount of information to be learned exceeds PM capacity -- the span of attention -- the term "supraspan" is often used). Words recalled from near the end of the list are drawn directly from PM, whereas items recalled early in the list depend on adequate rehersal for recall from secondary memory (Murdock, 1962). Most clinical memory batteries (e.g. Wechsler Memory Scale - Revised; Rivermeade Behavioural Memory Test) include a variant of one of the tasks noted above. MS memory investigations usually include at least one measure of PM, although, as will be discussed below, the unfortunate trend is to rely solely on verbal attention span.

Turning towards a description of durable memory, James' (1890) term, secondary memory (SM), will be used in reference to the system(s) responsible for the integration of information into and from longer lasting storage (also known as long-term memory). No single, comprehensive, and accurate model has been developed for SM because of the extreme complexity and scope of the topic. To make investigation and theory more manageable, researchers have explored fundamental components within SM. Before reviewing these distinctions, it is important to note that a huge amount of material has been published concerning the way in which information is stored, recalled, recognized, and otherwise manipulated for later use. Application to MS research is limited to the following points. One is that PM is necessary for intact SM functioning because it is quite difficult to store information when one cannot adequately attend to or manipulate material in immediate consciousness. Secondly, research indicates that some period of time is

needed to ensure that information is consolidated from PM to SM and that the consolidation may be distrupted by ECT, head trauma, toxic chemicals, surgical resection of cerebral tissue, and the like (Reynold & Flagg, 1983). A third point is that research questions on memory and MS tend not to be theory driven. Rather, investigation is limited to determining whether or not patients can recall or recognize information -- not why they fail to remember. More specific discussion about how SM processing is affected can be found in Estes (1982), Ashcraft (1989), and Tulving (1983).

The first functional division of SM to be discussed is that of episodic and semantic memory (e.g., Tulving, 1972). Episodic memory is an individual's autobiographical and experiential knowledge with attendant context as to when and where the information was learned. Examples range from the obvious, such as the memory of one's first kiss, to the less apparent such as the recall of a list of words in a memory experiment. By contrast, semantic memory may be conceptualized as knowledge per se, including memories for facts and concepts. Although most semantic memories are verbally-oriented -- hence the term <u>semantic</u> -- they need not be so. For example, semantic knowledge of colors or physical sensations may defy verbal description. Confusion about this point has led Ashcraft (1989) to suggest that <u>generic memory</u> be used, as it more adequately conveys the meaning of this type of memory than does semantic memory. In terms of application to the MS literature, the vast majority of clinical measures tap what is thought of as episodic memory: recall and recognition of word lists, paired words, paragraphs, faces, geometric figures, and

abstract designs. No MS investigations have been found that use tests specific to the semantic memory paradigm, although intelligence tests measure generic knowledge to some degree. One of the reasons for this scarcity in the literature is that older, well-learned, "retrograde", and "remote" memories (especially semantic, but also episodic) are robust to loss across many pathologies (cf. dementia).

Having just distinguished episodic from semantic memory, it is essential to recognize that the two cannot be separated totally in the real world. Semantic memory is derived from an accumulation of episodic events, our personal experience of the world. For example, Wilson (1982) reports that amnestics have great difficulty adding new semantic information, which she attributes to their impaired episodic memory. Conversely, acquisition of episodic memory is affected by our generic knowledge of the world as exemplified by Loftus' studies (e.g., 1979) on eyewitness testimony. The psychoanalytic literature has long recognized the importance of integrating the two through the mechanisms of accommodation (i.e., changing our view of the world to corroborate new experiences) and distortion (i.e., changing our recollection of events to meet our view of the world).

Two other SM distinctions will be discussed briefly here because, although research on MS has yet to employ these concepts, application may come soon. A flurry of interest and experiment has occurred following a paper reviewing implicit and explicit memory by Schacter and Graf (1986). Their comments stemmed from many prior observations that amnestics may show learning on tasks that do not

require explicit recollection of the information (e.g., forced choice answer format) while not being able to purposefully, accurately, or explicitly verbalize that knowledge. Schacter (1987) reviews previous discussion and investigation, including some from the psychoanalytic literature on the unconscious, that indicates that there can be a dissociation between what a person can recall overtly and behavior indicative of learning without conscious awareness. The concept of implicit memory raises several interesting questions about how we define and measure human memory. One is how implicit memory relates to the other components of primary and secondary memory. For example, implicit probably involves input from ontogenetically older memory systems (e.g., the sensory registers) but also from features of episodic and semantic memory. As Schacter notes, the implicit - explicit distinction is exciting because it may be applied to so many different aspects of memory with both traditional (e.g., attention; semantic and perceptual priming) and nontraditional topics (e.g., the effects of affective and social associations, hypnosis, and altered states of consciousness). Although some believe that recognition format tests used in MS research tap implicit memory, no one has used such data to draw inferences about implicit versus explicit memory functioning in MS.

A final way in which SM will be distinguished is the contrast of procedural and declarative memory. Anderson (e.g., 1976) uses the concept of procedural memory to represent knowledge of how to do things (e.g., pitching a baseball). Sometimes referred to as motor memory,

procedural memory is not necessarily restricted to overt, motoric behavior. Cognitive procedures also can be included such as knowing how to operate a calculator. Declarative memory refers to knowledge of basic facts and other easily verbalized information. Even with such a brief introduction, one can see similarities between procedural and declarative memory and other SM distinctions noted above. For example, the act of frying an egg could include aspects of episodic (e.g., how you cooked today's breakfast), semantic (e.g., recollection of several cookbook descriptions), and procedural memory (e.g., doing the act without conscious awareness). Before rejecting the notion of procedural memory as unspecific or redundant, one has only to recall the famous amnestic, H.M., with his intact procedural memory but devastating anterograde amnesia (Scoville & Milner, 1957), to recognize the validity of the concept of procedural memory. As with implicit memory, little has been done to investigate procedural memory functioning in MS (cf. Caroll, Gates, and Roldan, 1984).

In addition to the topics reviewed above, many other areas of research have yet to be applied to MS, especially in regards to modality differences. Memory for tastes, smells, tactile stimulation, music, and non-language sounds (e.g., bird calls) are poorly understood relative to visual and language systems, primarily because the latter are more important to human information processing. Investigation of verbal and nonverbal memory is extensive, however. Springer and Deutsch (1985) provide a good introduction to hemispheric organization of function, including memory, which indicates that parallel memory systems exist based on

a verbal - nonverbal distinction. This dissociation also can be found in clinical (e.g., Lezak, 1983) and cognitive literatures, including discussion on differences in the sensory registers, PM, and SM in the latter. MS research shows a similar interest in differences between verbal and nonverbal memory.

A brief discussion of a difficult measurement issue will conclude the introduction to memory functioning and MS. Mack (1986) reviews the problem of non-orthogonality in cognitive testing (i.e., tests purportedly measure only one, orthogonal function but really require multiple functions). This issue has two particularly important applications: discriminating verbal from visual and primary from secondary memories. Regarding the former, it is extremely difficult to obtain a "clean" (orthogonal) measure of nonverbal memory with most clinical tests. Tasks such as recognizing faces or recalling simple geometric designs are frequently used for this purpose, yet humans show a wonderful capacity to augment learning of nonverbal stimuli through the use of verbal strategies. The reverse situation also occurs when easily visualized words are used in a list learning test. Subjects are known to employ visual strategies to aid "verbal" memory performance (Wilson, 1982). When easily cross-cued tests are used, it is difficult to sort out the relative contributions of the verbal and visual memory systems. Researchers must carefully choose tests that minimize the possibility of cross-modality cuing. For example, Allen Baddeley is leading recent efforts to improve nonverbal test designs and his test of memory for pictures of doors will be available soon (personal communication,

1991).

Controlling for the effects of PM to yield a pure measure of SM is even more difficult than differentiating verbal versus visual memory. Because every memory task (or cognitive for that matter) requires at least some PM processing, one cannot assume that impaired performance on the test is indicative of SM deficits. Researchers have several ways in which to control for this measurement problem. One is to slow the presentation rate of information to be learned to allow adequate rehearsal time (i.e. access to SM processing). Another is to estimate the relative integrity of PM. If it is found to be intact, then one can safely assume that poor performance on tests of both PM and SM is due to SM deficit. Unfortunately, many clinical research protocols do not control for the effects of PM on tests of SM, thus making it difficult for a reviewer to determine why subjects' performance was impaired. One way to separate primary from secondary memory deficits post hoc is to compare tests that challenge PM to different degrees. Let us return to an example presented earlier: an immediate recall (supraspan) list learning task. It was noted that one could estimate the integrity of both primary and secondary memory by tracking the pattern of recall. Words recalled from early in the list are mediated through rehearsal and reflect SM processing, while items recalled from list end are straight from PM. Since most authors report only the total number of words recalled or the learning curve, a reviewer cannot comment on the relative contribution of PM and SM processing. Even if word were reported, we would still have difficulty making

assertions about PM and SM because individuals differ in their reliance on PM and SM processing. We can infer, though, that the "load" on the SM system for immediate supraspan recall is relatively greater than that for more orthogonal PM tasks such as the Brown-Peterson test. Similarly, a delayed recall task requires more SM processing than an immediate recall test. This method of estimating SM integrity in the absence of controls for PM will be used in the review on MS memory research.

Pathoanatomical Aspects

As with the section on memory functioning, introduction of the anatomical features of human memory will be limited to what is necessary for a review of the MS literature and the applications of this study.

Controversy over memory localization is a good starting point because a review of structures important to memory should not lead one to infer that memory exists outside of the context of the entire organism, including the brain. Centuries of study by localists (e.g., Gall, Broca, and Hebb) and wholists (e.g., Flourens, Koffka, and Lashley) has yet to resolve the issue of localization. One reason for the failure is the problem of level of analysis. While neurophysiologists' study of synaptic changes easily lends itself to a discussion of "where", psychologists interest in behavioral systems does not. In this author's view, the most reasonable answer to the question of memory localization is (with apologies to George Orwell):

All brain structures are equal
(but some are more equal than others)

One impetus for the current study is to help identify those

anatomical structures most important to predictions of memory dysfunction in MS.

Several relatively primative neurological systems have been identified that are associated with some forms of learning. For example, spinal cord reflex arcs subserve habituation to the auditory startle reflex (Tischler & Davis, 1983). The midbrain tectum supports some visual discrimination tasks as with cortically "blind" patients who show conditioned learning if this second visual system is intact (Cohen, 1984). Ontogenetically older neural substrates also contribute to explicit memory functioning, but since this role is neither clear nor extensive (Squire, 1991), we will move to anatomical correlates of "higher" memory functioning.

Outside of primate studies, most of the evidence on memory localization comes from the clinical literature, especially the amnesias. The implication of several medial temporal lobe and diencephalic structures will be reviewed, as well as the contribution of the cortex and other subcortical elements.

Identification of distinctive forms of amnesia led to to the conclusion that portions of both the medial temporal lobe and diencephalon are involved in memory functioning. Walsh (1985) does an admirable job of sorting out evidence for and descriptions of the functional characteristics of the two types of memory disturbance. It is important to note that the statements presented below are generalizations and that controversy exists over the relative and absolute degree of impairment across several aspects of PM and SM (e.g., Wilson, 1982). Primary and procedural memory are

relatively unimpaired in both temporal lobe and diencephalic amnesia, but they differ on most other comparisons. Functional features of medial temoral lobe amnesia (MTLA) include: intact retrieval of older, declarative memories (i.e., remote episodic and semantic memories); severe impairments in acquiring information; and self-awareness of memory deficits. Walsh notes that the failure to acquire new information seems due to impaired consolidation, as evidenced by the loss of some events before dysfunction onset and by a failure to profit from cuing. If a failure to learn was attributable to a retrieval deficit alone, cues would help. By contrast, diencephalic amnestics have a retrieval impairment and therefore are better able to recognize or otherwise gain from retrieval cues. Unfortunately, the retrieval impairment also results in retrograde amnesia in addition to the anterograde problems. Another important feature of diencephalic memory disturbance is the loss of organizational associations to memories, especially temporal and sequencing cues. It is speculated that the high frequency of confabulation in diencephalic amnestics is a consequence of their failure to know "when" and in "what order" events happen. Finally, diencephalic patients differ from their MTLA counterparts in that the former tend to be unaware of their memory impairments (e.g., Victor, Adams, & Collins, 1971).

The prevalence of diencephalic amnesia is signifcantly higher than MTLA, in great part because the former can be caused by severe alcohol abuse. Any thiamine-depleting condition (e.g., malnourished women on contraceptive medication) can cause diencephalic amnesia, as well as acute

encephalopathies, truama, thalamic infarct, and neoplasms (Wilson, 1982). Nevertheless, long-standing alcohol use remains the single best way of developing Wernicke's disease with Korsakoff's psychosis, of which diencephalic amnesia is a feature (see Victor & Adams, 1985; Lezak, 1983; Victor et al., 1971; and Wilson, 1982 for a taste of the Byzantine history and nosology of Korsakoff psychosis, Wernicke disease, Wernicke encephalopathy, Wernicke-Korsakoff syndrome, and their relationship to diencephalic amnesia).

The most notable cause of MTLA is bilateral surgical resection for intractable epilepsy (e.g., patient H.M., Scoville & Milner, 1957), while cases also have been reported in association with viral, anoxic, and ischemic encephalopathies and bilateral posterior cerebral artery occlusion. Unilateral involvement produces less severe and modality-specific dysfunction (i.e., left- and right-hemisphere involvement results in verbal and nonverbal impairments, respectively) (Squire, 1987). Considerable disagreement exists over which specific sites are involved in MTLA. The hippocampus (e.g., Scoville & Milner, 1957) is the most likely condidate, although others have argued for the temporal stem (e.g., Whitty & Zangwill, 1977; Horel, 1978). Squire's (1991) extensive review of pertinent research, including his own recent efforts involving the systematic ablation of various tissue in the macaque, concludes that only the hippocampus is critical and that destruction of the temporal stem, amygdala, uncus, and fornix is neither necessary nor sufficient to impair SM. This fine work notwithstanding, debate continues still. It is clear only that some area of the temporal lobe is

important to declarative SM, especially consolidation of information into long-term storage.

There is even greater disagreement about the specific lesion sites responsible for diencephalic amnesia. Wilson (1982) and Squire (1987) concur that current evidence is insufficient to determine whether the mammillary bodies (cf. Delay & Brion, 1969) and/or pulvinar and dorsomedial nuclei of the thalamus (cf. Victor et al., 1971) are the key anatomic feature. Despite the tremendous amount of data available, the failure to confirm may continue because the structures in question are quite small and because the most common etiologies of diencephalic amnesia produce deterioration across anatomic boundaries. At this juncture, one can infer only that some aspects of the diencephalon are involved in memory.

Unfortunately for our attempts to understand memory impairment in MS, the types of memory deficits and lesion locations in MS do not correspond to those noted with either diencephalic or medial temporal lobe amnesia. This point will be elaborated after further consideration of the data on memory functioning in MS.

The basal ganglia is a third anatomic region with hypothesized associations to memory. Before continuing, it should be noted that the evidence supporting basal ganglia involvement is almost entirely clinical and that its functional picture often is grouped with so-called subcortical dementias whose pathoanatomic correlates include structures other than the basal ganglia (e.g. thalamus). Thus, one must be careful not to confuse functional syndromes with anatomic systems and the pathologies that cut

across both anatomic and functional distinctions. The controversy over and differences between subcortical and cortical dementia will be discussed later.

Pathological conditions that affect basal ganglia functioning include Huntington's (HD) and Parkinson's disease (PD), progressive subnuclear palsy, stroke, tumor, various encephalopathies, and several inherited metabolic disorders. HD and PD are most studied and involve the dopaminergic pathways of the mesencephalon (e.g., caudate, putamen, globus pallidus, and substantia nigra). Because these two conditions are significant more for their specific association to a neurotransmitter rather than to an anatomic structure, it is hypothesized that changes in memory result from biochemical abnormalities (Victor & Adams, 1985). Memory impairment in Huntington's disease is chracterized by a general retrieval deficit resulting in both anterograde and retrograde SM memory loss. The retrograde disturbance is distinguished by its lack of a temporal gradient (cf. diencephalic amnesia) -- performance on uncued recall of old memories was equally poor regardless of the relative age of the memories (Albert, Butter, & Brandt, 1981). Other aspects of SM and PM appear relatively intact (Cummings, 1990) and the severity of SM impairment generally is less pronounced in comparison to both medial temporal lobe and diencephalic amnesia. There is disagreement regarding memory function similarities between PD and HD, as well as with the other conditions that affect the basal ganglia. One reason for the controversy is the presence of other cognitive deficits, including impaired executive functions and general slowing of information processing (e.g., Lezak,

1983) that hamper identification of specific types of memory impairments.

Data pertaining to memory and the basal ganglia are of limited use in studies of MS, despite arguments that there are similarities in symptom patterns (e.g., Cummings & Benson, 1984). As will be discussed later, basal ganglia involvement is a minor pathoanatomic feature in MS and, therefore, cannot account for all memory dysfunctions.

The cerebral cortex is the last anatomic area that will be reviewed here and it will be given very brief treatment. One reason is that the types of memory problems seen in MS are not comparable to those observed in conditions resulting in cortical pathological changes. Also, cortical involvement is a relatively minor feature in MS pathoanatomy. These issues will be discussed at greater length following a review of memory functioning in MS and the role of MRI.

Cortical grey-matter is thought to be important to many SM and PM functions. A wealth of animal studies (see revies in Squire, 1987; Squire & Butters, 1984) support the role of cortex in memory, including evidence of cortical plasticity as a function of learning. Experiments on human subjects, while limited for obvious reasons, implicates cortex as a storage site. For example, electrostimulation of the cortex evokes powerful, memory-like experiences (Penfield, 1958). Conditions that affect the cortex often result in devasting losses to many memory functions, including procedual, semantic, and primary memory. In fact, the presence of PM deficits is purported to separate the cortical (e.g., Alzheimer's and Pick's disease) from the

subcortical dementias and amnesias (e.g., Cummings, 1990). Aside from the dementias, cortically-related memory impairment may result from head truama, neuroma, exposure to neurotoxins, hydrocephalus, stroke, anoxia, ischemia, aging, and numerous infectious agents.

The clinical literature also indicates that localized areas of the cortex support separate memory functions. For example, right infratemporal cortex has been associated with visual memory processes; inferior parietal lobe gray matter has been linked to memory for spatial location; somatosensory cortex is implicated in the storage of tactile patterns; and degradation of Wernicke's and Broca's areas results in language-specific learning loss (e.g., Walsh, 1987). Because the cortex also seems necessary for all kinds of information processing tasks, however, modality-specific memory loss also may reflect the secondary effects of deficits in other cognitive functions (see Luria, 1966 for a discussion on cortical association areas). Squire (1987) writes that the evidence for cortical localization also reflects such factors as cortical plasticity and equivalency. Thus, localization per se probably occurs only on the level of specific memories, while memory as an information processing system depends on the mass action of combined cortical and subcortical systems. A better description of the role of cortex with memory also is hindered by the fact that so many of the pathologies that attack the cortex also produce subcortical insult.

To conclude this introduction to memory and anatomy, we will return to previous comments regarding the necessity of a wholistic view of human memory. In addition to the

regions discussed above, learning depends on the limbic system for motivation, the frontal lobes for executive functions, and intact language, motor, and sensory systems for the input and output of information. This wholistic view seems especially pertinent to MS because much of what is known about memory anatomy and function is not easily applied to MS. A certain amount of creativity will be needed to explain how memory deficits are produced in MS and what pathoanatomic features are related to those changes. With this in mind, we will turn to a description of memory and MS.

Memory Functioning in MS

Introduction

Investigations of memory in MS have lagged behind those of other cognitive, as well as motor and sensory, functions. Most studies have been limited to a simple description of test performance through traditional clinical neuropsychological methods. Cumulative evidence indicates that, compared with PM, SM is more likely to be impaired and to a greater degree. The single most distinctive feature of MS-related memory impairment is the tremendous variation between patients. The review presents theoretical and methodological issues relevant to subsequent predictions of lesion burden - memory relationships.

Historically, it is difficult to track what was known about memory in MS because it was not treated separately from other cognitive processes. Charcot (1877) described "enfeeblement of memory" as a symptom of MS in his original series of patients. For approximately the next half-century

after Charcot's observations, studies of cognition were limited to anecdotal, clinical impressions and, in fact, early authors debated whether mentation (including memory) actually was affected in MS. Psychometrically-sound comfirmation of at least occasional memory deterioration, rudimentary description of its relevant aspects, and the separation of discrete cognitive processes began only with the appearance of standarized and empirically-based assessment methods in the mid-1900's. The overwhelming majority of these research reports still dealt primarily with generalized cognitive functioning; memory was a peripheral concern (Trimble & Grant, 1982). For a more comprehensive review of this pre-1980 research, see Trimble and Grant (1982) or Marsh (1980).

Research with a more substantial focus on memory began with Jambor's (1969) study of 103 chronic MS patients. He found that MS patients had significant decrements in performance on learning and recall tasks relative to psychiatric, muscular dystrophy, and normal control groups. It would be almost another 10 years before the appearance of the next study (Beatty & Gange, 1977). Investigations have followed fairly regularly since then, particularly those concerned with memory.

Despite the increased activity, research on memory functioning in MS still lags behind studies of other causes of memory disturbance. There are several reasons for this. Memory impairments are not so prominent a feature of MS as they are in many other conditions. Thus, memory dysfunction is more easily identifed and studied in, for example, the dementias than in MS. As a consequence, a more extensive

empirical and theoretical base exists with which to fuel subsequent research on memory impairments in conditions other than MS. The relative paucity of memory research in MS also reflects the lower incidence of MS compared to other conditions producing changes in memory; thus, access to subject populations is not comparable across pathologies. Empirical treatment began and has continued in spite of these hurdles, however, and as is often the case in new fields of endeavor, initial research focused on description.

The single most apparent aspect of memory functioning in MS is the marked individual variation within and across subject populations -- exactly paralleling non-cognitive symptoms and signs. As a group, patients clearly show deficits in comparison to normals and other chronically ill control groups (e.g., head injury, muscular dystrophy) on a wide range of memory measures. However, the prevalence and severity of memory disturbances is idiosyncratic. For example, Rao, Hammeke, McQuillen, Khartri, and Lloyd's (1984) cluster analysis of 44 chronic progressive MS subjects showed that one subset (20%) had significant deficits, a second group (43%) had more moderate impairments, while the third subset's (36%) performance was normal on a range of memory measures. The overall rate of "clinically noticable" memory problems in this sample was 40 percent. Inter- and intra-individual variations in specific types of memory also are widely reported and will be reviewed next.

Functional Features

Memory functioning in MS has been examined almost exclusively from a clinical neuropsychological perspective.

Cognitive paradigms have had relatively little play, and neurobiochemical models, none at all. The focus has been on aspects of secondary memory capacities, mostly declarative and episodic, while little data exist on procedural, semantic, autobiographical, and perceptual memory (cf. Carrol et al., 1984). Some attempts have been made to tie in the types of memory disturbances seen in MS with those of conditions known to produce memory impairment, but most MS investigations are descriptive only. Before continuing with the review, some commonly found methodological problems will be discussed as they bear on the conclusions that are drawn from the data. First, it is very difficult to compare findings across studies because of the plethora of tests used -- over 20 by Fischer's (1988) estimate. Generalizations also are hampered by inadequate and confounded test designs such as failure to control for the effects of modality cross-cuing or PM processing on tests of SM. Finally, the variable course of MS makes it difficult to determine the degree and frequency of memory impairments in the population. No longitudinal studies could be found that speak to the question whether memory functioning, like many motor and sensory abilities, fluctuates over time. Temporal fluctuations could explain many of the discrepant findings reported in the literature and until course distinctions are well-identified, all existing research on memory must be viewed with some caution. With this rather sobering introduction, we will begin the review of memory functioning in MS.

Primary Memory

Many studies have concluded that PM is not affected in MS. However, almost all of the data are based on tests of PM capacity (i.e., digit span) without evaluation of other PM processes. Inadequate study design also precludes a reliable estimate of the prevalence and severity of SM impairments.

The data on verbal PM capacity, as measured by digit span, are conflicting. Fischer (1988), Lyon-Caen, Jouvent, Hauser, Chaunu, Benoit, Widlocher, and Lhermitte (1986), and Huber, Paulson, Shuttleworth, Chakeres, Clapp, Pakalnis, Weiss, and Rammohan (1987) each reported that mean verbal digit span scores in MS were significantly below those of controls. Conversely, Heaton, Nelson, Thompson, Burks, and Franklin (1985), Jambor (1969), Litvan, Grafman, Vendrell, Martinez, Junque, Vendrell, and Barraquer-Bordas (1988b), Marsh (1980), Rao et al. (1984), and Rao, Leo, and St-Aubin-Faubert (1989) concluded that verbal digit span was not significantly different from control subjects. Contrasting scoring methods may explain, in part, these discrepant reports. For example, Lyon-Caen et al. (1986) and Huber et al. (1987) used only the forward score in their analyses, while all the others used a combined digits forward and backward score. Fischer's (1988) study used the WMS-R and its slightly different scoring system from the WMS. Studies that used the Wechsler Adult Intelligence Scale (WAIS) (Brainin, Goldenberg, Ahlers, Reisner, Neuhold, & Deecke, 1988; Heaton et al., 1985; Jambor, 1969; Litvan et al., 1988b; Marsh, 1980) and the WAIS-R (Rao et al., 1989) are not comparable to those using the WMS (Huber et al., 1987;

Lyon-Caen et al., 1986; Rao et al., 1984) or WMS-R (Fischer, 1989) because subject performance is reported in terms of standard scores with the former, while studies using the Wechsler memory scales typically reported raw scores. This prevented a meta-analysis of the data. It was determined that all MS subject mean scores on the WAIS or WAIS-R were within one standard score of the subtest mean (i.e., 10), which suggests no gross disturbances in the patient samples. And with one exception (Hirschenfang & Benton, 1966), this finding also was true of pre-1980 studies reviewed by Marsh (1980).

Only one study could be found that tested non-verbal PM capacity. Fischer (1988) found no significant differences between her samples of MS patients and normal controls on the WMS-R Visual Memory Span substest. Fischer offered the explanation that, in contrast to the verbal digit span subtest, visual memory span is not subject to interference (i.e., telephone numbers). Possible interference effects notwithstanding, there is no a priori reason to suspect that non-verbal PM capacity is any more or less susceptible to impairment than verbal PM limits.

It is not clear whether PM functions other than capacity are impaired in MS. Callanan, Logsdail, Ron, and Warrington (1989) reported deficits on verbal and visual cancellation tasks hypothesized to measures vigalance. However, these results should be catuiously interpreted because Callanan et al.'s subjects were not confirmed MS patients (clinically-probable). Using a visual concellation task similar to Callanan et al.'s (1989), Franklin, Heaton, Nelson, Filley, and Seibert (1988) reported a significant

increase in task time indicative of PM impairment, but total number of errors was in the normal range. Two studies using a Brown-Peterson task reported conflicting results. Beatty, Goodkin, Monson, Beatty, and Hertzgaard (1988) observed significantly impaired recall because the authors did not describe their exact procedure; however, interpretation is difficult. Grant et al. (1984) also demonstrated significant performance decrements as interference task difficulty increased (i.e., 3, 6, 9, and 18 seconds of counting backwards by "threes") in comparison to controls. However, no difference between patients and controls was seen in the 18 second condition -- where interference effects should have been strongest. Both Litvan et al. (1988b) and Rao et al. (1989) also failed to find patient versus control group differences with versions of the Brown-Peterson similar to that used by Grant et al.

In summary, MS patients do not consistently show impairments on various measures of PM capacity. These discordant findings do not appear to be due to differences in subject characteristics (e.g., age, sex, education, SES) or disease factors (disease length and physical disability) because both affirming and disconfirming results have been reported across these characteristics. Psychotropic medication (Beatty & Gange, 1977; Fischer, 1988; Grant et al., 1984) and fatigue effects (van den Burg, van Zomeran, Minderhoud, Prangs, & Meijer, 1987) were evaluated specifically and found to be unrelated to test performance.

It is argued strongly that, after the consideration of the following two issue, the evidence suggesting that PM is not impaired is questionable. First, the failure to observe

PM deficits in some studies may be explained by a reliance on tests of digit span alone. As noted previously, digit span is fairly automatized (especially digits forward). Automatized cognitive tasks do not challenge the PM system (Mack, 1986) and are, therefore, unreliable as a measure of PM.

The second issue that may have obscured the demonstration of PM impairment involves the use of mean group comparisons as the only method of analysis. If the prevalence rate of PM deficits is relatively low or the impairments are not continuously distributed across the population, then studies employing simple mean group comparisons seriously underreport deficit prevalence and/or severity. A few patients with a significantly decreased test score may not be recognized if the remaining sample test scores are sufficiently normal to compensate for the small number of patients with PM impairments and if only mean group scores are analyzed. Let us use a disturbance in micturation to exemplify the point. Matthews (1985) review of epidemiological studies reports that changes in micturation occur as an initial symptom in only 5% of all clinically-definite MS cases. Let us say that a study measured micturation as a continuous variable (as attention span is operationalized) on a sample of 100 clinically-definite MS patients and 100 normal controls. The authors would conclude that micturation is not affected in MS if only the mean scores of the two groups were compared. This would be a spurious conclusion based solely on the fact that base prevalence rate of micturation is low. Where one has an a priori belief that a low prevalence rate may abnormally

affect the power of the analysis (as was the case in our example), one must use alternative comparisons. One example would be to compare the percentage of subjects in the experimental and control groups falling below one standard deviation on the measure. Another is to use a cluster-analysis or others methods that allow comparisons of subgroups on the basis of test performance. And in fact, studies using subgroup analyses were more likely to report PM impairments (e.g., Beatty et al., 1988; Fischer, 1988; Rao, Glatt, Hammeke, McQuillen, Khatri, Rhodes, & Pollard, 1985) than those investigations that relied on a single group (e.g., Marsh, 1980).

Secondary Memory.

Before reviewing these data, recall that the tests used to measure SM also are sensitive to PM deficits. This problem has not been addressed in the MS literature, in part, because most researchers believe that MS patients do not have PM deficits. Given the cautions noted in the previous section, I believe that this is a dangerous assumption. This point aside, there is no disagreement that, in comparison to PM, impairments of SM appear to be more prevalent, consistent, and severe across all types of tests as well as patient and disease factors. It is believed that these conclusions are reliable in spite of the possible confound of inadequate controls for PM. One reason why it is believed that the conclusions are reliable is that impaired performance on supraspan memory tests are so universally reported. Another factor uses the previously described method of comparing results across tests that differentially challenge PM and SM processing. That is, if

SM deficits are relatively more frequent or severe than PM impairments, then MS patients should be particularly prone to increased task complexity.

The data appear to support this prediction. With the exception of Heaton et al., (1985), all studies testing some form of supraspan immediate recall reported deficits by their MS patients. In the case of Heaton et al., the authors simply did not report the performance of their sample on the WMS logical memory and visual reproduction subtests. Otherwise, impaired patient performance occurred whether in comparison to normal controls (Beatty & Gange, 1977; Beatty et al., 1988; Fischer, 1988; Grant et al., 1984; Litvan, Grafman, Vendrell, & Martinez, 1988a; Rao et al., 1984; Rao et al., 1989; and van den Burg et al., 1987) or non-MS patient controls (Rao et al., 1984) with verbal material (Beatty & Gange, 1977; Beatty et al., 1988; Fischer, 1988; Grant et al., 1984; Litvan et al., 1988a; Rao et al., 1984; Rao et al., 1989; van den Burg et al., 1987) or nonverbal information (Beatty et al., 1988; Fischer, 1988; and Rao et al., 1984).

MS patients consistently perform poorly on other clinical measures that tap both primary and secondary memory processes. These deficits are found whether the task was verbally (e.g., Beatty & Grange, 1977) or nonverbally mediated (e.g., Fischer, 1988); in unaided recall (e.g., van den Berg et al., 1987), paired (aided) recall (e.g., Fischer, 1988) or recognition format (e.g., Beatty et al., 1988); in single trial (e.g., Beatty & Gange, 1977) or multi-trial learning (e.g., Franklin et al., 1987); whether subjects had short (Grant et al, 1984) or long latency since

disease onset (Rao et al., 1984); or whether the patients had a remitting/relapsing (Heaton et al., 1985) or chronic progressive course (Branin, Goldenberg, Ahlers, Reisner, Neuhold, & Deeke, 1988). While studies clearly show significant intra-sample test performance variability (e.g., Fischer, 1988; Rao et al., 1984), the pattern of findings supports the hypothesis that memory deficits are more frequently seen and more severe when present as tasks increase involvement of SM. Thus, impairment is most significant on tests of delayed recall (e.g., Rao et al., 1984, 1985, & 1989), less marked with list and paired-stimuli learning (Brainin et al., 1988; Fischer, 1988; Huber et al., 1987; Litvan et al., 1988b; Rao et al., 1984), and least apparent on recognition format (Callanan et al., 1989; Carroll et al., 1984; Elpern, Gunderson, Kattah, & Kirsch, 1984; Fischer, 1988; Rao et al., 1984; van den Burg et al., 1987).

Retrieval processes have been proposed as the chief cause of SM disturbance as evidenced by less pronounced decrements in recognition versus unaided recall, increased rates of forgetting (e.g., Rao et al., 1989), and difficulties recalling even well-learned material (Petersen & Kokmen, 1989). Beatty et al.'s (1988) interesting study of retrograde, "remote" memory impairment also implicates retrieval mechanisms. They reported significant differences on a sample of 38 chronic progressive MS and 36 age- and education-matched controls using a test of famous names and events of the past.

Encoding difficulties also may occur in MS. One way in which encoding processes are implicated is that recognition

test performance may be disturbed, albeit less so than on unaided recall format tests (Petersen & Kokmen, 1989). Also, Carrol et al. (1984) observed that MS patients were less likely to use an encoding strategy in a learning task than were 22 matched controls. More importantly, even in those cases where a strategy was used, MS subjects' performance was significantly poorer than that of controls. The strongest evidence that SM may be impaired by encoding deficiencies stems from the fact that flatter than normal learning curves on multi-trial tests are almost universally found with both verbally- and nonverbally-mediated material (e.g., Fischer, 1988; Rao et al., 1984, 1989; van den Burg et al., 1987).

Our best understanding of primary and secondary memory in MS is that the prevalence and severity of SM deficits are relatively greater, but that individual variation is still high. For example, prevalence rate estimates for PM deficits range from approximately 20 (severe range) to 40 percent (mild-to-moderate range) (Fischer, 1988). Conversely, the prevalence of severe SM impairments may be as high as 40 percent (Beatty et al., 1988; Fischer, 1988) and 60 (Beatty et al., 1988), while milder deficits can approach 70 percent (Fischer, 1988). Retrieval is particularly susceptable to disturbance, although other processes necessary for intact SM functioning (e.g., attention, temporary storage, and encoding) may be affected. Increased task complexity (quantitatively, qualitatively, and temporally) may also increase the probability of disturbance. The findings reviewed above support the view that the randomness of lesion location places all memory

systems at risk. Thus, predicting which MS patients will have what types of impairments may require knowledge of lesion-specific variables (e.g, location).

Comparative Functioning

The pattern of memory deficits reported in MS does not appear to be closely related to those seen in other memory impairment syndromes and conditions. One taxonomy popular in the neuropsychological literature and applied to MS is the sub-cortical versus cortical dementia schema (e.g., Albert, Feldman, & Willis, 1974). Several authors contest the view that the cognitive changes seen in MS are consistent with a sub-cortical dementia (e.g., Cummings & Benson, 1984; Rao et al., 1986). Proponents point to the fact that, unlike the cortically demented, MS patients have relatively intact perceptual memory (e.g., Carrol et al., 1984) and recognition capacities (e.g. Rao et al., 1984), show at least some incremental learning, and perform comparatively well on delayed recall tasks. Also, MS patients infrequently exhibit signs of aphasia, apraxia, agnosia, or other symptoms of the cortical dementias (Olmos-Lau, Ginsber, & Geller, 1977; Rao, 1986). The only study specifically designed to measure cognitive impairments crucial to discriminating sub-cortical and cortical dementia in MS reported evidence supporting the subcortical hypothesis. Beatty et al. (1988) observed that, with the exception of anomic deficits (an impairment more typically seen in cortical dementia), the pattern of memory and other cognitive impairments best matched those found in sub-cortical dementia. Finally, the predominant location of lesion in white matter tracts is supportive of the

proposition.

Petersen and Kokmen (1989) protest this characterization of MS as a subcortical syndrome. Their disagreement is based primarily on a rejection of the validity of the sub-cortical/cortical distinction, rather than whether MS cognitive dysfunctions match that nosology. Petersen and Kokmen concur with others (e.g., Mack, personal communication, 1990) that the cortical - subcortical distinction lacks adequate empirical support on the basis of both functional and anatomical factors. Petersen and Kokmen review evidence suggesting that, even in those conditions archetypal of subcortical (e.g., Parkinson's disease) and cortical dementia (e.g., Alzheimer's disease), pathological involvement is located throughout the cerebrum. A mixture of cortical and sub-cortical plaque is not uncommon in MS. For example, a grey-matter prevalence rate of 94% has been reported (Lumsden, 1970). Functional differences in memory between the subcortical syndrome and MS are reported, including severity (e.g., Caine, Bamford, Schiffer, Shoulson, & Levy, 1986) and presence of PM deficits (e.g., Fischer, 1988). Overall, the controversial nature of the subcortical versus cortical dementia classification and inconsistent empirical evidence argue for extreme caution in applying the nosology to MS.

The severity and pattern of memory deficits in MS also is different from both the diencephalic and medial temporal lobe amnesias. Memory dysfunction clearly is more pronounced in the amnesias and several qualitative differences distinguish memory in MS. For example, Rao et al. (1989) note that diencephalic patients, unlike their MS

counterparts, experience almost total loss of encoding capacities. MTLA patients' recognition memory is severely impaired, suggestive of increased forgetting rates. Rao et al. (1989) suggest that MS memory impairments most closely approximate the pattern of deficits (albeit less severely) seen in Huntington's Disease (HD) in that retrieval problems occur in the absence of disturbed encoding and forgetting. I disagree with Rao et al.'s conclusions on several points. First, the marked difference in degree of impairment should not be ignored. Also, Rao et al. believe that, as is the case in HD, encoding and PM are not affected in MS -- previously presented evidence suggests otherwise. Morover, and as Rao et al. note, the quantity and quality of SM retrieval deficits seen in MS also resemble those seen in closed-head injury and normal aging. Thus, the SM retrieval problems seen in MS are not specific to HD or other subcortical dementias. Pathoanatomic differences between MS and HD (i.e., more restricted lesion location and extent in the latter) also may preclude comparability.

Controversy notwithstanding, the data do not clearly support contentions that the memory deficits in MS are comparable to those seen elsewhere. Given the gross and histological pathology differences between MS and previously described conditions, this conclusion is not particularly surprising. We will return to these structural comparisons in our discussion of patho-anatomical correlates of memory functioning because they have important implications for the use of MRI in evaluating memory changes in MS.

Predictors of Disturbance

Researchers have looked towards characteristics of MS in an attempt to account for differential changes in memory, but these efforts have been routinely unsuccessful. Only small or insignificant correlations have been found between all types of memory functioning and disease length -- whether measured by the latency since symptom onset or diagnosis (Beatty & Gange, 1977; Fischer, 1988; Grant et al., 1984; Heaton et al., 1985; Ivnik, 1978; Rao et al., 1984; Rao et al., 1985; Rao et al., 1989). These findings are entirely consistent with those for motor and perceptual disturbance correlations with the same independent variables. We can, therefore, comfortably infer that the pathological processes responsible for idiosyncratic changes in memory are not closely related to the length of time one has MS.

Disease course also has been examined as an associate of memory disturbance. Data pertinent to this question, however, are limited, contradictory, and controversial. For example, no studies have compared samples that include either the benign or acute subtypes. This leaves us in the untenable position of having to draw inferences about patho-clinical relationships from only the progressive and remittent courses -- when pathological features specific to benign and/or acute MS actually may be critical to understanding patho-clinical relationships. All but three studies either did not report course distinctions in their sample (e.g., Jambor, 1969), did not analyze the impact of course on their dependent variables (e.g., Litvan et al., 1988), or recruited subjects on the basis of having a

similar course, typically chronic-progressive (e.g., Rao et al., 1985; Franklin et al., 1988). Finally, the three studies that did examine the possible mediating effects of course on memory reported discrepant findings. Heaton et al., (1985) and van den Burg et al. (1987) found that patients with chronic progressive MS were more likely to experience memory difficulties and that these deficits are more severe in comparison to relapsing-remitting MS and normal control subjects. Conversely, Fischer's (1988) results suggest that relapsing-progressive patients, a subset of the relapsing-remitting course, are more susceptible to severe memory decline than other course types. Differences between the samples and methodologies of these studies do not allow reliable comparisons. Equivocal controls for covariance of age and other possible moderators between course and memory also make the conclusions of these studies tenuous. Given the difficulies in making accurate course determinations, it is not surprising that identifying course - memory relationships has been difficult. For example, studying asymptomatic and acutely-affected subjects presents serious methodological concerns, not the least of which is ascertaining whether such cases are, in fact, extreme examples of MS. Delineating the importance of course on memory may have to await longitudinal designs and an understanding of whether MS has inherently different subtypes.

Until recently, disease activity was largely ignored as another potential predictor of memory functioning. One reason is that the field lacks a consistent and valid operational definition of disease activity. Previous to in

vivo radiographic techniques, disease activity was inferred directly from clinical course because most laboratory techniques (e.g., CSF cell studies) were too insensitive to pathophysiological activity. That is, MS was deemed to be "active" when one had an exacerbation or de novo appearance of a symptom. As will be discussed in the section on MRI, radiographic investigation indicates that clinical and pathophysiological activity are not exactly comparable. Thus, one now must be clear to state whether disease activity was defined either clinically or radiographically. In the review below, disease activity is clinically determined.

In the memory literature, most authors do not comment on clincial activity state. Of those reporting on activity, the majority merely sampled to ensure comparability (Beatty, et al., 1988; Brainin et al., 1988; Heaton et al., 1985; Litvan et al., 1988b; van den Burg et al., 1987). Fischer (1988) did analyze whether symptom activity helped account for placement into one of three memory functioning subtypes. Eighty-nine percent of the subjects who clustered in the most impaired group had an active disease state; however, activity did not differ significantly in the other two (less impaired) clusters. No other comparisons were made, nor does Fischer make clear the criteria used for "active/non-active" status. Lyon-Caen et al. (1986) found no significant relationship between the degree of memory impairment and disease activity in their sample of 21 "recent-onset" MS subjects. It is difficult to draw conclusions from this study also because the authors do not explain their "acute active", "remission", and "clinically

inactive" designations. Also, their sample may have included some non-MS cases of demyelinating disease, since 10 subjects were only "probable" MS (Poser criteria). Grant et al. (1984) did find a limited relationship between an "active" disease state and susceptibility to interference effects on a Brown-Peterson memory task. However, disease activity did not predict Wechsler Memory Scale (WMS) scores. Generalization of their results is problematic given the lack of explicit inclusion criteria and use of 11 subjects with only "probable" MS (McDonald system) in their prospective sample. Finally, Callanan et al. (1989) found no relationship between "stable versus relapse" status and various aspects of memory functioning, although there was a significant correlation between being in relapse and decreased intelligence as measured by an IQ deficit score. Inferences drawn from these findings are limited because their prospective sample necessitated inclusion of subjects without confirmed MS. However, Callanan et al. (1989) did describe their criteria for clinical relapse (Poser et al., 1983).

In summary, the absence or presence of clinical exacerbation (of any kind) does not appear to predict memory test performance. But because of cursory treatment, frequent use of subject populations only in the early stages of MS, and inadequately described operationalization of disease activity, the question is neither answered nor adequately investigated. One other point requires comment and that concerns controlling for decreased memory performance secondary to the effects of clinical relapse and/or chronic disability. That is, memory can be impaired

by the general effects of being sick (e.g., increased distractibility; decreased effort) regardless of the type of illness. Therefore, decreased memory test performance during a period of exacerbation relative to a period of remittence simply may not be due to the effects of demyelination per se, but to the general deleterious effects of disease on memory. Comparison with numerous control subject population types (e.g. muscular dystrophy) with general disease sequelae similar to MS suggests that the memory changes seen in MS are not a secondary phenomenon (e.g., Jambor, 1969). However, it is not clear how to control for general illness effects within MS samples. One would have to find another condition with a relapsing - remitting course but without primary deficits of memory or other cognitive features.

Investigators also have explored co-ocurring motor, perceptual, and psychiatric symptoms as predictors of memory dysfunction. Changes in memory appear unrelated to the physical severity of illness as measured by the Kurtzke EDSS or other global measures of motor and sensory functioning (e.g., Fischer, 1988; Heaton et al., 1985; Litvan et al., 1988a; Rao et al., 1984, Rao et al., 1985; Rao et al., 1989). The two studies that did observe a significant positive correlation between physical and memory debilities (van den Burg et al., 1987; Grant et al., 1984) used a more restricted sample (i.e., subjects less severely physically disabled or "enrolled in the early phases of disease") than the samples used in investigations not reporting such a relationship. Also, it is not clear, theoretically, why only early/less severe physical symptoms would be

significantly related to memory functioning.

Depression also does not appear to predict memory deficits, although other psychiatric symptoms may. Depression correlates have been frequently studied and found not to be related to the presence or severity of memory dysfunction. For example, Rao et al. (1989) found no correlation between scores on the Zung Depression scale and performance on an array of memory tests even though the MS group was significantly more depressed. Similarly, Zambor's (1969) well-designed study contrasting MS subjects with and without anxiety or depression observed that the anxious/depressed group actually performed <u>better</u> on various measures of memory than the MS group. Zambor concluded that the "...cognitive impairment [including memory] of patients suffering from multiple sclerosis, particularly if present to a marked degree, is unlikely to be due to concommitant mood disturbances" (pg. 775). Fischer (1988) found no significant relationship between the Beck Depression Inventory (BDI) and degree of memory disturbance as marked by placement into one of three subgroups based on performance on the Wechsler Memory Scale - Revised (WMS-R). Beatty et al.'s (1988) study, alone, reported a significant correlation between depression (as measured by the BDI) and memory deficits. It is difficult to resolve these findings with those reported earlier, especially Fischer's, since both used the BDI to measure depression.

There has been limited demonstration of a correlation between memory disturbance and emotional symptoms other than depression. For example, Rao et al. (1984) found "atypical" MMPI profiles indicative of emotional disturbance in a

subgroup that performed most poorly on a battery of memory tests. These results are consistent with Lyon-Caen et al.'s (1986) study, which concluded that "...qualitative mood abnormalities [i.e., emotional expressiveness, reactivity, and overall lability] were closely correlated with the presence of cognitive and memory disturbances; thus, ten of 14 patients with mood abnormalities also exhibited signs of cognitive impairment" (p. 1139). Overall, there are insufficient data with which to conclude, reliably, that non-depressive emotional problems are related to memory difficulties. Several criticisms of this line of investigation have been forwarded, including the previously described issue of sorting out primary from secondary effects of illness on memory. Also, it is difficult to imagine that the processes responsible for memory disturbance are directly related to those for psychiatric morbidity. There is little evidence to suggest that the pathophysiological changes responsible for memory deficits are the same (e.g., lesion location) as those for emotional distress. Moreover, several variables important to psychiatric morbidity (e.g., personality structure) are not particularly relevant to intact memory functioning. Thus, even if a relationship between memory and psychiatric symptoms was demonstrated, it is not clear how this information could be useful in determing the associations between MS pathology and memory.

To summarize, researchers have looked at the type, severity, and course of several disease characterisitics in hopes of understanding variations in MS memory functioning. The data strongly disconfirm disease length and co-occurring

motor/perceptual disturbances as reliable predictors. The case for disease course and activity and psychiatric symptomology is less clear, but evidence will now be presented that suggests that aspects of lesion dissemination factors (e.g., extent, location, and temporal changes) are more likely to account for memory dysfunction than are the factors noted above.

Pathoanatomical Relationships to Memory Disturbance

Introduction.

Relatively little is known about memory functioning in MS. Linking pathoanatomical with functional memory changes offers hope in understanding the causes of memory impairment and its widespread variability. Associating MS pathology with clinical manifestations regardless of function area is, however, in its formative stages. For example, the latest edition of McAlpine's Multiple Sclerosis (1985) commits but four paragraphs to the topic. This neglect is not purposeful but, rather, reflects prominent methodological and substantive issues.

Until quite recently, studies attempting to discern important patho-clinical features were limited to correlating past symptomology with postmortem examination (Charcot, 1877; Dawson, 1916; Namerow & Thompson, 1969), and these investigators found few consistencies between pathology and symptomology (Field, 1988). For example, with the exception of some brain stem and optic tract lesions, plaque location did not correlate significantly with the appearance of many sensory and motor deficits (Namerow & Thompson, 1969). Further, numerous studies have reported

the existence of clinically "silent" lesions; sometimes extensive areas of plaque were found at autopsy without apparent accompanying symptomology (e.g., Castaigne, Lhermitte, Escourelle, Hauw, Gray, & Lyon-Caen, 1981; MacKay & Hirano, 1967; Morariu & Klutzow, 1976).

Poser (1980) and others have turned to environmental factors in hopes of explaining why structural and functional changes are frequently inconsistent. Emotional stress, physical trauma, exercise, and temperature correlate positively with symptom relapse, exacerbation, and/or de novo appearance (Matthews, 1985). The natural history of lesions such as seen in acute versus chronic plaques (Weller, 1985) and antibody-response effects on neurons (see Field, 1989) also are thought to mediate the relationship between structural and clinical changes. The exact mechanisms for these associations are poorly understood and several counterarguments to environment-as-mediator models have been offered. One is that some lesions do immediately produce observable clinical manifestations; thus, environmental influences are not always necessary (Hallpike, 1983). Secondly, centrifugal spread of lesions, remyelination, and other properties of deteriorated conduction may be more closely tied to the lack of more consistent patho-clinical changes than are environmental factors (Rao, 1986).

Others have cited the poor quality of investigations to explain lower than expected correlations between observed lesion and functioning. One such argument is that current methods of clinical assessment may not be sufficiently sensitive to detect more subtle and/or early-stage symptoms.

This criticism is unsurprising given earlier comments about the difficulties inherent in diagnosing MS, and is especially less so when one considers that a majority of studies were retrospective analyses -- correlating symptoms with autopsy confirmation of plaque extent and location. Attempting to verify symptoms that frequently date back scores of years is an insurmountable reliability problem. One cannot be sure that the pathology observed post-mortem is equivalent to that of in-vivo lesion. Any differences between the two could obscure significant clinico-pathology associations. Simply put, autopsy studies are inadequate to deal with the task at hand. Aside from these issues of reliability and validity, no autopsy investigations could be found that correlated neuropathology with memory functioning. Thus, in-vivo investigation is both logical and mandatory.

The scientific community has long awaited the advance of evaluation tools capable of such in-vivo lesion assessment. Techniques such as X-ray, pneumoencephalography, angiography, and radioisotope scanning (including positron emission tomography -- PET) were tried soon after they became available. However, these procedures were deemed useful only in aiding differential diagnosis because MS lesions usually were not evidenced and only general signs of atrophy could be reliably gleaned from these procedures (Ormerod, du Boulay, & McDonald, 1986).

Computerized axial tomography (CT) proved to be considerably more sensitive and, for the first time, MS lesions could be non-invasively visualized (Cala & Mastaglia, 1976) and correlated with clinical symptoms

(e.g., Rao et al., 1985). CT-imaged plaque has been confirmed at autopsy (Wurthrich, Gigli, Wiggli, Muller, Elke, & Hunig, 1976) and a predilection for lesions in the periventricular white-matter corroborate post-mortem examinations (Delouvrier, Tritschler, Desbeldes, Cambier, & Nahum, 1980). Some inroads were made with CT in understanding the relationship between lesion and dysfunction (De Weerd, 1979; Hershey, Gado, & Trotter, 1979; Rao et al., 1985). For example, Rao et al. (1985) found that increased ventrical enlargement was associated with decreased memory and other cognitive capacities. However, concurrent investigations demonstrated serious limitations in CT imaging and these problems have prevented CT from becoming a reliable procedure for studies of MS.

One shortcoming of CT is that ventrical hypertrophy and cortical hypotrophy are more often detected than specific MS lesions (Gyldensted, 1976; Jacob & Kinkel, 1976). Such general measures of pathology lack the specificity needed for more accurate description of patho-clinical relationships (Rao et al. 1985). Some individual plaques can be observed via CT, but their number and size are often grossly underestimated. For example, Haughton, Williams, and Eldevik's (1979) study correlating CT sensitivity with post-mortem examination found that lesions less than 7 mm are not visualized on CT, and that even larger lesions can be missed if located near the lateral ventricles -- a frequent site of plaque. A large proportion of subjects may not show positive scans with estimates ranging from 65% (Cala, Mastatglia, & Black, 1978) to 89% (Hershey et al., 1979) of all probable MS cases, and as high as 75% in

clinically definite-MS (Paty, Oger, Kastrukoff, Hashimoto, Hooge, Eisen, Eisen, Purves, Low, Branddejs, Robertson, & Li, 1988; Sheldon, Disshathan, Tobias, Sheremata, Soila, & Viamonte, 1985). Sophisticated enhancing media and delayed-scanning procedures can bolster CT sensitivity, but these benefits usually are limited to severe, acute cases and still fail to adequately account for the entire pathological picture even in these cases (Matthews, 1985). Other limitations of CT include a restriction to axial-plane views and to the fact that CT is particularly insensitive to lesions in the brainstem and optic tracts -- two frequent sites of MS plaque (Ormerod et al., 1986). Despite these shortcomings and in the absence of alternatives, CT would have continued to be the technique of choice had MRI not appeared on the scene. The latter's imaging superiority was readily apparent, however, and soon replaced CT in many clinical and research settings.

MRI Physics

Some working knowledge of MRI is warranted at this juncture. More extensive treatment than is provided below may be found in Elster (1988), Elster, Handel, and Goldman (1986), Stark and Bradley (1988), and Young (1984).

MRI is based on measurement of electromagnetic features of particular atomic nuclei. Hydrogen is almost exclusively used in clinical settings because of its ubiquitousness within the human body and because its most abundant isotope has the odd-number of protons or neutrons required by the process. The subject is placed within a powerful magnetic field, which aligns the hydrogen nuclei into static parallel vectors. A second magnetic source then introduces a pulse

of energy (radiofrequency pulse or RF) at a certain frequency (known as the resonance frequency) and at a vector perpendicular (90 degrees) to the original static field. Explainable via quantum physics, the beginning and end of the RF burst results in the absorption and re-emission of the electromagnetic energy as nuclei change quantum levels. This process is described as nuclear magnetic resonance. Movement amoung quantum levels causes detectable changes in the vectors of the hydrogen nuclei (aligning "in phase" with the RF pulse vector and perpindicular to the original static field vector). This, in turn, produces measurable signals picked up by a receiver coil. Signal characteristics are determined by the proton density (proportion of protons) of the tissues involved and two measures of nuclei relaxation, T1 and T2. The relaxation times represent the interval from the end of the RF pulse until the absorbed energy is released and is a function of neighboring nuclei's re-emission efficiency (T1), while T2 is the relative robustness towards returning to the original vector (i.e., loss of "in-phase" alignment with the RF pulse). For any given static magnetic field strength, various media (i.e., CSF, myelin, and grey matter) have different but relatively constant T1, and T2 values. For example, the lipids in myelin are much more efficient in transferring energy in comparison to CSF and grey matter and, therefore, have shorter T1 relaxation times. T2 times are more dependent on the proton density of the medium such that liquids, with less hydrogen per volume (e.g., CSF), have longer values than the relatively proton-dense structure of solids such as white matter and muscle. Scanning parameters are

manipulated to provide varying degrees of contrast between tissue types (including pathological tissue) via differences in proton density and T1 and T2 times according to the needs of the user. Different relaxation times and proton densities are seen in varying shades of grey (from black to white) as computer programs translate the information from the receiver coils onto X-ray film.

Aside from physical properties inherent in the process, operator-controlled variables also determine image characteristics. These include: pulse sequence, pulse time intervals, number of signal averages, slice thickness, matrix size, image plane, "windowing", and field of view.

The pattern of RF pulses used is known by its pulse sequence. To improve signal quality, typically more than one RF pulse is applied to the static magnetic field and the entire process (or sequence) may be repeated. Partial saturation (PS), inversion recovery (IR), and spin-echo (SE) are the most common patterns of RF pulse latencies and sequences used in clinical settings. Spin-echo is the sequence of choice for MS because it provides information about tissue T2 values in addition to proton density and T1 values. The former is particularly important since it has been found to be most sensitive to pathology (Elster et al., 1987) and IR and PS sequences are not especially geared for T2 measurements (Stark & Bradley, 1988). The spin-echo technique starts with a 90 degree RF pulse, which, as described before, synchronizes the nuclei into a vector perpendicular to the static field vector. This synchronization pulse is followed by a pulse of 180 degrees -- which helps minimize background noise -- and the

resulting "echo" signal is then measured. Subsequent repetitions of the rephasing pulse with its attendent echo signal (known as multi-echo sequencing) have been found to improve imaging quality, especially for MS imaging uses. Other factors, however, limit its usefulness beyond two or four echoes.

Two pulse time sequences are important to the multi-echo technique. TE (echo time) is the time between the synchronizing (90 degree) and the echo signal. TR (repetition time) marks the latency between the synchronizing (90 degree) pulses. By varying TE and TR, the operator takes advantage of proton density and T1 and T2 tissues differences to create contrasts suited for his/her needs. For example, "long" TE's (i.e., > 75 msec) combined with "long" TR's (i.e., > 2000 msec) produce a T2-weighted image, more sensitive to variations in T2 relaxation times than either T1 or proton density values. Numerous investigations have shown that such T_2-weighted, compared to proton density- and T_1-weighted images, are more efficient in detecting MS lesions (e.g., Robertson, Li, Mayo, Genton, & Paty, 1985; Smith, Weinstein, Modic, Pavlicek, Rogers, Budd, Bukowski, Purvis, Weick, & Duchesneau, 1985). If the T_2 weighting is too heavy, however, MS lesions can become indistinguishible from the CSF found in the ventricles. This can be remedied by using a multi-echo series and specifying long, medium, and short TE's in combination with a long TR. Comparing this series of progressively lighter T2-loads allows better contrast between CSF and MS lesion and, in general, greater ability to visulize more subtle lesions. Hence, Stark and Bradley (1988) recommend multi-

echoes with TE set near 30, 60, and 90 msec and TR values from between 2000 and 3000 msec for MS scanning purposes.

Multiple signals (i.e., signal averaging) can be used to derive composite images superior to that produced from one signal. Marginal utility quickly decreases though because as the number of signals increases, imaging time rises exponentially and movement artifacts become more likely (movements by the patient during imaging can seriously blur the image). The concern with imaging time is not misspent, since per hour scanner charges can run as high as $2,000 and research scanning protocols lasting longer than 30 minutes are common. Furthermore, the scanning bore -- where the patient lies during the imaging process -- is uncomfortably tight for many. Patient comfort and ability to remain motionless, therefore, decrease as imaging time increases. Signal averages are determined by the cost-benefit ratio needs of the operator and are usually set at two or four.

Manipulation of slice thickness and matrix size also seriously escalate costs for fairly small increases in visual quality. Most scanners obtain slices from 2 mm to 10 mm thick. More tissue area can be seen and in better detail with thin slices but with marked increases in imaging time and noise-to-signal ratios. Similarly, greater matrix size increases spatial resolution, but with scanning time and noise-to-signal ratio increase. Most matrices are 128 x 128, 128 x 256, and 256 x 256 and produce picture elements (i.e., pixels) ranging from 1.7 to 0.8 mm, respectively.

Unlike CT, MRI can produce images from the axial, sagittal, and coronal plane with equal facility. Choice of

scanning, from one to all planes, depends on the needs and resources of the operator. A review of research protocols indicates that axial views are almost universally used, occasionally complemented by sagittal (especially where evaluation of the brainstem and spinal cord is critical) and coronal cuts (e.g., orbital/optic tract assessment). The reliance on axial projections is a carryover from radiologists' previous experience with CT, although axial cuts actually are preferred for many MS applications. For example, the periventricular regions are especially well-visualized axially. Compared to other more focally distributed pathologies, choice of plane is not as critical for MS. Ideally, MS protocols would include series from all three planes; however, scanning costs often prevent such comprehensive coverage.

The size of area to be imaged also is under operator control and can be manipulated to improve imaging quality. The field of view is roughly spheroid with a diameter ranging from 10 to 30 mm (Elster, 1988). For ideal scanning, the field of view should coincide with the size of the structure imaged. The only significant restraint is that the field of view must be at least as large as the target structure; if not, a "fold-over" artifact will result (Stark & Bradley, 1988). For most cranial protocols, the field of view is set near 25 cm (Elster, 1988).

With this introduction, let us turn to applications of MRI to MS and memory.

MS Applications

MRI was first used in conjunction with MS by Young, Hall, Pallis, Legg, Bydder, and Steiner, (1981). They

compared both normal and contrast-enhanced CT with MRI scans on 10 MS patients. In addition to the 19 lesions seen on CT, 112 other plauqes also were identified by MRI. Subsequent studies have confirmed MRI's superior sensitivity to CT for most MS-related imaging (e.g., Gerbarski, Gabrielsen, Gilman, Knake, Latack, & Aisen, 1985; Lukes, Crooks, Aminoff, Kaufman, Panitch, Mills, & Norman, 1983; Paty, Oger, Kastrukoff et al., 1988; Sheldon et al., 1985; Smith, Weinstein, Modic et al., 1985).

Considerable evidence indicates that the signal-contrasted areas seen on MRI are, at least in part, MS plaque. MRI-imaged in-vivo lesions correspond to histological examination at autopsy (Ormerod, Miller, McDonald, Boulay, Rudge, Kendall, Moseley, Johnson, Tofts, Halliday, Bronstein, Scaravilli, Harding, Barnes, & Zilka, 1987), post-mortem MRI scanning (Stewart, Hall, Berry, & Paty, 1984) and previous autopsy descriptions (e.g., Brownell & Hughes, 1962; Fog, 1965) of plaque site, size, and the like. MRI-imaged lesions also coincide with previous evidence of MS predelection for certain sites. For example, most MRI observed plaque is found in the periventricular regions, centrum semiovale, brain stem, and cerebellum (Ormerod et al., 1986). Cerebral and corpus collosal atrophy, ventricle hypertrophy, and spinal cord, basal ganglia, and some grey-matter involvement also are seen on MRI (e.g., Elster, 1988; Stark & Bradley, 1988).

The exact nature of the pathological changes seen on MRI have not been confirmed. MS plaque show as different T1 and T2 relaxation times relative to surrounding tissue; for example, increased T1 and T2 versus healthy white matter

(Stark & Bradely, 1988). Disease activity has been proposed as responsible for signal differences where general inflamation, disruption of the blood-brain barrier (BBB), and increased unbound water from edema mark acute lesions. Demeylination and gliosis are thought to be responsible for the signal contrast between chronic plaque and normal tissue on MRI. Ormerod et al. (1987) present conceptual and emprirical support for a slightly different model. These authors hypothesized that the gliosis prominent in chronic plaques certainly results in direct changes in signal characteristics. That is, increased plaque T2 values occur because gliosal tissue contains more water per unit volume (hence more hydrogen protons) and possibly in a form more easily imaged (i.e., more dense macromolecular state) than the normal myelin it replaces. Ormerod et al.'s (1987) histological examination of post-mortem brains found positive MRI signal correlates with glial growth. This finding, in combination with previous evidence of increased water per unit volume in MS lesions with significant gliosis (Tourtellote & Parker, 1968), strongly affirms that portion of their model pertaining to signal characteristics of gliosis. In contrast to other theories, Ormerod et al. do not believe that relaxation time differences between chronic plaque and normal tissue are due directly to the loss of myelin. This portion of their model is supported by evidence by Pykett and Rosen (1983) and Bottomley, Hart, Edelstein, Schenck, Smith, Leue, Mueller, and Redington (1984) that the number of hydrogen protons in myelin is proportionately smaller than that in surrounding tissues such that hydrogen proton loss contributes minimally to MRI

signal. Ormerod et al. (1987) do note that changes secondary to the loss of myelin (i.e., replacement of myelin by non-gliosal tissue with imaging qualities similar to gliosis) also may occur, which produce the signal contrast associated with chronic plaque. Larsson, Frederiksen, Kjaer, Henriksen, and Olesen's (1988) careful study of MRI signal characterisitics in MS and normal control subjects revealed that plaque T1 and T2 values vary considerably between and within subjects -- a finding consistent with Ormerod et al.'s disease activity hypothesis. However, neither Ormerod et al. (1987) nor Larsson et al.'s (1988) could seperate MRI signal into those processes attributable to gliosis versus possible secondary effects of demyelination. In summary, gliosis clearly contributes to MRI signal changes associated with chronic plaque. However, evidence is lacking as to whether myelin loss per se also produces MRI signal differences or whether non-gliosal changes secondary to demyelination also are at work.

In support of the acute lesion portion of the model, Ormerod et al. (1987) cite experimentally-induced edema- and glial-producing pathologies (e.g., tin intoxication) in cats. Acute and chronic plaque relaxation times could be differentiated presumably on the basis of water content, macromolecular structure, disrupted BBB, and other intra- and inter-cellular sequelae known to occur from such insult (e.g., Barnes, McDonald, Johnson, Tofts, & Landon, 1987). Based on previous histological evidence of similar tissue changes associated with active MS lesion (Adams, 1983; Weller, 1985), Ormerod et al. suggest that these processes (i.e., water content, macromolecular structure, disrupted

BBB) result in the MRI signals observed in acute lesions. The fact that gadolinium enhancement differentiates active from inactive lesion, where the enhancement medium is able to pass the disrupted BBB in active lesions (Grossman, Gonsalez-Scarano, Atlas, Galetta, & Silverberg, 1986) also supports the notion that different histo-pathological processes are at work in producing the similar imaging (noncontrast) characteristics in acute versus chronic plaque.

Moving from a description of "what" is imaged to temporal considerations, changes in lesion size are an excellent source of information regarding the natural history of MS. Longitudinal, multi-study MRI investigations are able to track disease activity through the observation of lesion flux over the period of a few months. Uhlenbrock, Seidel, Gehlen, Beyer, Haan, Dickman, Zeit, and Herbe (1988) imaged 22 MS patients during acute relapse and at two subsequent times -- four to six weeks and three months after the initial MRI. Between the first and second and second and third scannings:

- roughly 75% of the lesions did not change size
- 5 - 7% decreased in size
- 4 - 10% increased in size
- 41 lesions disappeared
- 34 new lesions appeared

These variations in lesion size are indicative of disease activity; the waxing and waning probably correspond to the acute changes (e.g., the appearance and disappearance of edemal-related substances) as noted by Adams (1983).

Subsequent studies by Isaac, Li, Genton, Jardine,

Grochowski, Palmer, Kastrukoff, Oger, and Paty (1988), Kappos, Stadtr, Ratzka, Keil, Schneiderbanger-Grygier, Heitzer, Poser, and Nadjm (1988), and Willoughby, Grochowski, Li, Oger, Kastrukoff, and Paty (1989) suggest that new plaque growth maximizes between one and two months and gradually fades in signal intensity until plateau after two to four months. Relatively large, acute plaques frequently left residual MRI-signal comparable to those of unvarying and presumably chronic lesions. Smaller lesions often disappeared entirely, but such evidence certainly does not rule out the possibility that microscopic changes remained. Willoughby et al. (1989) observed that acute lesions tended to arise from "healthy" white-matter tissue. However, they also appeared from previously stable chronic-lesion areas. In line with the disease activity model, these authors suggest that edema, and, possibly, secondary demyelination effects were responsible for the period of greatest lesion signal-intensity. Given the similarity of relaxation times between non-fluxing and the residual plaques, Willoughby et al. (1989) suggested that:

> "...the expanding and contrasting new lesions are the basic or primary lesion in MS, that the characteristic demyelinated plaque is represented by the small residual area that these lesions shrink down to, and that the typical collection of scattered white-matter lesions in chronic MS may represent the accumulated residua of dozens or more of these active lesions occurring over many years " (p. 43).

When combined with previously described evidence that morphological alterations occur on a histological level in tissue that had been previously described as unaffected upon gross analysis (e.g., Adams, 1983) longitudinal data indicate that early-stage and/or more subtle pathological

alterations are not always seen via MRI. Also, the microscopic changes associated with pathological activity cannot be verified via visual inspection of MRI at this time. For example, end-stage gliosis appears almost identically on MRI as resolved, formerly acute lesions. As a result we can infer progressions in disease activity from multi-study MRI, but not the pathological changes underlying such activity.

Longitudinal investigations also have observed that pathological changes are independent within a given patient. That is, lesion growth occurs simultaneously with shrinkage in other plaques, while still other lesions will show no evidence of change (e.g., Willoughby et al., 1989). This finding supports the hypothesis that pathogenic factors are localized; however, proponents of the diffuse pathogenesis model (e.g., Adams) can argue otherwise. Visual analyses of MRI detect only more macro-level changes. Yet, histological deterioration could occur throughout the CNS in a diffuse manner (as is hinted at in the preliminary analyses of white matter relaxation times by Larsson et al., 1988) without being observed by MRI.

Although strongly suggestive, verification of disease activity's impact on MRI signal via multi-study designs is incomplete and hindered by the same methodological issues noted with single-study MRI. First, no current techniques exist that can cross-validate acute pathophysiological effects on MRI signal. Post-mortem examinations, for example, are unable to track acute changes (Isaac et al., 1988). Conversely, although lipid loss <u>is</u> measurable at autopsy (Stewart et al., 1986), lipid loss is not seen

easily in vivo MRI (Ormerod et al., 1987). Separating signal attributable to glial growth from non-glial tissue gains or actual myelin loss remains undemonstrated even with multi-study designs.

Numerous studies confirm MRI's superiority to CT in detecting MS plaques and providing diagnostic evidence complementary to clinical history (e.g., Gerbarski et al., 1985; Paty et al., 1988). Two exceptions to this superiority lessen MRI's usefullness in describing lesion - function associations. One is that, like CT, MRI is relatively poor at detecting lesions in the optic nerves and chiasm and to a lesser degree the spinal cord -- all high predilection areas for MS lesion (Gerbarski et al., 1985; Sheldon et al., 1985; Stevens, Farlow, Edwards, & Yu, 1986). Stevens et al. (1986) have suggested that MRI's insensitivity to these locations may help explain the frequent failure of attempts to correlate lesion burden with sensory and motor deficits. Typical measures of functioning (e.g., Kurtske DSS and EDSS, and clinical history) are heavily influenced by optic and spinal functioning changes, whereas the pathology in these regions is frequently missed by MRI. Spuriously low correlations between lesion and function will continue unless the over-weighting of sensory and motor manisfestations on functioning indices is somehow balanced. Recent advances in scanning parameters and hardware have improved imaging of the spinal cord, especially the cervical region (Stark & Bradley, 1988); however, the possibility of missing plaque in hard-to-image locales remains frustratingly high.

The second caution regarding over-optimistic use of MRI

returns us to the earlier discussion on disease activity and MRI signal. Non-enhanced MRI is not reliable in visually discriminating acute versus chronic areas of demyelination on a single study (non-visual methods may be an exception and will be discussed below) (Ebers, Paty, & Sears 1984). And although gadolinium-enhanced (e.g., Grossman et al., 1986) and serial MRI scans (e.g., Uhlenbrock et al., 1988) can discern inactive from active plaques, these methods incur considerable tradeoffs. Gadolinium enhancement is an invasive procedure with attending increases in time, money, and subject discomfort and complications. Prospective, serial scanning also entails considerable additions in study time and cost. Thus, the traditional, one-time, cross-sectional MRI study is more frequently used in spite of its unselectiveness with respect to disease activity.

This practice may hamper investigation of structural-functional correlates. If it is determined that different stages of disease activity produce dissimilar effects on clinical functioning, then cross-sectional MRI investigations may be insufficent for describing the association between pathological and functional alterations. At the very least, understanding the relationship between disease activity and functioning will help us draw reliable inferences from single-study MRI investigations.

Many efforts to describe the relationship between pathophysiology and functional changes have been insidiously confounded. Prior to MRI, disease activity was inferred from the increase in or appearance of clinical manifestations, in part because laboratory techniques were unreliable in determining disease activity (e.g.,

oligodendroglial bands in the CSF). Symptoms were assumed to reflect pathophysiological activity; however, this logic is circular. One cannot determine the relationship between disease activity and clinical changes if disease activity is defined merely from evidence of the latter. Fortunately, three types of MRI investigation provide an indicator of pathophysiological change independent of clinical functioning: nonvisual comparisons of relaxation times, gadolinium-enhanced MRI, and multiple-study MRI. These data suggest that the relationship between lesion activity and function is not so clear, nor so strong as was originally hypothesized.

Ormerod et al. (1987) and Larsson et al. (1988) scanned a variety of tissues in samples of MS and control patients. Rather than translating the information to visually-inspectable X-ray film, they recorded the T1 and T2 relaxation times on computer for statistical comparisons. Both investigations found that the relaxation times of plaques differed markedly within subjects and in a pattern that could predict disease activity. The results also suggested that the direct analysis of relaxation times is more sensitive to pathological changes than is visual inspection and that disease activity can be discerned with a single (nonenhanced) scan. Most importantly, Larsson et al.'s (1988) study indicated that significant lesion activity did not affect functioning. Subjects were chosen specifically not to have had any clinical episodes in the previous 12 months. Thus, changes in relaxation time indicative of pathophysiological activity occurred independently of alterations in function. Additional

confirmation is needed before moving on this important finding, especially in light of apparently contradictory results with gadolinium enhancement. Also, because Larson et al.'s sample did have stable clinical manifestations, one cannot draw inferences about how different phases of pathological activity can be associated with unchanging symptoms.

Of value in a later discussion, Ormerod et al. (1986) and Larsson et al. (1988) also found that what was though to be "healthy" (undetectable via visual examination of MRI) white-matter of MS patients was significantly different from that of normal controls and in the direction expected if this white-matter were undergoing early-stage deterioration. Moreover, relaxation times of "healthy" versus "involved" tissue overlapped with a wide variation within subjects. These results tie in nicely with Adams' (1983) assertion that MS is a diffuse, rather than, multi-focal process. The implications for memory deficit/lesion relationships will be addressed below.

Longitudinal investigations also report minimal correlations between lesion activity and symptoms. Isaac et al. (1988), Paty et al., (1988), Uhlenbrock et al. (1988), and Willoughby et al. (1989) observed no correspondence between lesion changes (over one to six months) and the appearance of de novo and/or exacerbation of old symptoms. The consensus of these data, in combination with nonvisual relaxation time studies, strongly indicates that MRI observed lesion activity is not significantly associated with alterations in function.

In contrast to direct relaxation time and longitudinal

investigations, gadolinium-enhanced MRI studies provide stronger support for a relationship between disease activity and clincial manifestations. For example, Grossman et al. (1986) observed that lesion enhancement (i.e., active plaque) occurred in a majority of patients in clinical relapse. Brorson, Braffman, Grossman, Silberberg, and Gonzalez-Scarano (1988) found that the number of enhancing lesions was positively and significantly correlated with clinically-derived disease activity in a study of 45 clinically definite MS patients. However, both studies also reported enhancing plaques in patients who were in remission. Thus, enhancement is not specific with respect to symptom exacerbation.

In summary, three types of MRI study provide contradictory evidence that lesion activity is associated with symptom appearance. A case could be made for a relationship between new clinical manifestations and acute plaque processes based on the gadolinium studies. However, gadolinium study is not consistent with the other two methods and none of the three sources have disease activity relationships to stable deficits. Before concluding that pathophysiological activity is not particularly relevant to functioning, one must consider the following issues.

First, disease activity effects on functioning need not be an all-or-none phenomenon but can be viewed as one of many factors contributing to the appearance of dysfunction. For example, many would argue that lesion characteristics (e.g., size and location) and subject factors (e.g., current level of stress) affects the possibility of symptom appearance. Secondly, the literature is filled with reports

of asymptomatic lesions, presumably both active and inactive plaque (e.g., Koopsman, Li, Grochowski, Cutler, & Paty, 1989). We do not understand why only some lesions produce impairments, but for the plaques that do, we may find that different processes are responsible for functional changes and disease activity may be involved only in some subset of those processes. For example, increased glial scarring may increase blockage of neural transmission in chronic plaque -- a process that is not associated with acute disease activity. Also, the edema produced during an active phase of the disease may prevent communication in only some neural tracts, those already weakened by previous bouts of demyelination. Thus, while disease activity may not be related to all lesion effects on functioning, it may be related to some. As Ormerod et al. (1987) nicely summarize:

> "The failure to identify an abnormality after the acute development of a symptom may not mean that none was present earlier or that none will be obvious later; and the apparent disappearance of a lesion...need not imply resolution of the pathological changes with restoration of normal structure." (p. 1612)

Common sense dictates that some aspects of pathophysiological activity contribute to dysfunction despite our inability currently to characterise them with any degree of certainty. Teuber's dictum holds true here: a lack of evidence for a relationship is not evidence that the relationship does not exist. All three methods hold great promise for the future and should be vigorously pursued.

Given the probable lack of one-to-one correspondence between pathophysiological lesion activity and symptom, disease activity designations must be made more carefully. Disease activity may refer to either clinical or

pathophysiological dynamics. The data suggest that for any given clinical relapse (acute symptomology), lesions may be both active (acute) and inactive (chronic). Similarly, patients in "clinical remission" may have both active and inactive lesions.

A final comment concerns possible differences between cross-sectional and longitudinal MRI studies. Lesion - function studies frequently involve some measurement of the amount of pathology involved. Given Isaac et al.'s (1988) and others findings that plaque number and size change over a few months, one might infer that cross-sectional study is unreliable because it cannot speak to these variations. That is, single-study MRI may over- or under-estimate total lesion burden depending on the state of disease activity of the patient when imaged. A number of factors, however, argue against such a conclusion. First, prospective studies have shown that the evolution of plaques is independent within subjects. Lesions may grow, shrink, appear, and/or disappear concurrently (Willoughby et al., 1989). Thus, gains and losses in total lesion volume should balance to some degree with the aggregate total remaining relatively stable -- at least for latencies less than one year and across relatively large areas of the CNS. Preliminary results support this hypothesis, as the actual amount of lesion volume change is relatively small. For example, Isaac et al. (1989) observed seven subjects over six months and found that total lesion volume (mm^2) differed by no more than 13% for any given subject, a statistically insignificant difference when compared with total lesion volume. This figure is comparable to the 14 - 15% lesion

volume change observed by Kappos et al. (1988) in 74 MS subjects scanned five to seven months apart during two medication trials. Although methodological concerns reduce the reliability of both studies, their results suggest that longitudinal and cross-sectional studies will obtain similar estimates of lesion burden. Finally, this investigation's hypotheses are based on the premise that lesion burden is correlated with memory functioning at any given point in time. Cross-sectional MRI is an appropriate procedure for testing such a premise. Whether multiple-study measures of lesion burden are more effective than single-study design in accounting for variations in functioning is a separate empirical question.

Motor and Sensory Functioning

Reports of the strength of the relationship between MRI-imaged pathology and motor and sensory symptoms have varied from negligible (e.g., Crisp, Kleiner, DeFillip, Greenstein, Liu, & Sommers, 1985; Kiel, Greenspun, & Grossman, 1988; Kirshner, Tsai, Runge, & Price, 1985) to significant (Bogousslavsky, Fox, Carey, Vinitski, Bass, Noseworthy, Ebers, and Barnett, 1986; Edwards, Farlow, & Stevens, 1986; Jacobs, Kinkel, Polachini, & Kinkel, 1986; Matias-Guiu, Sanz, Gili, Molins, Bonaventura, & Capdevila, 1986; Sheldon et al., 1985; Stevens et al., 1986). Inadequacies in study design, MRI insensitivity, poor measures of lesion burden and functioning, and the presence of so-called "silent lesions" and "silent areas" have been posited as responsible for less-than-expected correlations between lesion burden and functional decline.

Generally, correlations between lesions and symptoms

have been weaker where sample size was small (e.g., Kiel et al., 1988) or possible/probable MS cases were examined (e.g., Kirshner et al., 1985; Sheldon et al., 1985), while prediction of clinical symptoms from lesion burden improved in larger and definite MS samples (e.g., Edwards et al., 1986; Sheldon et al., 1985; Stevens et al., 1986). Incomplete, unreliable, or gross indices of impairment also detract from accurate measurement of lesion - symptom relationships. For example, self- report is frequently used but is susceptible to patient and/or interviewer subjectivity. The Kurtzke DSS/EDSS is perhaps the best grading system for overall functioning in MS (Matthews, 1985) but as such may lack the sensitivity and flexibility needed for finer-grained examination. For example, the Kurtzke scales overweight functions whose structures are not especially appreciable via MRI.

Weaknesses of MRI scoring systems include neglect of important information. For example, one frequent index used is the total number of lesions. This type of measure fails to account for plaque size or location. Another shortcoming of MRI indices is that scoring criteria are frequently based on ease of scoring or general anatomical considerations rather than classifications important to possible functional localization. Kirshner et al.'s (1985) system is provided as an example of a system not functionally-derived. They grouped subjects' MRI's into one of four grades:

grade 1 = lesions only in periatrial and supraperiventricular regions

grade 2 = same as grade one but with lesions greater than 2.5 mm

grade 3 = PV and periatrial lesions greater than 5 mm and plaque in four cerebral lobes and capsular region

grade 4 = PV, cerebral lobe, brainstem, and "more distant white-matter" lesions

This schema reflects expected MRI differences between patients rather than ratings of lesion burden features most likely to discriminate clinical manisfestations. Conversely, Sheldon et al.'s (1985) laudable design grouped MRI results into four locations relevant to functional localization (optic nerves, cerebrum, posterior fossa, and spinal cord).

Authors have cited limitations in MRI sensitivity not only in hard to visualize areas but also in locales that are more easily imaged (e.g., posterior fossa) to explain lower-than-expected correlations. For example, Sheldon et al. (1985) reported that none of 34 patients with optic neuritis showed MRI-confirmed lesion in the optic nerves. Although improvements in plaque visualization have been reported with enhancing media, surface coils, and the like, it is apparent that some lesions will be missed and will cause artifactual decreases in lesion - function correlations.

There is considerable empirical evidence that small lesion - function correlations occur because some lesions simply are asymptomatic. As reported earlier, longitudinal studies indicate that lesion activity (whether de novo or reactivation of chronic lesions) does not always result in clinical manifestations. Asymptomatic plaques also have been described via autopsy examination (e.g., MacKay & Hirano, 1967), CT with and without enhancement (e.g., Ebers, Paty, & Sears, 1984), and most recently with MRI cross-

sectionally (e.g., Ormerod et al., 1987). A contrast between true and false positive concordance rates of symptoms with lesions was highlighted by Sheldon et al. (1985). Although 83% of their patients with symptoms localizable to the brainstem or cerebellum had positive MRI in those areas, 43% of patients with lesions observed in the posterior fossa did not have localized deficits. These results suggest that, although most patients with symptoms have lesions in relevant structures, the reverse is not necessarily true. The degree to which this relationship holds for changes in mentation and memory may be important to ascertain. One might hypothesize that concordance rates will be even more discrepant in memory since more variables are likely to mediate the association between structure and function with memory than with relatively simpler sensory and motor neuronal networks.

Sheldon et al.'s (1985) observations about so-called "silent areas" provide an appropriate transition from the description of asymptomatic plaque. In trying to explain their failure to demonstrate stronger lesion - symptom correlations, they state "...(cerebral) plaques usually occur in cerebral association areas that tend to be clinically silent" (p. 953). Although the accuracy of this statement has not been confirmed, it does raise several important questions. Association areas may be more robust to the effects of lesions, or at least result in less easily measured deficits. This point is extremely important, since it bears greatly on the degree to which researchers have adequately measured sensory and motor symptoms. As discussed by Luria (1966), associative areas are thought to

integrate raw data from primary cerebral regions into workable information for all functional systems. Destruction of a primary zone is likely to result in a loss of specific function, while insult to an associative area would interfere with more general abilities -- the so-called "higher cortical functions". For example, the loss of the primary visual zone in the occipital lobe can cause the loss of any visual sensation, a defict known as "cortical blindness". On the other hand, lesions in visual associative areas are thought to result in integrative perceptual deficits such as the failure to recognize a large building as a skyscraper or to understand the layout of chesspieces as a checkmate scenario. One difficulty with current research is that the functional measures used are more sensitive to primary zone than to associative area impairments. Thus, plaque in "silent areas" (associative regions) may not actually be asymptomatic but, rather, the subtle deficits produced by associative area lesions probably are not being evaluated adequately.

Even if this problem of overreliance on measures of primary zones were addressed, however, difficulties may still arise simply because of our relative ignorance of the ways in which association areas work. That is, even in a perfectly designed study, wherein all relevant primary and "higher" cortical functions are adequately measured, it is quite probable that we may still find "asymptomatic" lesions because association areas may have more redundant pathways or alternative ways of processing the information necessary for intact integrative, generalized functioning.

Finally, "silent" areas and lesions probably reflect

factors previously described as contributing to disruption of neuronal functioning (e.g., patient stress, CNS plasticity, remyelination, and centrifugal dissemination). Thus, even if MRI could accurately determine the extent and location of every plaque and all functional changes were completely described, we still would not have accounted for all the variance associated with MRI-observed lesion and dysfunction relationships. For example, Stevens et al. (1986) secured the highest correlations between MRI-observed lesion and symptoms reported to date, yet plaque accounted for only approximately 20% to 35% of the variance in sensory-motor functioning. The variance accounted for dropped further still -- to 15% -- when the authors attempted to correlate lesion burden with mood and mentation. This latter finding is highlighted because it foreshadows the exponential rise in measurement difficulties encountered when one moves from examining sensory-motor to higher cortical functions. For example, researchers of sensory-motor symptoms can be more certain which locales to score (e.g. cerebellum for gait disturbances) than those who investigate intelligence, judgment, memory, and the like.

Cognitive and Memory Functioning

Few attempts have been made to evaluate the association between MRI indices of plaque and memory impairments, and generally negative findings were reported. However, numerous methodological problems render their results inconclusive. As is true in studies of motor and sensory deficits, these difficulties include inadequate measures of memory functioning and lesion burden, improper matches

between the two, and small sample size. Where these concerns have been addressed, preliminary evidence suggests that some of the individual variation in memory function may be predicted by MRI-confirmed lesion burden.

Seven studies have been published to date that include some attempt to measure the degree of relationship between MRI-imaged lesion burden and memory functioning. Three investigations did not examine memory separately from other cognitive functions, making it difficult to incorporate their findings. Given the relatively small number of studies, it is possible to briefly describe each as a means of illuminating pertinent measurement issues, conclusions that can be drawn from the data, and the basis for the current study's hypotheses. The descriptions appear in the chronological order in which they were published.

Huber et al. (1987) administered the Kurtzke EDSS, Mini-Mental Status Examination (MMSE), and brief measures of language, praxis, and visual-spatial perception to 32 clincially-definite MS patients (Poser criteria) and 12 normal controls. The digit span and word-pairs learning tests from the WMS were used as measures of memory. Proton-, T1-, and T2-weighted MRI scans were obtained, although the authors were not clear which planes were scored -- only saggital cuts were mentioned. The films were scored for four indices of MS pathology extent: 1) quantity of lesions (i.e., total area of all observed plaque) 2) general parenchymal atrophy (i.e., global rating on a scale from one to five based on appearance of gyri, sulci, ventricles, cisterns, and "parenchymal atrophy") 3) corpus collosal atrophy (i.e., global rating from one to five for CC atrophy

and number of lesions), and 4) PV involvement (i.e., global rating from one to five for percentage of lateral ventricle encasement). Patients were placed in one of three functioning groups with those labeled "demented" scoring at least two standard deviations below controls on at least three of the cognitive measures; "moderate" patients performed poorly on any two measures; and the "minimal" group had below normal functioning on one or none of the tests. The authors found that the three dementia groups significantly differed only on the CC index of plaque, although the other three measures showed trends in the predicted direction.

The Huber study is notable for its well-considered MRI scoring system, using group comparisons to help adjust for individual variations, and proposing that the corpus collosum is a more sensitive indicator of global cognitive functioning than are other indices. Because the authors did not analyze different types of functioning, however, it is impossible to draw inferences specific to memory.

Medaer et al. (1987) administered the WAIS, the Progressive Matrices Test (an analytical reasoning measure), the Rey Verbal Learning Test (RVLT), the Benton Revised Visual Retention Test (a measure of visuo-spatial perception and memory), and a search task purportedly sensitive to attention and concentration to a number of laboratory-supported definite MS patients. Thirty-three of these patients were matched on age, sex, and disease duration for placement into three groups based on a global rating of impairment from the cognitive tests. Those in group one (GI) showed no impairment; GII subjects had "moderate

impairment at least in some tests"; and GIII were "seriously impaired with deficts on most tests." The authors also reported that some WAIS performance subtests were not given when patients "showed marked visual or motor disability" (p. 87). It is unclear from their description how the MRI data were obtained or analyzed. As best as can be determined, T2-weighted images were obtained from an axial plane with further multi-echo slices made if plaque was discovered. Each patient was given a global MRI score from zero to five: 0) one lesion only 1) small PV lesions 2) broad PV and confluent lesions 3) #2 criteria plus peripheral lesions 4) #2 criteria plus enlarged ventricles and 5) #3 criteria plus enlarged ventricles. The authors did not state whether the entire brain or, for example, only the cerebral hemispheres were scored.

At first glance, the results appear to support the authors' conclusion that MRI measures of pathology predict global estimates of cognitive functioning. The three groups differed significantly on the MRI score such that GI subjects had lower MRI ratings in comparison to subjects in GII and GIII. However, the GII and GIII contrast was not significant and there was sufficient overlap between groups such that some subjects in the GII had greater MRI scores than those in GIII. These results led the authors to conclude that "...the interindividual variation in MRI scores seen within the groups (especially group II) indicates that an overall MRI score alone is not sufficient to account for more specific differences in cognitive functioning " (pg. 88).

Because of serious methodological issues, even this

conclusion may be unreliable. It is not clear how group membership was determined or how the MRI's were evaluated. Another concern pertains to the apparent lack of functional considerations in the MRI indices and the use of such constructs as "small," "broad," and "confluent." Scoring criteria should reflect the pathological picture in a way that is functionally relevant if lesion - dysfunction relationships are to be adequately investigated. The scoring system also is vulnerable to errors of reliability as succeeding investigators choose different values for "small." The inconclusive results also may be attributed to their use of indirect indices of MS lesion. For example, parts of Medaer et al.'s grading system depended on variations in ventricle enlargement. Most would agree that ventricle hypertrophy is merely reflective of white-matter plaque in the cerebrum and not a cause of functional changes per se. It may be that only direct measures of plaque are significantly associated with changes in cognition. Additional evidence supporting this hypothesis will be reviewed below.

In contrast to Medaer et al., Brainin et al. (1988) employed more direct measures of MS plaque and scored for locales implicated in the mediation of cognition and memory. The authors administered the WAIS Information, Similarities, Picture Completion, and Digit Span subtests and the WMS Logical Memory and Paired Associative Learning subtests to 20 clinically definite, chronic-progressive MS subjects (McDonald criteria). T1 and T2-weighted, spin-echo coronal and saggital MRI scans were scored for "extensive lesions in the frontal white matter;" thinning and lining of the corpus

collosum; and uni- and bi-lateral involvement of the cingulate gyrus, temporal horns, and "mediotemporal (lobe) regions". A cluster analysis of combined scores on the WMS Logical Memory and Paired Associates subtests was performed to place subjects in severely-, moderately-, or un-impaired groups. Analyses determined that lateralized plaque in the medial temporal lobes predicted membership into the memory functioning groups. Bilateral lesions were associated with severe impairment and unilateral plaque with moderate deficits. No pathology was seen in either temporal lobe in the unimpaired group. Demyelination in other sites did not differentiate the memory functioning groups. The authors offered demyelination of hippocampal pathways as the most likely cause of the observed memory deficits.

The reliability of these provocative findings is decreased by small sample size and gross quantification of MRI data. Most problematic, however, is the authors' inferences regarding localization. Exact lesion sites were not described, so it is not certain that plaque existed in the hippocampus. Even if MRI confirmed that there were lesions in hippocampal formations, one must respect Teuber's (1959) warning of the necessity for double dissociation in localizing functional deficits: "...double dissociation requires that symptom A appear in lesions in one structure but not with those in another, and that symptom B appear with lesions of the other but not of the one. Whenever such dissociation is lacking, specificity in the effects of the lesion has not been demonstrated" (p. 187). In this case, Brainin et al. have fulfilled only the first half of Teuber's first statement and this only partially: symptom A

(memory deficit) appears in one structure (hippocampus). The authors do not provide data that memory deficits appear with lesions in other areas or that lesions in the hippocampus produced deficits in other functions.

The perils of failure to doubly dissociate also are exemplified by another finding of the Brainin et al. study. They reported that four of the five "unilateral" medial temporal lobe subjects had their lesions in the right rather than the left hemisphere despite suffering moderate impairments on verbally-mediated memory measures. Brainin et al. note that unidentified lesions in the left thalamus may be responsible for the apparently incongruent laterality of the lesion -- nicely exemplifying the need for Teuber's caution.

The authors' use of only two verbal subtests from the WMS as the only estimate of memory functioning also is highly questionable. Concluding that a person has severe memory impairments requires more extensive and specific testing (i.e., nonverbal memory), especially since Brainin et al. draw parallels to medial temporal lobe amnesia. Despite the unreliability of their specific findings and conclusions, Brainin et al.'s study deserves praise on other points. MRI scores were theoretically and functionally driven and their results spark interest in examining temporal lobe plaque involvement in memory functioning.

The third and fourth studies to be reviewed, Litvan et al. (1988a) and (1988b), concluded that MRI measures were insensitive to cognitive deficits. Small sample size seriously limits the reliability of their results and other measurement issues also may have contributed to negative

findings. In the first study (1988a), 16 clinically-definite MS patients (Poser criteria) were administered the WMS battery (with 30 minute delayed recall of the Logical Memory and Paired Associates subtests), a verbal list learning test (Rey AVLT), and measures of verbal (Paced Auditory Serial Additions Task and a variation of the Sternberg Memory Scanning Paradigm) and motor processing speed (Purdue Pegboard). The authors did not describe MRI procedures except to report that films were "of variable quality," and that they were scored for the total number of lesions and the "degree of PV involvement." Spearman correlations were insignificant between these two measures of demyelination and any of the WMS or processing speed tests.

Very small sample size leaves their study open to serious sampling error and the inadequate description of their MRI protocol prevents reproduction. Some conclusions may be drawn if applied with caution. One is that a simple count of plaque may be an insensitive index of lesion burden; it does not consider plaque location or size. Their study also furthers questions as to whether MRI-observed PV involvement alone is sufficent to discriminate memory deficits (e.g., Huber et al., 1987; Medaer et al., 1987). On a more positive note, the use of the WMS and a verbal list learning task are an improvement over previous studies in that there was a much greater sampling of memory processes. Unfortunately, the WMS has a number of shortcomings (for review see Herman, 1988; see also Erickson and Scott, 1977, and Prigatano, 1978).

The second Litvan et al. (1988b) investigation reported

slightly different analyses of MRI-imaged plaque and cognition with the same sample used in the first study. In addition to the WMS and Rey AVLT, subjects were administered modified Brown-Peterson tasks to evaluate Baddeley's working memory verbal articulatory loop. MRI procedures were described in this article and may be the same ones used in the previous publication. Six axial, T2-weighted slices were scored for the number and location of lesions. Subjects were placed in one of three groups according to the following schema: 1) "plaques formed PV lines or nodules" 2) the "configuration of plaques was in bands in both horns of the lateral ventricles" and 3) "PV bands surrounded the ventricles".

No significant relationships were found between the cognitive measures and either MRI index -- plaque number or lesion grades. These findings contribute to previous evidence that PV ratings (Huber et al., 1987; Medaer et al., 1987) and a simple numerical count of lesions (Huber et al., 1987) are not predictive of memory functioning. Litvan et al. (1988b) acknowledge the probable insensitivity of their MRI measures, stating that: "...the level of analysis may have been too gross...", (p. 610). As with its predecessor, the inferences drawn from the second study are unreliable because of small sample size.

Franklin et al. (1988) produced the most methodologically-sound investigation to date, which, not incidently, demonstrated the strongest relationships between MRI-imaged plaque and cognitive dysfunction yet reported. Sixty clinically-definite, chronic-progressive (Schumacher criteria) MS patients were administered a

cognitive test battery designed by the authors. The subtests of this Neuropsychological Screening Battery (NSB) were duplicate or abbreviated forms of well-known neuropsychological measures. The NSB samples aspects of visual attention; verbal and visual learning with delayed recall; visual perception and construction; and a variety of language capacities. The battery also included two tests previously identified as especially sensitive to cognitive impairment across several functions (i.e. Symbol-Digit Modalities and Trails A & B). Two summary indices were derived from this battery: a Total score using all tests and a Pure (cognitive) score which excluded tasks requiring intact motor functioning (e.g., visuo-spatial construction). Each patient's T2-weighted, multi-echo, axial and coronal slice MRI images were scored for bi-, uni- and quad-hemispheric cerebral locations and weighted lesion size.

Their results clearly indicate that MRI-observed plaque can account for variations in cognitive functioning, including memory. For example, the bi-hemispheric lesion score correlated significantly with both the Total and Pure cognitive scores ($r = .46$ and $.35$ respectively) and every memory subtest except the nonverbal learning test. The authors also reported that the bi-, right-, and left-hemisphere lesion scores accurately predicted those subjects with unimpaired versus impaired performance on the Pure (cognitive) subtests.

The authors offer a number of explanations for the success of their study, especially in comparison to previous efforts. One factor cited was that the localization formula limited scoring of pathology to those areas thought to be

most directly related to cognitive and memory processing (i.e., the cerebrum) while specifically excluding plaque in structures thought to be relatively less pertinent to intact cognition (i.e., the brainstem and cerebellum). Franklin et al. also note that their MRI scoring formula provided estimates of both the number and size of plaque. In contrast to previous investigations, Franlin et al. employed a relatively large and homogeneous subject population (with respect to course) and more fully measured a range of cognitive capacities. The latter two points warrant further consideration.

Franklin et al.'s (1988) study suggests that cerebral lesion area is more sensitive to cognitive disturbance than other lesion burden measures, including PV and total brain involvement, total number of lesions, ventricle hypertrophy, cerebral atrophy, peripheral and confluent lesions, and frontal white-matter involvement. Direct comparison of these MRI measures on the same sample could provide substantial evidence that cerebral lesion area best documents the plaque burden responsible for cognitive dysfunction.

Despite Franklin et al.'s success, it should be noted that only 12% of memory functioning variance was accounted for by cerebral lesion area. This relatively small relationship probably reflects previously described factors that are thought to reduce associations between MRI-observed pathology and dysfunction (e.g., histological-level processes). Another factor that may have reduced the strength their lesion - memory correlations involves the extent of measurement. Franklin et al.'s battery is

admirable in its breadth, lacking only a verbally-mediated PM task and verbal and nonverbal recognition format tests for what many would deem to be complete coverage of memory functioning. However, the NSB is relatively light in the depth of its coverage as reflected by its 30 to 45 minute total administration time. Thus, a more detailed battery of memory tasks may obtain even stronger correlations between MRI-observed plaque and memory dyfunction.

Callanan et al. (1989) is the most current publication on MRI-observed plaque and cognitive functioning. As a substudy of Ormerod et al.'s (1987) project, the authors compared the cognitive functioning of 48 patients with clinically isolated lesions typically associated with initial-stage MS (e.g., neuritis of the optic nerves, brainstem, and cervical spine). Due to the difficulties inherent in scanning these areas, a very complex imaging procedure was used (see Ormerod et al., 1987). MRI films were scored for a frontal index (lesions in the frontal lobe and frontal horns of the lateral ventricles), a temporal score (temporal and parietal lobes and temporal horns of the lateral ventricles), and periventricular score (all ventricle regions). A total brain rating (cerebrum, cerebellum, optic nerves, brainstem, and cervical cord) as well as subdivisions of the telencephalon (i.e., internal capsule and basal ganglia) also were compiled.

Memory was evaluated with an auditory and a visual cancellation task and verbal (word) and visual (faces) recognition memory tests. Other cognitive abilites were measured with the National Adult Reading Test, the WAIS, the Wisconsin Card Sort Test, and an object naming task. Seven

function areas were derived from these tests and each subject received a grade within each and then across all function areas (summed score) based on the following criteria:

G0 = score > 50th percentile of control group scores

G1 = 50th ≥ score ≥ 25th control percentile

G2 = 25th ≥ score 5th control percentile

G3 = score < 5th percentile of control group scores

In general, the observed correlations were weak and did not support many of the hypothesized lesion - function relationships. For example, although the total brain lesion score did differentiate the most and least cognitively impaired subjects (G0 versus G3), it did not appear to distinguish the other impairment groups. In regards to separate tests, the total brain lesion score correlated significantly only with the auditory PM measure and the Wisconsin Card Sort Test. Finally, none of the other lesion areas (e.g., frontal score) were found to be meaningfully associated with any of the memory or other cognitive measures.

Callanan et al.'s inconsistent results may be explained, in part, by the type of sample used. Subjects were not definite MS cases, but were people most likely to be determined to have MS in the near future. Most diagnostic criteria require bouts separated by at least six months before they are considered to have clinically-definite MS. Callanan's subjects had had only one episode. Thus, while many will be diagnosed as definite cases, the sample probably included cases who do not have MS. These cases aside, it also is not clear what differences exist

between early-stage MS patients and those with clinically-definite MS. One cannot assume that the types of lesions or dysfunctions are comparable. Another factor that may have reduced the strength of memory - lesion correlations is the type and extent of memory testing. MS patients would be least likely to show performance decrements on recognition memory tests and PM tasks.

Summary and Rationale

Investigations of MRI-observed lesion burden and memory only recently have begun and early results are disappointing. However, several methodological issues make it difficult to draw reliable conclusions about the strength or quality of memory - lesion associations. Where at least some of these issues have been addressed, significant correlations were observed between memory functioning and lesion burden (e.g., Brainin et al., 1988; Franklin et al., 1988).

Small sample size has plagued many investigations, severely limiting the power of their analyses (Brainin et al., 1988; Huber et al., 1987; Litvan et al., 1988a; Litvan et al., 1988b; Medaer et al., 1987). Inadequate measurement of memory functioning has been another problem. Memory tests were not matched appropriately with plaque measures (e.g., Brainin et al., 1989), were questionably normed or designed (e.g., Huber et al., 1987), or simply were insufficient to allow reliable conclusions (e.g., Callanan et al., 1988). Preliminary evidence suggests that sampling from a wide range of PM and SM functions would increase the probability of detecting subject differences and maximize

correlations with lesion burden.

Difficulties with lesion scoring systems also have hampered attempts to describe pathoanatomical predictors of memory disturbance. MRI measures have been poorly described (e.g., Litvan et al., 1988a) and overly gross (e.g., Litvan et al., 1988b), derived to ease scoring, or discriminate patients on the basis of anatomy without considering function (e.g., Medaer et al., 1987). A simple count of the number of lesions may be insensitive to changes in memory (e.g., Litvan et al. (1988a), especially in comparison to measures of lesion area (e.g., Huber et al., 1987).

It is unclear whether localizing the plaque appreciably adds to the predictive accuracy of lesion burden measures on memory changes, in part, because development of localization criteria has been difficult. One issue is that memory is not particularly localized. Rather, intact memory depends on a combination of anatomical systems, and poor memory test performance may result from one of several types of dysfunctions that, in turn, may be subserved by various neural networks. Several anatomic regions have been identified as especially important to memory functioning, but application to MS is limited. Sclerotic plaque does not occur in these areas with sufficient frequency to explain most memory impairments (e.g., Callanan et al., 1989; Maravilla, 1988). Thus, although a few cases of memory deficits may be explained by plaque in strategically important areas -- as Brainin et al. (1988) may have illuminated -- one may conclude that the majority are not. Another problem is that the severity and types of memory impairments seen in MS are not very similar to those seen in

other memory syndromes. For example, the devastated antereograde and more moderately impaired retrograde SM functions seen in the diencephalic and medial temporal lobe amnesia are not seen frequently in MS (e.g., Rao, et al., 1989).

In the absence of better guides to determining localization criteria, it may be useful first to identify which regions may be excluded from MRI scoring systems. Inclusion of irrelevant anatomic regions in estimates of lesion burden may have contributed to the weak associations between MRI-imaged plaque and memory functioning in previous studies. Infratentorial structures warrant attention as exclusion candidate. This hypothesis is based on a best guess that the memory deficits seen in MS are produced by accumulated disruptions in the lines of communication between the various cortical and subcortical structures responsible for encoding, consolidation, storage, and retrieval. Since the primary inter-region communication networks in the brain are the subcortical white-matter tracts and because most MS lesions are also found there, one may hypothesize that the lesions most responsible for memory impairment are located in the cerebrum. Conversely, most would agree that the spinal cord, brainstem, cerebellum, and midbrain are not as involved with memory processes as the cerebrum (e.g., Carlson, 1983). This is not to say that lesions below the tentorium may not contribute to memory deficits. For example, the reticular formation subserves wakefullness and lesions there may disturb PM and, thereby, encoding of information for storage and recall. Rather, it is believed that measurement of only those regions most

directly involved with memory will produce the most sensitive predictors of dysfunction. Preliminary data support this hypothesis. Studies using an MRI index that included scoring of infratentoral lesions tended to observed weak associations between that score and memory (Callanan et al., 1989; Litvan et al., 1988a; Litvan, et al., 1988b). Conversely, those that excluded the spine, brainstem, and cerebellum from their MRI protocols reported more significant findings (i.e., Brainin et al., 1988; Franklin et al., 1988). If the hypothesis that infratentorial lesions contribute relatively little to the prediction of memory, then one should see stronger correlations with cerebral indices than with measures of whole-brain lesion burden.

Several studies reported using MRI measures that included scoring of anatomical regions not usually considered as important to memory and, therefore, are exclusion candidates (i.e., periventricular and corpus collosal involvement). MRI evidence suggests that measures of these areas are not sensitive to cognitive deficit and any relationship is thought to be due to their representational nature. That is, prediction of dysfunction from such "representational" indices occurs because the pathology measure is reflective of the lesion actually responsible for the disturbance. Because data pertaining specifically to memory are sparse, it would be useful to compare CC and PV involvement and a direct measure of cerebral lesion in their relationship to memory functioning.

Periventricular involvement as a predictor of cognitive impairment has not been supported across a wide range of

criteria: percentage of lateral ventricle encasement or ventricle hypertrophy (Huber et al., 1987); small, broad, and/or confluent PV lesions (Medaer et al., 1987); degree of PV involvement (Litvan et al., 1988a); and periventricular lines/nodules, encasement of both lateral ventricle horns, and complete encasement of the lateral ventricles (Litvan et al., 1988b). Outright rejection of possible associations between PV and memory changes must be withheld until several issues are addressed. The most critical problem is that memory functioning was not the primary focus in these studies. Small sample size and unclear MRI parameters also make it difficult to determine whether the localization criteria (periventricular involvement) alone resulted in the negative findings.

Outside the MRI literature, there is little evidence, either positive or negative, that the white-matter tracts surrounding the ventricles support memory. An exception is that of Rao and his co-authors (1984, 1985), who have suggested that the periventricular prefrontal-limbic pathways serve some memory functions. This hypothesis was inferred from their work with CT wherein various PV indices (e.g., degree of hypertrophy) were found to be correlated with several types of cognitive defict, including memory (Rao et al., 1984). However, Rao et al. (1985) also note the possibility that PV hypertrophy predicts dysfunction merely because it reflects the degree of pathology elsewhere (i.e., a representational measure). As noted previously, representational measures may not be as sensitive to dysfunction as are more direct ones. For example, ratings of parynchemal atrophy failed to discriminate three levels

of dementia (Huber et al., 1987), whereas Franklin et al.'s (1989) gradings of total cerebral lesion area were significantly correlated with several cognitive tests. However, evidence specific to memory has not been reported as to whether direct measures are superior to representational ones. Given the fairly consistent findings with MRI, it is hypothesized that a direct measure of cerebral lesion will better predict memory test performance than will indices of PV plaque.

Corpus collosal involvement also has been proposed to be a correlate of cognitive changes in MS. Huber et al.'s (1987) MRI measure predicted membership to severely-, moderately-, and minimally-impaired dementia groups. However, memory deficit measurement was limited to the WMS Digit Span Forward and Paired-Associative Learning subtests and group differences on these tests were not given. Thus, this study cannot speak to the predictive strength of corpus collosal involvement to memory functioning per se. An autopsy study of MS also revealed a significant relationship between CC atrophy and previous history of dementia (Barnard & Triggs, 1974), but these results also were not specific to memory. Given that investigations of the corpus collosum assign little direct role to it in memory processing (e.g., Lesak, 1983), Huber et al. (1987) concluded that corpus collosal involvement is merely a general indicator of the degree of pathology in other areas of the brain -- exactly paralleling earlier hypotheses with PV involvement. The existing data on the corpus collosal plaque suggest that, at best, it serves as a rough gauge of the degree of lesion thoughout the brain. It is believed that a direct indicator

of lesion burden (i.e., cerebral lesion area) will account for more individual variation in memory functioning than will representational measures such as those derived from the corpus collosum.

A final way this study will attempt to improve localization criteria involves the possibility that lesion lateralization may predict modality-specific memory deficits. Brainin et al. (1988) reported a significant correlations between MRI indices of bi- and uni-lateral medial temporal lobe regions and combined scores on a paragraph recall and a paired associative learning test. Bilateral involvement predicted severely-impaired performance, lateralized plaque was associated with moderately-deficient test scores, and normal-range performance was observed in patients free of medial temporal lobe involvement. Their results were deemed unreliable for several reasons, but especially because of small sample size, the reliance on only two verbal memory measures, and questionable localization inferences (i.e., five out of six of the moderately impaired patients reportedly had right-sided lesion even though memory measures were verbally-mediated). Franklin et al. (1988) observed significant correlations between uni-lateral cerebral lesion area and several measures of verbal and nonverbal, primary and secondary memory. Unfortunately, specific data pertaining to potential modality and localization differences were not reported. No other study has examined the relationship between uni-hemisphere plaque distributions and verbal and nonverbal memory. This neglect may reflect the fact that MS lesion is usually bilaterally distributed (e.g., Lumsden,

1970). The lack of notable left- and right-sided lesion differences hampers any lateralized predictions because of restriction of range. Nevertheless, limited successes by Franklin et al. and Brainin et al. argue that the topic deserves further attention. Given the copious amount of data on hemispheric asymmetry of function (e.g., Springer & Deutsch, 1985) it is easy to assign the directionality of predictions. That is, non-verbal memory performance should correlate more highly with a right- versus a left-hemisphere lesion score.

The material just presented discusses MRI scoring factors that are hypothesized to maximize predictions of individual variation in memory functioning. Similar discussion is necessary when considering how memory should be evaluated for such investigations. Few guidelines are available from existing research because most studies have sampled memory only as a subset of several cognitive processes (e.g., Callanan et al., 1989). However, memory test selection has been treated in rather cavalier fashion even in investigations that purportedly focus on memory. One need only return to Brainin et al.'s (1987) attempt to discern the role of medial temporal lobe involvement--while using only digit span and paragraph recall tests--to illustrate this point. Common sense dictates that successful assessment of brain - behavior relationships requires a comprehensive evaluation of memory functioning, including measures of verbal and nonverbal PM and SM.

A subsequent question concerns the way in which test scores should be compared with lesion burden indices. Because some of the MRI measures to be used are global with

respect to localization, it may be useful to compare them with a summary memory score that reflects the total degree of impairment across functions. A score such as the WMS Memory Quotient does not adequately account for orthogonal functions. The index employed by Franklin et al. (1988), however, appears to be sufficently comprehensive, while minimizing sacrifices in specificity. The authors used cut-off scores for each cognitive test within their battery. Test performance below one standard deviation was assigned a "+1", those below two standard deviations a "+2", and the resulting sum was correlated with MRI scores. A similar system easily could be developed for memory factors, with cut-off scores for verbal and nonverbal attention span, paired associative and list learning, recognition, and immediate and delayed recall tests.

More specific measures of memory also will be used to explore the possibility that MRI lesion burden will better predict SM than PM functioning. Although no MRI studies have specifically tested this hypothesis, converging lines of evidence support the proposition. The first conceptualization stems from the observation that previous studies' failure to demonstrate significant lesion - memory relationships may have been due to the fact that memory functioning appeared intact (e.g., Callanan et al., 1989). It may be that lesion burden is most predictive at the most deficient range of functioning. Since most evidence suggests that SM processes, in comparison to PM, are more likely to be impaired, it is predicted that MRI scores will correlate more highly with tests of SM (e.g., delayed recall) than of PM (e.g., digit span).

The second source of deductions also depend on the assumption that SM is more susceptible to impairment than PM. That is, as memory task complexity increases from PM to SM processing, both the prevalence and severity of impairments may increase. At least some of the factors responsible for this relationship may be associated with MRI-observed lesion burden. For example, since more neuronal networks may be tapped with SM than with PM processing tasks, increasing amounts of plaque would be more likely to interfere with SM than PM functioning. Therefore, it is predicted that MRI scores will be correlated more highly on tests with more demands on the SM than PM systems.

The last group of hypotheses is drawn from Sheldon et al.'s (1985) analysis of concordance rates in correlating sensory and motor symptoms with MRI-observed pathology. Recall that they found that, while a proponderance of subjects with localizable symptoms (e.g., gait disturbance) had lesions in the predicted area (e.g., cerebellum) the reverse relationship was significantly weaker. For example, a majority of subjects with lesions in the posterior fossa did <u>not</u> present with measurable symptoms. Those patients with clinically significant changes in function, however, were very likely to have plaque in the predicted area. The authors ascribed these findings to aspects previously identified as possibly mediating the strength of lesion - symptom associations. These include but are not limited to "internal" factors such as: remyelination, the extent of gliosal changes, the centrifugal pattern of lesion growth, and the relative importance of the structure to the function. For example, the deleterious effects to vision of

a lesion in the optic nerve may be proportionately more significant than that of plaque in the visual association cortex. "External" factors may include body temperature, exercise, and emotional and physical stressors. Comparison of figures such as obtained by Sheldon et al. (1985) may be conceptualized as a rough estimate of the proportion of variance accounted for by these factors.

Despite the potential usefulness of comparing concordance rates, they have not been obtained with memory or any other cognitive function. Predictions specific to memory are inferred directly from Sheldon et al.'s (1985) pattern of findings. Subjects with significant memory impairments are predicted to have an increased cerebral lesion burden, but not all subjects with significant lesion burden will have notable memory deficits. It is also predicted that this relationship will hold across separate memory functions and lesion burden scores.

METHOD

This investigation is part of a larger research project; therefore, only the methodology relevent to this particular study will be discussed.

Subjects

Forty-one subjects were recruited through MS support groups located near a small Midwestern city. Support groups were contacted and asked to distribute flyers describing the project and to schedule a guest speaker at an upcoming meeting of the group. The speaker explained the nature of the study, asked attendees to participate as subjects, and answered any resulting questions. Those indicating interest received follow-up phone calls to schedule a testing session.

Referrals also were taken from private neurologists; local neurologists were informed of the aims and referral needs of the study. These subjects also received a full description of the project before agreeing to participate.

Diagnostic criteria were based on Poser, Paty, Scheinberg, et al.'s (1984) research guidelines. Only subjects with clinically-definite MS were included. Otherwise, inclusion in the study was by means of consecutive referrals.

Procedure

Two subjects were scheduled per day. Half the subjects were assigned randomly to begin with speech and language testing, the other half started with the other cognitive

measures. These conditions were reversed after an hour break for lunch. MRI's were obtained at the Michigan State University Clinical Center following completion of neuropsychological testing. Medical histories were taken after the MRI.

Sessions lasted approximately eight hours, including two regularly scheduled 10-minute breaks and an hour for lunch. Additional breaks were taken if requested by the subject. Because of access to only one imager, one subject waited approximately 60 minutes before beginning the MRI.

Upon the completion of the testing, subjects were debriefed, thanked for their participation, and informed that they would receive personal feedback of their results when data gathering for the entire project was completed. Additional questions were handled by the interviewers.

The neuropsychological testing was administered either by a professor or one of two graduate students in clinical psychology. All had previous training and experience with the respective assessment procedures.

Tests and Measures

Magnetic Resonance Imaging (MRI) - The MRI examinations were performed on a 1.5 Telsa General Electric Signa System. Three series of sequences were obtained per subject. For each series, the acquisition matrix was 256 x 128 with a nexus of 2, while the section thickness was 5 mm and the distance between slices was 2.5 mm. The first series obtained was T1-weighted sagittal-plane images with a TR of 500 ms, and TE of 25 ms taken at the midline and 30 mm left and right of this position. Sagittal SE sequences with a TR of 2500 ms and TE's of 30, 60, 90, and 120 ms comprised the

second series. Finally, T2-weighted, axial SE sequences with a TR of 2500 ms and TE's of 30, 60, 90, and 120 ms and compensated for flow effects were obtained.

Signa Cursor - The cursor and accompanying soft-ware package were developed and sold by Signa. The cursor is a pen-shaped device with a sensor in its tip that was developed to aid objective measurement of X-ray film. When the tip of cursor is drawn around the contour of an image (e.g., corpus collosum), the visual signal is relayed to the computer that translates the data into an estimate of the total area.

Three judges, who were blind to the results of the neuropsychological tests, scored MRI films according to the following protocol. All lesion burden indices were derived from the T2 - weighted axial plane films, with the exception of the corpus collosum measures. Plaque were scored for size and location. Lesion size was measured as its total area in square millimeters. Lesion area was estimated by multiplying the lesions greatest diameter by its heighth at the greatest diameter perpendicular to the first diameter. Because analyses were based on total area rather than the number of lesions, no attempt was made to differentiate areas of lesion confluence (i.e., multiple lesions in close proximity to each other) from single, large lesion areas with diffuse signal intensity. Lesions were scored for several locations: medulla, pons, midbrain, cerebellum, basal ganglia, internal capusule, thalamus, internal capsule, and the lobes of the cerebrum. Eight lesion lesion burden indices were developed:

1. Total Lesion Area (Brain) - all plaque summed across all slices.
2. Cerebral Lesion Area (Cerebral): all cerebral plaque
3. Left-Hemisphere Cerebral Lesion Area (Left) - all left hemisphere cerebral plaque
4. Right-Hemisphere Cerebral Lesion Area (Right) - all right-hemisphere cerebral plaque
5. Periventricular Involvement (PVinvolve) - subjective ratings of total plaque area in the PV regions, ordinally-scaled from one (representing no involvement) to five (total encasement of the ventricles by plaque).
6. Periventricular Confluence (PVconflu) - subjective ratings of the degree of PV confluence, ordinally scaled from one (representing no confluence) to three (greatest degree of confluence)
7. Corpus Collosum Lesion Area (CCarea) - all plaque found in the CC
8. Corpus Collosum Atrophy (CCatrophy) - total area of the corpus collosum

The following procedure was used to derive the lesion burden indices. The lesion area for each location was summed across all slices for each judge. This total was summed across the three judges and divided by three to provide the average lesion area. Lesion burden indices were then computed by summing the average lesion area across relevant locations. For example, the cerebral lesion area index (Cerebral) was the sum of the average lesion areas of the frontal, parietal, temporal, occipital lobes, and the

basal ganglia.

The PV ratings were summed across judges and divided by three to produce an average rating. The average rating was used in the analyses.

The corpus collosal scores were derived from the T2 weighted sagittal sequences. The corpus collosal lesion area score (CClesion) for each patient was computed by summing total lesion area across the three slices. The total was summed across the three judges and divided by three. The corpus collosal atrophy score (CCatrophy) was obtained via cursor measurement of the midline slice. To aid comparability with the other lesion measures, the direction of corpus collosal atrophy score was reversed (from a positive to a negative value) in the correlational analyses.

Inter-rater reliability coefficients are reported in Appendix A. One judge's measurements and ratings were significantly different from those of the other two judges. The disparity was sufficiently large to seriously affect the reliability of the measures. Because it was believed that the discrepancy was not due to the measurement procedures used, a decision was made to remove all scores and ratings of the outlying judge. All data reported below are based on only the two remaining judges.

Wechsler Memory Scale - Revised (WMS-R) (Wechsler, 1988) is an individually administered, clinically-oriented measure of memory functioning. Thirteen subtests tap various aspects of episodic primary and secondary memory, including temporal gradients (recall or recognition within a few seconds or delayed approximately 30 minutes after

initial presentation) and input-modality (verbal versus visually-mediated material). Subtests also differ on output-modality (oral, drawing, and pointing to desired responses) and the type and extent of support provided to the subject in retrieving information. The latter helps identify what, if any, material is stored and includes extensive cuing (recognition format), partial cuing (paired-associative learning paradigm), and no aid (pure recall) conditions to the subject. The following is a list of the names and a brief description of each subtest:

1. Information and Orientation - The subtest has sixteen questions of biographical data (e.g., subject's mother's first name); orientation (e.g., time and and date); and information that may help with interpreting the remaining test data (e.g., handedness and color-blindness).

2. Mental Control - This subtest consists of three exercises: counting backwards from 20 to one by ones, reciting the alphabet, and counting forward by three's.

3. Figural Memory - Sets of abstract designs are presented to the subject. Upon removal, the subject is asked to point out the designs from sets of distractor stimuli.

4. Logical Memory I - subjects are read two brief stories and asked to repeat them immediately after each presentation.

5. Visual Paired Associates I - six colored squares are paired with six abstract line drawings and these six sets of these stimuli are presented to subjects one at a time. Each line drawing is immediately re-presented to the subject, who is asked to point to the correct color from a

board showing all six colors. The task is repeated until one of two criteria is reached: perfect performance or six failed trials.

6. Verbal Paired Associates I - eight pairs of words are presented one pair at a time. The initial word of each pair is then re-presented and the subject is asked to recall its pair. Four pairs are deemed "easy" owing to the clear semantic association between words (e.g., fruit - apple) and the remaining four pairs are deemed "hard" (e.g., crush - dark). As with the Visual Paired Associates, the task is repeated until either perfect performance or six trials and only the first three trials are scored. Summary scores are also computed for performance on "hard" versus "easy" items.

7. Visual Reproduction I - subjects are shown a simple geometric design for 10 seconds. Upon its removal, subjects are asked to draw the figure from memory. There are four items.

8. Digit Span - subjects must repeat several series of digits until two trials of the same length are failed. This task is done both with a forward and reverse condition.

9. Visual Memory Span - subjects must tap series of squares in the same and reverse order of that presented by the examiner. For each condition, the number of squares to be tapped increases until the subject fails two consecutive series of identical length.

10. Logical Memory II - approximately 30 minutes after the original subtest, the subject is asked to repeat as much of each story as possible. If the subject cannot recall even one aspect of a story, the examiner can privde a brief, standarized cue.

11. Visual Paired Associates II - subjects are represented each line drawing and asked to point to the correct associated color.

12. Verbal Paired Associates II - subjects are represented each initial word and asked to recall its matched word.

13. Visual Reproduction II - subjects are asked to draw from memory each of the four geometric designs.

The scale provides normative and reliability data for five composite indices: General Memory, Verbal Memory, Visual Memory, Attention/Concentration, and Delayed Recall. For each index, relevant subtest scores are weighted and summed to be presented as a normalized standard scores with a mean of 100 and standard deviation of 15. The indices are not independent because some subtests are used in more than one index. For example, the General Memory Index is a composite of the Verbal and Visual Memory Indices. Percentile norms are provided for some subtests (Digit Span and Visual Memory Span forward and backward; immediate and delayed recall conditions of Logical Memory and Visual Reproduction). Reliability and validity data may be found in the manual.

California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1983) - the CVLT is an individually-administered measure of verbal learning and memory. Subjects are asked to recall a list of 16 words, four words from each of four semantic groups (clothing, spices, tools, and fruits) for five trials. The entire list is represented to the subject after each of the first four

trials. This is immediately followed by the presentation and recall of an interference list of 16 words (Trial B), also consisting of four words for each of four semantic categories. Subjects then are asked to recall the original 16 words (short delay free recall); and again when cued by having the four semantic categories provided to them (long-delay cued recall). Following a delay period, there is another free (long-delay free recall) and cued (long-delay cued recall) recall of the original list. Finally, subjects must recognize the original words from 28 distractor items. Five types of possible distractors are used: similarity to actual test items 1) semantically and 2) phonemically; words from the second list that are semantically 3) similar and 4) dissimilar to the original items; and 5) a set of words that has no objective similarity to any previous test items.

The CVLT manual provides normative, reliability, and validity data for numerous measures of primary and secondary verbal memory.

A summary memory index was developed (Total Memory Index - TMI) from the five WMS-R indices and six subtests from the CVLT: Trial 1, Trial 5, Trial B, short- (SDFR) and long-delay free recall (LDFR), and recognition memory hit rate (Recog - total number of correct responses). A subject's score on each of the five WMS-R and six CVLT measures was compared to the normative sample mean score, which is stratified by age and sex. Subject scores within the normal range were assigned a "0"; scores above or below one standard deviation from the normative sample mean score were assigned a "+1" or "-1", respectively; scores above or below two standard deviations were assigned a "+2" or "-2",

respectively. These scores were summed across subjects to produce the TMI.

Hypotheses

1. It is hypothesized that the correlation between the Total Memory Index and Cerebral Lesion Area score will be significantly greater than that between the Total Memory Index and each of the following MRI indices of pathology:
- Total Lesion Area
- Corpus Collosal Lesion Area
- Corpus Collosal Atrophy
- Periventricular Involvement
- PV Confluence

2. It is hypothesized that the Cerebral Lesion Area score, in comparison to each of the other measures of lesion burden, will be more significantly correlated to each of five WMS-R memory indices:

1. Attention/Concentration Memory Index
2. Verbal Memory Index
3. Visual Memory Index
4. General Memory Index
5. Delayed Recall Memory Index

3. It is hypothesized that, in comparison to the Right Hemisphere Lesion Area score, the Left Hemisphere Lesion Area score will correlate more highly with the Verbal Memory Index. Conversely, it is hypothesized that, in comparison to the Left Hemisphere Lesion Area score, the Right Hemisphere Lesion Area score will correlate more highly with the Visual Memory Index.

4. It is hypothesized that a significant memory deficit will better predict a large lesion burden than the reverse. This hypothesis will be operationalized as follows: subjects' scores on the Total Memory Index, each of the five WMS-R indices, and Cerebral Lesion Area will be split at the median. A "high" (< 50th percentile) memory score reflects significant memory impairment; a "low" ($\geq$ 50th percentile) memory score represents those who have relatively intact memory. Membership in the "high" Cerebral Lesion Area group indicates a large lesion burden and "low" Cerebral Lesion Area reflects a low lesion burden. Specific hypotheses are as follows:

a) the probability that a subject has a high TMI score given a high Cerebral Lesion Area score will be significantly lower than the probability that subject has a high Cerebral Lesion Area score given a high TMI score.

b) the probability that a subject has a high WMS-R Attention Memory Index score given a high Cerebral Lesion Area score will be significantly lower than the probability that a subject has a high Cerebral Lesion Area score given a high WMS-R Attention Index score.

c) the probability that a subject has a high Verbal Memory Index Score score given a high Cerebral Lesion Area score will be significantly lower than the probability that a subject has a high Cerebral Lesion Area score given a high Verbal Memory Index score.

d) the probability that a subject has a high Visual Memory Index score given a high Cerebral Lesion Area score will be significantly lower than the probability that a subject has a high Cerebral Lesion Area score given a high

Verbal Memory Index score.

e) the probability that a subject has a high General Memory Index score given a high Cerebral Lesion Area score will be significantly lower than the probability that a subject has a high Cerebral Lesion Area score given a high General Memory Index score.

f) the probability that a subject has a high Delayed Memory Index score given a high Cerebral Lesion Area score will be significantly lower than the probability that a subject has a high Cerebral Lesion Area score given a high Delayed Index Memory score.

RESULTS

A description of preliminary lesion and memory data will be provided before reviewing the results of the major analyses. Scores on the WMS-R and CVLT indicate the presence of significant memory deficits across the sample. At least some dysfunction has been hypothesized as necessary for optimal prediction of memory functioning by MRI-observed lesion. The MRI measures appear to be normally distributed and are thought to be valid estimates of lesion burden and its relationship to memory functioning.

Preliminary Analyses

Memory Test Performance

Table 1 shows descriptive statistics of the five WMS-R indices and six CVLT measure used in subsequent analyses involving MRI data. Sample score distributions satisfy all assumptions for normality.

Patient mean scores on these measures were compared to normative sample means as one method of estimating memory dysfunction within the patient sample. Normative data were drawn from the WMS-R and CVLT validation samples (complete descriptions of the performance of normative samples can be found in tests respective manuals). All WMS-R Index normative sample means are 100. CVLT normative means were derived from age- and sex-matched cohorts for each measure. Because of how it was developed, the Total Memory Index normal mean is zero. Because the large number of comparisons increases the possibility of random positive

Table 1

Distribution of Patient Memory Test Scores

Measure	M	SD	Md	Max	Min
WMS-R					
Verbal	94.62	15.89	97	125	58
Visual	102.15	17.12	103	138	63
General	95.59	14.57	97	124	68
Attention	95.95	15.22	96	127	64
Delayed	94.46	15.19	94	131	67
CVLT					
Trial 1	7.05	1.70	7	11	3
Trial 5	13.00	2.26	14	16	8
Total	52.79	12.34	56	73	35
Trial B	6.82	2.05	7	13	4
SDFR	10.74	3.08	11	15	3
LDFR	11.15	2.97	11	16	4
Recog	14.56	1.64	15	16	9

Note. N=39. M=mean; SD=standard deviation; Md=median; Max = maximum; Min = minimum. WMS-R = Wechsler Memory Scale - Revised. WMS-R: Verbal = Verbal Memory Index; Visual = Visual Memory Index; General = General Memory Index; Attention = Attention/Concentration Memory Index; Delayed = Delayed Memory Index. CVLT = California Verbal Learning Test. CVLT: Total = total number words trials 1-5; SDFR = Short-Delay Free Recall Trial; LDFR = Long-Delay Free Recall Trial; Recog = total number words correct on recognition trial.

findings, multivariate analyses of variance (MANOVA) first were used on the five WMS-R indices and then the six CVLT scores. A one-way univariate analysis of variance (ANOVA) was performed on the TMI. As shown in Table 2, all three analyses were significant, indicating that (a) some patient mean scores were significantly below normative sample means, (b) memory impairment exists within the patient sample, and (c) further comparison of patient versus normative sample performance was warranted.

Next, patient and normative sample mean scores for each of the five WMS-R indices and CVLT measures were compared with one-way univariate ANOVA's to identify specific areas of deficient performance. As indicated in Table 3, patient mean scores generally are lower than normative sample means, although the difference reaches significance only with the WMS-R Verbal and Delayed Memory Indices and the CVLT Trial 1 and Short-delay Free Recall measures. Trends in the predicted direction also were observed with the WMS-R General and Attention/Concentration Indices and the CVLT Long-delay Free Recall and Recognition Hits measures.

Comparison of group means provides only some evidence of memory deficit in the patient sample. Deficit prevalence rates subsequently were obtained because previous investigation suggests that analysis of mean scores, alone, can result in under-identification of sample impairment. Deficit prevalence rates were analyzed by calculating the percentage of patients with deficient performance on memory measures (operationalized as scores one standard deviation below the normative sample stratified by age and sex) and comparing this observed prevalence figure with that expected

Table 2

Patient vs. Normative Sample Mean Memory Scores: Preliminary Analyses

	Multivariate Analysis of Variance			
Source	Hotellings T^2	F	df	p
WMS-R	.64	4.38	34	.003[a]
CVLT	.87	3.96	32	.003[a]

	Univariate Analysis of Variance				
	Patient M	Normal M	F	df	p
TMI	-4.69	0.0	13.69	38	.001[a]

Note. N=39. TMI = Total Memory Index.

[a] all p-values are one-tailed.

Table 3

Patient vs. Normative Sample Mean Memory Scores: ANOVA Comparisons

Measure	Patient M	Normal M	F	p
WMS-R				
Verbal	94.62	100	4.48	.04
Visual	102.15	100	.62	NS
General	95.59	100	3.58	.07
Attention	95.95	100	2.76	.10
Delayed	94.46	100	5.19	.03
CVLT				
Trial 1	7.05	8.0	12.14	.01
Trial 5	13.00	13.0	0.00	NS
Total	52.79	56.0	2.63	NS
Trial B	6.82	7.0	0.30	NS
SDFR	10.74	12.0	6.51	.02
LDFR	11.15	12.0	3.17	.08
Recog	14.56	15.0	2.77	.10

Note. N=39. All p-values are one-tailed.

in a normal distribution via a Z-score significance test. The results provided in Table 4 strongly suggest that memory impairment is widespread across the patient sample. The prevalence of impaired performance on all scores and indices is significantly higher than expected, with the exception of the WMS-R Visual and General Memory Indices. Using CVLT Trial 1 scores as an example, 24 patients (62% of the sample) scored at least one standard deviation below the normative sample mean for their age and sex. A normal distribution would have resulted in a prevalence figure of approximately 16%. The resulting Z-score (7.84) is significant at $p < .00001$.

Overall, patient performance on the WMS-R and CVLT is comparable to previous reports of memory dysfunction in MS (e.g., Fischer, 1988) and is assumed to be valid for the purposes of the study. One exception -- the apparent lack of visual memory impairment -- requires additional comment. At least some impairment is thought to be a necessary precondition for maximizing prediction of memory functioning by lesion burden measures. Because this condition is not met, subsequent analyses involving visual memory will receive special attention.

MRI Lesion Measures

Some lesion measure distributions were sufficiently skewed that they violated the assumptions necessary for parametric statistics. Using the Statistical Package for the Social Sciences - Personal Computer (SSPS-PC) program "Examine", two cases were determined to be responsible for the majority of the distortion. When the two cases were deleted, lesion score distributions fell within acceptable

Table 4

Observed vs. Expected Memory Deficit Prevalence Rates

Measure	# below 1 SD	% below 1 SD	expected % below 1 SD	Z
WMS-R				
Verbal	10	26	16	1.70*
Visual	6	15	16	0.17
General	8	21	16	0.85
Attention	10	26	16	1.70*
Delayed	11	28	16	2.04*
CVLT				
Trial 1	24	62	16	7.84***
Trial 5	18	46	16	5.11***
Total	13	33	16	2.90**
Trial B	18	46	16	5.11***
SDFR	20	51	16	5.96***
LDFR	19	48	16	5.45***
Recog	16	41	16	4.26***

Note. N=39.

* $p<.05$, one-tailed. ** $p<.01$, one-tailed. *** $p<.001$, one-tailed.

limits for use of parametic statistics. Table 5 shows the MRI score distributions with the adjusted sample (N = 39).

Next, Pearson-product moment correlations between each of the MRI measures were compared to identify possible relationships important to subsequent analyses involving memory functioning. Table 6 shows that, with the exception of the correlation between corpus collosal atrophy (CCATROPHY) and corpus collosum lesion area (CCLESION), all correlations are significant at $p < .001$ (two-tailed). Relatively high lesion variable intercorrelations were predicted as an estimate of measurement reliability and validity. That is, if scoring procedures are reliable and valid, one should have seen fairly strong correlations between plaque measure. However, the extremely high correlations observed in some cases warrant further attention. Of particular interest are the correlations between the whole brain (Brain), bi-hemisphere cerebral (Cerebral), left-hemisphere cerebral (Left), and right-hemisphere cerebral (Right) lesion area measures. The almost perfect correlation between the Brain and Cerebrum indices is due to the paucity of infratentorial lesion; cerebellar and brain stem plaque was a small fraction (less than five percent) of total lesion area within the brain. This could reflect sampling error or poor visualization of the infratentorium by the MRI. Because of the lack of difference between the two measures, a decision was made to drop the total brain score from future analyses.

Overall, preliminary analyses provide sufficient evidence that the conditions necessary for valid examination of proposed hypotheses are met. Variable distributions are

Table 5

Lesion Measure Distributions

Measure	M	SD	Md	Max	Min
CClesion[a]	97	107	67	418	0
CCatrophy[a]	480	106	475	715	276
Brain[a]	2585	1834	1826	6080	139
Cerebral[a]	2525	1791	1792	6066	139
Left[a]	1221	908	974	3363	74
Right[a]	1304	934	995	3086	61
PVinvolve[b]	2.4	1.3	2.0	5.0	1.0
PVconflu[c]	2.1	0.8	2.0	3.0	1.0

Note. N=39. CClesion = corpus collosal lesion area. CCatrophy = total corpus collosal area. Brain = brain lesion area. Cerebral = cerebral lesion area. Left = left-hemisphere cerebral lesion area. Right = right-hemisphere cerebral lesion area. PVinvolve = periventricular involvement ratings. PVconflu = periventricular confluence ratings.

[a] units are mm^2. [b] units are ordinally scaled, 1-5. [c] units are ordinally scaled, 1-3.

Table 6

Lesion Measure Intercorrelations

	CC atrophy	PV involve	PV conflu	Left	Right	Cerebral	Brain
CClesion	.40*	.58	.49	.69	.77	.75	.75
CCatrophy		.70	.65	.70	.53	.63	.63
PVinvolve			.84	.85	.80	.85	.85
PVconflu				.75	.71	.75	.75
Left					.89	.97	.97
Right						.97	.97
Cerebral							.99

Note. N=39.

* $p<.01$, two-tailed. All others $p<.001$, two-tailed.

within normal limits. Measures of lesion burden and memory do not appear to be significantly different from previous studies using similar methodology. We will turn now to the analyses for the major hypotheses.

Primary Analyses

Hypothesis 1

The first prediction was that the correlation between the TMI and cerebral lesion area would be greater than that between the TMI and each of the other measures of lesion burden. To test the hypothesis, the first step was to obtain correlations between lesion variables and the TMI. One-tailed significance levels were used since there was no empirical or theoretical basis to suggest that memory performance would improve with increased lesion loads. Table 7 shows that only cerebral lesion area and ratings of periventricular confluence were significantly correlated with the TMI ($p < .05$, one-tailed). Next, a priori t-tests for dependent correlations were used to contrast the correlation between TMI and cerebral lesion area with the correlation between TMI and the other lesion indices. The results shown in Table 7 indicate that only the contrast involving corpus collosal lesion area (CCLESION) was significant and in the predicted direction [$t(36) = 2.04$, $p < .05$, two-tailed).

Hypothesis 2

The second prediction was that cerebral lesion area, in comparison to the other lesion measures, would correlate most highly with the five WMS-R indices. To test this hypothesis, the same methodology was used as for Hypothesis

Table 7

Lesion Measure Correlations with Total Memory Index: Comparison with Cerebral Lesion Area

Pearson Correlations

Measure	CC lesion	CC atrophy	PV involve	PV conflu	Cerebral
TMI	-.08	-.20	-.24	-.36*	-.30*

Note. N=39.

* $p<.05$, one-tailed.

Cerebral Lesion Area vs. Other Lesion Measures: Correlations with TMI

Cerebral vs:	difference	t	v	p
CClesion	.22	2.04	36	.05
CCatrophy	.10	.73	36	NS
PVinvolve	.06	.69	36	NS
PVconflu	-.06	-.54	36	NS

Note. N=39. All t-tests two-tailed.

#1 except that a more conservative critical value was used to control for the larger number of correlations and comparisons. The correlation matrix of lesion variables with WMS-R is provided in Table 8. Only three correlations were statistically significant: Visual Memory with cerebral lesion area ($r = -.50$, $p < .001$, one-tailed), ratings of periventricular involvement ($r = -.43$, $p < .01$, one-tailed), and corpus collosal atrophy ($r = -.53$, $p < .001$, one-tailed).

Despite the preponderance of insignificant correlations, a decision was made to carry through with the planned comparisons. T-tests for dependent correlations with a critical value yielding rejection at the $p = .01$ level (two-tailed) were used to reduce the probability of a Type I error. Although largely in the predicted direction, cerebral lesion area appeared more strongly related to memory functioning only in two instances: versus corpus collosal lesion area on WMS-R Visual Memory Index [$t(36) = 2.73$, $p < .01$] and Delayed Recall [$t(36) = 2.95$, $p < .01$].

A similar method was used to investigate whether lesion measure correlations with the CVLT were more in keeping with predictions that cerebral lesion area would be more highly correlated than the other lesion measures with memory performance. Actual rejection of the null hypothesis ($r = .00$) was made at $p < .01$ to control for the large number of correlations. Again, one-tailed significance levels were used since there was no empirical or theoretical basis to suggest that memory would improve with increased lesion loads. The correlation matrix of lesion and specific CVLT measures is shown in Table 9. Generally, the pattern of

Table 8

Lesion Measure Correlations with WMS-R Indices

Measure	CC lesion	CC atrophy	PV involve	PV conflu	Cerebral
WMS-R					
Verbal	.15	.10	.01	-.13	.01
Visual	-.23	-.53**	-.43*	-.34	-.50**
General	.07	-.15	-.18	-.24	-.18
Attention	-.25	-.29	-.23	-.28	-.28
Delayed	.08	-.08	-.26	-.20	-.27

Note. N=39.

* $p<.01$, one-tailed. ** $p<.001$, one-tailed.

Table 9

Lesion and CVLT Measure Correlations

Measure	CC lesion	CC atrophy	PV involve	PV conflu	Cerebral
CVLT					
Trial 1	-.03	-.16	-.11	-.37*	-.21
Trial 5	-.08	-.20	-.30	-.47*	-.33
Total	-.01	-.24	-.12	-.37*	-.20
Trial B	-.12	-.16	-.13	-.30	-.29
SDFR	-.14	-.32	-.42*	-.43*	-.49**
LDFR	-.07	-.32	-.35	-.39*	-.39*
Recog	.00	.00	-.13	-.21	-.15

Note. N=39.

* $p<.01$, one-tailed. ** $p<.001$, one-tailed.

results using the CVLT measures was similar to those observed with the TMI; however, the CVLT measures did provide more support for the hypothesis. In comparison to the WMS-R indices, more CVLT correlations reached significance and, in general, cerebral lesion area correlations were larger than the other lesion burden measures. However, t-tests for dependent correlations showed that cerebral lesion area correlations were significantly greater than the other lesion measures only in comparison to corpus collosal lesion area on the CVLT Trial 1 and 5, and Short- and Long-delay Free Recall measures (for all comparisons $p < .01$, two-tailed).

Hypothesis 3

It was predicted that left hemisphere cerebral lesion area would be more highly correlated with the WMS-R Verbal Memory Index than right hemisphere lesion area. Similarly, it was predicted that right hemisphere cerebral lesion area would be more highly correlated with the WMS-R Visual Memory Index than left hemisphere lesion area. Observed correlations between left- and right-hemisphere cerebral lesion area and the Verbal Memory Index were $r = .001$ and $r = .01$, respectively. An a priori t-test for dependent correlations performed to contrast these correlations was insignificant [$t(36) = .11$, $p > .50$, two-tailed]. Correlations with the Visual Memory Index were $r = -.52$ for the right hemisphere and $r = -.46$ for the left hemisphere cerebral lesion areas. The difference between the two correlations was not significant [$t(36) = -.33$, $p > .20$, two-tailed]. Similar analyses were attempted on all WMS-R Verbal and Visual Memory Index subtests, as well as the six

CVLT measures. This was done to reveal whether more detailed investigation might demonstrate the hypothesized relationship between lateralized plaque and modality-specific memory dysfunction. However, only one significant contrast was observed. CVLT recognition hit rate scores correlated more highly with right-hemisphere lesion area ($r = -.24$) than left-hemisphere lesion area ($r = -.06$), $t(36) = 2.72$, $p < .05$ (two-tailed). Moreover, this relationship was in the opposite direction of what would be predicted given normal lateralization of function. That is, the left-hemisphere measure should have been more highly associated with a verbal memory measure than the right-hemisphere score. Finally, preliminary analyses also indicated that the two cerebral indices also did not differ in terms of ability to predict memory functioning relative to the other lesion measures.

Hypothesis 4

The fourth prediction was that subjects with significant memory deficits would have significant amounts of cerebral lesion, but that subjects with significant cerebral lesion would not necessarily have significant memory deficits. Operationally, the hypothesis states that the conditional probability of having a "high" amount of cerebral lesion (i.e., above the sample median) given a "high" memory deficit (i.e., performance below the median) would be higher than the conditional probability of a "high" memory deficit given a "high" degree of cerebral lesion. This relationship was tested by comparing the conditional probabilities and by contrasting the observed frequency of each condition (i.e., high deficit given high lesion; high

lesion given high deficit) with the frequency expected if there were no relationship between cerebral lesion area and memory performance. These analyses were completed with the TMI and each of the five WMS-R indices. Figures 1 through 6 (found on pages 135 - 140) provide a visual presentation of the data including the raw frequencies, the expected and observed conditional probabilities, and resulting p-values.

As predicted, the conditional probabilities are in the expected direction for all six memory measures; however, none of the differences are sufficient to support the hypothesis. Using the data associated with the TMI as an example, Figure 1 shows that the probability of having a memory deficit (i.e., "high deficit"), given a large amount of cerebral lesion (i.e., "high lesion") is .60. Conversely, the probability of having a large amount of lesion, given a low Verbal Memory Index Score, is .67. The difference between the conditional probabilites, while in the predicted direction, is relatively small.

Similarly, comparison of the probability that the observed versus the expected conditional probabilities would occur randomly across the two conditions did not not support the hypotheses. Returning to the example of the Total Memory Index, the bottom half of Figure 1 shows that there is little difference between the probabilities of the observed versus expected conditions (i.e., p = .12 versus .07, respectively) in the two probability statements.

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	13	7
	Low	6	13

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.65	.50	.07
Probability of high lesion given high deficit:	.68	.50	.05

Figure 1. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and Total Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	12	8
	Low	6	13

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.60	.50	.12
Probability of high lesion given high deficit:	.67	.50	.07

Figure 2. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and WMS-R Verbal Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	11	9
	Low	7	12

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.55	.50	.17
Probability of high lesion given high deficit:	.61	.50	.12

Figure 3. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and WMS-R Visual Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	12	8
	Low	6	13

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.60	.50	.12
Probability of high lesion given high deficit:	.67	.50	.07

Figure 4. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and WMS-R General Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	13	7
	Low	5	14

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.65	.50	.07
Probability of high lesion given high deficit:	.72	.50	.03

Figure 5. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and WMS-R Attention Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Frequency Distribution

		Memory Deficit	
		High	Low
Lesion	High	12	8
	Low	7	12

Conditional Probability

	Observed	Expected	p
Probability of high deficit given high lesion:	.60	.50	.12
Probability of high lesion given high deficit:	.63	.50	.09

Figure 6. Frequency and Conditional Probability of Membership to Median Splits of Cerebral Lesion Area and WMS-R Delayed Memory Index. (N=39. High = $\geq$ 50th percentile. Low = < 50th percentile. p = probability that the difference between the observed and expected conditional probabilities would occur by chance.)

Supplementary Analyses

The lower than expected correlations between many lesion and memory measures led to a search for possible mediator variables. Three disease factors (course type, illness duration, and number of years since diagnosis) and three patient characteristics (handedness, education, and IQ) were evaluated.

Three course-types were represented in the sample -- chronic-progressive, relapsing-remitting, and benign -- and evaluated first by a univariate ANOVA with TMI as the dependent variable. This analysis failed to reveal any apparent difference between course types [$F(2, 36) = .51$, $p > .60$]. Next, a MANOVA was performed to test whether there were any course differences across the five WMS-R indices. The resulting Hoetellings T^2 value was insignificant ($F(5, 34) = .24$, $p > .40$]; therefore subsequent ANOVAs with each WMS-R index were not obtained. Finally, Pearson product-moment correlations between lesion burden measures and the TMI and WMS-R indices were compared with second-order, partial correlations between the same variables (i.e., the correlation between lesion burden and memory measures with the effects of course partialed out). Little or no difference was observed between the zero- and second-order correlations, again suggesting that course does not mediate the relationship between lesion burden and memory.

Since illness duration and years since diagnosis are continuously distributed variables, analysis of variance was not the appropriate statistical method for evaluating their impact on lesion burden - memory relationships. Instead, zero-order correlations were obtained between the two

temporal disease measures and the six memory (i.e., the TMI and five WMS-R indices) and five lesion burden variables. As observed in Table 10, only one reached significance even using a very liberal critical value for post-hoc analyses. The more generous critical value was used to minimize the possibility of failing to reject a false null hypothesis (Type II error). The Verbal Memory Index was significantly correlated with years since diagnosis ($r = -.35$, $p < .05$, two-tailed). However, when patient age subsequently was partialled out of both temporal disease variables, all correlations between memory and the two measures of disease duration fell to less than .10 -- an insignificant level of correlation.

One final attempt was made to estimate the degree to which disease characteristics may mediate the relationship between lesion variables and the TMI and WMS-R indices. Disease characterisitics were held constant through second-order partial correlations. The resulting partial correlations between lesion and memory measures then were compared to original zero-order correlations between lesion and memory indices. There were no significant differences between the zero-order and partial correlations with the TMI or WMS-R indices, suggesting that these disease characteristics do not mediate the relationship between memory and lesion burden.

A similar methodology was used to examine the possible mediating effects of IQ and education on lesion burden correlations with memory dysfunction. Zero-order correlations were obtained between the TMI and WMS-R indices and education (in years) and IQ (WAIS-R Full Scale, Verbal,

Table 10

Illness Length Correlations with Memory Functioning

Measure	Illness Duration	Years Since Diagnosis
TMI	-.04	-.15
WMS-R		
Verbal	-.21	-.35*
Visual	-.05	.00
General	-.20	-.30
Attention	-.03	-.12
Delayed	-.09	-.20

Note. N=39.

* $p < .05$, two-tailed.

and Performance IQ scores). As shown in Table 11, both IQ and education are highly and positively correlated with the TMI and WMS-R indices. A subsequent step would be to obtain partial correlations--correlations between lesion burden and memory performance while controlling for IQ and education.

Before proceeding, however, an attempt was made to determine whether the cognitive capacities tested on the WAIS-R were affected by MS. If so, WAIS-R IQ scores cannot be used in the proposed partial correlations because IQ would be confounded with lesion burden. This question was tested by obtaining correlations between WAIS-R IQ scores and the five lesion measures (Table 12). One-tailed significance levels were used because previously reviewed data clearly indicates that intelligence test performance does not increase with increased lesion load. Converesely, large negative correlations would indicate that performance on the WAIS-R decreases as lesion load increases -- evidence that cognitive impairment resulted from MS and that WAIS-R scores would not be a valid measure of premorbid cognitive functioning. This appears to be the case, as the correlations generally are large and negative, especially those associated with FIQ and PIQ. These findings necessitated that the WAIS-R be dropped as a way of determining the relationship between lesion burden and memory deficit while controlling for the effects of premorbid cognitive functioning.

On the other hand, it was believed that education would not be confounded with lesion burden since most subjects had completed their education before onset of MS. And, in fact, correlations between lesion variables and years of education

Table 11

Memory Functioning Correlations with Education and WAIS-R IQ

Measure	WAIS-R FIQ	WAIS-R VIQ	WAIS-R PIQ	Years of Education
TMI	.69**	.66**	.52**	.35
WMS-R				
Verbal	.32	.45*	.08	.35
Visual	.65**	.40	.69**	.02
General	.52**	.53**	.35	.34
Attention	.66**	.58**	.54**	.14
Delayed	.62**	.47*	.56**	.25

Note. N=39. FIQ = WAIS-R Full Scale IQ; VIQ = WAIS-R Verbal Scale IQ; PIQ = WAIS-R Performance Scale IQ.

* $p < .01$, two-tailed. ** $p \leq .001$, two-tailed.

Table 12

Lesion Measure Correlations with WAIS-R IQ

	WAIS-R		
Measure	FIQ	VIQ	PIQ
CClesion	-.16	.02	-.30
CCatrophy	-.39*	-.18	-.49**
PVinvolve	-.27	-.08	-.38*
PVconflu	-.35	-.21	-.39*
Cerebral	-.36*	-.13	-.49**

Note. N=39.

* $p<.01$, one-tailed. ** $p<.001$, one-tailed.

were insignificant (r = .03, -.13, -.20, -.07, and .01 for CCLESION, CCATROPHY, PVINVOLVE, PVCONFLU, and CEREBRAL, respectively) using a very liberal critical value ($p < .05$, two-tailed). Although recognizing that years of education is only a rough estimate of premorbid cognitive capacities, it was used to obtain an estimate of the relationship between memory performance and lesion burden while controlling for premorbid cognitive ability. These partial correlations are found in Table 13 with the original zero-order correlations in parentheses. Visual inspection shows almost no difference between the zero-order and partial correlations. These findings suggest that education and possibly premorbid intellectual capacity do not mediate the relationship between lesion burden and memory functioning.

Table 13

Lesion and Memory Measure Correlations With and Without Education Effects

Measure	CC lesion	CC atrophy	PV involve	PV conflu	Cerebral
TMI	-.09 (-.08)	-.16 (-.20)	-.23 (-.24)	-.31* (-.36*)	-.32* (-.30*)
WMS-R					
Verbal	.15 (.15)	-.16 (.10)	.04 (.01)	-.05 (-.13)	.00 (.01)
Visual	-.23 (-.23)	-.53*** (-.53***)	-.43** (-.43**)	-.34* (-.34*)	-.50*** (-.50***)
General	.07 (.04)	-.11 (-.15)	-.16 (-.18)	-.18 (-.24)	-.20 (-.18)
Attention	-.26 (-.25)	-.28 (-.29)	-.23 (-.23)	-.27 (-.28)	-.28 (-.28)
Delayed	.03 (.08)	-.05 (-.08)	-.25 (-.26)	-.15 (-.20)	-.28 (-.27)

Note. N=39. All parentheses indicate zero-order correlations between lesion and memory measures. All others are the partial correlation between lesion and memory measures with the effects of education held constant.

* $p<.05$, one-tailed. ** $p<.01$, one-tailed. *** $p<.001$, one-tailed.

DISCUSSION

The main thesis of the study, that cerebral lesion area would be associated more strongly with memory test performance than other measures of MS lesion burden, received little support. Several issues are offered to explain these findings, including the role of acute versus chronic lesion flux. Lower than expected correlations between cerebral lesion area and memory may due, in part, to a nonlinear relationship between acute lesion area and functioning. It is suggested that, as lesion size increases during relapse, the strength of the relationship to functioning decreases proportionately. Because chronic lesion area is not thought to ebb and flow over time, it is suggested that chronic lesion extent may be more linearly related to and more predictive of memory disturbance than acute plaque. Some practical difficulties in measuring lesion dissemination are proposed as responsible for the failure of hypotheses relating to infra- versus supratentorial plaque and left versus right hemisphere lesion. Finally, variables that may mediate the relationship between lesion - memory relationships are discussed. Although several potential factors were evaluated in this study, it is not clear that features such as disease course or premorbid functioning of the patient are not involved with lesion burden and memory deficit associations.

Relative and Absolute Values of Lesion Measures

Cerebral Lesion Area

Cerebral lesion area was not clearly more sensitive to memory functioning than other MRI indices of lesion burden. In its relationship to several measures of memory, cerebral lesion area was comparable to ratings of periventricular confluence, inconclusively superior to corpus collosal atrophy and ratings of periventricular involvement, and clearly superior to corpus collosal lesion area. One implication of these findings is that total lesion area may be quite similar to representational indices in its sensitivity to memory disturbances in MS. This author had attributed, in part, Franklin et al.'s (1988) successful investigation to their use of more direct, as opposed to representational, measures of lesion burden. This position does not appear to be tenable, at least in the specific case of single-study cerebral lesion area. A model is offered that may help explain the current study's findings as well as previous failures to demonstrate a significant correlation between lesion area and cognitive functioning (e.g., Callanan et al., 1989; Huber et al., 1987).

The explanation returns us to the discussion on imaging differences between acute and chronic plaque. Longitudinal MRI (e.g., Willoughby et al., 1989) and assessment of nonvisualized relaxation times (e.g., Larsson et al., 1988) suggested that large changes in plaque size are not closely associated with changes in the clinical picture. Several pathophysiological processes associated with acute disease activity (e.g., edema) are thought to produce rather large increases in MRI-visualized plaque with correspondingly less

impact on functioning. On the other hand, chronic gliosis-ridden plaque may disrupt functioning with smaller total area and considerably less fluctuation in size than acute lesion (e.g., Willoughby et al., 1989). Because cross-sectional studies derive total lesion area from a sum of both acute and chronic plaques, the strength of the correlation between lesion area and symptom is diluted. A measure only of acute lesion would be bi-modally distributed with respect to its association to symptoms. At the lower end of the lesion area - symptom curve, little dysfunction is seen. More symptoms appear as lesion area increases but only to the point where acute lesion area rises exponentially -- as during an active disease phase. Past this asymptote, the correlation between lesion area and symptoms will decline because the large, puffy areas of confluence seen in acute phases are relatively less disruptive to functioning. On the other hand, chronic plaque area would show a fairly straight-forward linear relationship -- as chronic plaque area increases, more symptoms would appear and the correlation between the two would remain largely unchanged. A measure that combines acute and chronic plaque area would result in a deficit - lesion curve shaped like the acute lesion area curve: linear at lower lesion area levels, curvilinear in between (with an asymptote at the peak of the active phase), and a linear relationship at the upper end of the curve. The return to a linear relationship with larger lesion areas reflects the fact that correlations between lesion area and symptom again would increase when the combined lesion area curve includes more chronic plaque relative to acute changes (i.e., the

acute phase has ended and relatively fewer "blooming" lesions are seen). The overall relationship of acute lesion area to functioning would be decreased because middle portions of the curve would cancel out the linear extremes. By comparison, a combination lesion area index would have slightly higher symptom correlations because it includes measurement of chronic plaque. Conversely, the combination lesion area index would show less of a consistent relationship with dysfunction than a measure specific to chronic plaque.

Returning to the cerebral lesion area measure used in this study, the borderline significant correlations with memory test performance may reflect the consistent relationship with chronic plaque and the blurred association with acute lesion area. Acute lesion fluctuation would explain the lower than expected correlation values reported elsewhere (e.g., Huber et al., 1987) in a similar fashion. Decreased lesion - symptoms correlations due to acute lesion area flux also is consistent with investigations reporting significant lesion area associations with dysfunction (i.e., Franklin et al., 1988). Their correlations between cerebral lesion area grades and several measures of memory ranged from r = -.28 to -.36; very comparable to those reported in this study. The only difference between Franklin et al. and the current study is that the former's sample size of 60 allows for lower critical values. Acute lesion fluctuation effects also could explain the failure to demonstrate cerebral lesion area superiority to representational measures of plaque burden. Cerebral lesion area would appear comparable to representational measures because both

are equally reflective of chronic and acute plaque burden.

Future investigations easily could test the acute lesion area fluctuation hypothesis. It suggests that estimates of chronic lesion area would be more sensitive to dysfunction than either an acute or a combined acute-chronic lesion area measure. Gadolinium-enhanced MRI, longitudinal MRI, and evaluation of specific MRI relaxation times could provide such data.

The difference between chronic and acute lesion area change is not the only factor which may account for generally low lesion - function correlations. Several others will be discussed, including the direct versus representational dichotomy.

Total Brain Lesion Area

Comparison of the relative strength of cerebral versus whole brain lesion area was not tested adequately. The prevalence of posterior fossa lesion in this sample was well below previous reports using similar MRI protocols. It is not clear whether this finding represents a sampling artifact, poor judgement on the part of the raters, or a combination of the two. Distinguishing lesion from normal brain stem and cerebellar tissue is a difficult task owing to the dense white-matter and surrounding CSF found in these areas. This problem is reflected in the lower inter-rater reliability figures shown in Appendix A. Even if a more representative sample of brain stem and cerebellar involvement were observed, however, the ratio of infra- to supratentorial plaque area still may be so small as to obscure an understanding of their relative effects on memory. Lesion area in the brain stem and cerebellum is a

small fraction of all brain plaque (Lumsden, 1970). The issue of proportionality, in addition to problems associated with acute plaque flux, suggests that lesion area probably is not the best way of discriminating the relative strength of cerebral versus noncerebral lesion burden relationships to cognitive changes.

Corpus Collosal Involvement

Comparative analyses of corpus collosal atrophy and cerebral lesion area were inconclusive. There was no marked difference between the two measures across WMS-R subtests, although cerebral lesion area was more highly correlated with performance on the CVLT and the TMI. Because of methodological differences, it is difficult to resolve these results with Huber et al.'s (1987) findings that suggested that corpus collosal atrophy was superior to cerebral lesion area in predicting cognitive dysfunction. Huber et al. used a five-point rating scale of atrophy rather than cursor tracings yielding total corpus collosal area. Also, their MRI measures were used to predict membership to one of three degrees of general cognitive impairment rather than memory dysfunction. The results of the current study certainly do not force a reappraisal of Huber et al.'s (1987) conclusion that cognitive deficit is predicted by corpus collosal atrophy because it reflects lesion involvement elsewhere. Research on commissurotomy patients suggests that they perform within normal limits on most standard tests of cognition (including memory), but struggle on those tasks requiring integrated transmission of information between the hemispheres (e.g., LeDoux, Risse, Springer, Wilson, & Gazzaniga, 1977; Springer & Deutsch, 1985). Given that

corpus collosal atrophy allows at least some interhemispheric traffic, it is probably the case that corpus collosal atrophy interferes with intact performance only on tasks with relatively significant communication between the hemispheres. If this attribution is correct, corpus collosal atrophy would be a direct indicator of clinico-pathology associations only where memory tests involve heavy interhemispheric transmission of information. Because neither the WMS-R nor the CVLT appear similar to tasks known to produce such effects, it would seem that corpus collosal atrophy sensitivity to WMS-R and CVLT performance occurs because the atrophy reflects pathology elsewhere.

The strongest findings of this study were that corpus collosal lesion area predicts memory functioning rather poorly, both absolutely and in comparison to cerebral lesion area and across all memory tasks and patient and disease factors. No previous reports could be found that used corpus collosal lesion area as a predictor of any aspect of cognition. Therefore, it is not clear why there were such consistent differences between corpus collosal and cerebral lesion area or collosal atrophy in their sensitivity to memory impairment. Review of the literature on the corpus collosum and topics other than MS gave no warning that atrophy and lesion area would correlate differently with memory. One possible explanation begins with the assumption that the WMS-R and CVLT do not require intact corpus collosal functioning. Given findings that corpus collosal atrophy is more strongly related to WMS-R and CVLT scores than corpus collosal lesion area, one can infer that,

although corpus collosal atrophy is a representational measure, corpus collosal lesion area is not. If so, then a measure that is specific to pathology in the corpus collosum only -- such as lesion area -- would not be expected to correlate highly with performance on the WMS-R or CVLT.

A subsequent step would be to determine why MS plaque in other areas of the brain is reflected by the degree of CC atrophy, but not actual corpus collosum lesion. One possibility returns us to the discussion on imaging of acute versus chronic lesions and their association to functioning. While not specifically addressed by Weller (1985) and others (e.g., Ormerod et al., 1987), their data suggest that the atrophic changes seen on MRI reflect the permanent loss of myelin and oligodendroglial cells over a long period of time. If accurate, an atrophic measure would show more consistent correlations with symptoms because atrophy is more reflective of chronic than acute lesion burden, whereas corpus collosal lesion area includes the measurement fluctuation problems of acute plaque.

Periventricular Involvement

No marked differences were observed between the two indices of PV involvement and cerebral lesion area their association to memory. PV confluence was one of only two measures (with cerebral lesion area) to correlate significantly with the Total Memory Index, but confluence ratings did not consistently outperform other MRI measures. Like the corpus collosum, previous explanations of the effectiveness of periventricular involvement in predicting cognitive dysfunction included direct versus representational conceptualizations. Rao et al. (1984)

suggest that demyelination of prefrontal-limbic pathways running near the ventricles can result in memory loss. Thus, ratings of PV involvement may directly measure neural demyelination. Conversely, Huber at al. (1987) write that PV measures are useful only because they accurately reflect extent of CNS pathology throughout. These positions are not mutually exclusive, however. In fact, the relative success of some PV indices in predicting cognitive deficit may indicate a combination of both direct and indirect measurement. This study's methodology, unfortunately, does not allow one to differentiate between PV involvement as a specific, representational, or combinatory index of MS lesion burden.

Regardless of the outcome of the direct versus representational issue, the lack of consistent differences between the two PV measures and cerebral lesion area can be explained through two other factors. One involves the acute lesion fluctuation model. Because both PV indices included ratings of acute plaque, one would predict generally poor correlations with memory functioning as well as little dissociation between other measures that include measurement of acute plaque -- such as cerebral lesion area.

The second factor concerns the high degree of correlation between the two PV ratings and cerebral lesion area (Table 6). It is not clear that these three MRI measures were sufficiently different to make reliable statements about their relative sensitivity to memory test performance. Theoretically it may be that PV involvement is less predictive of memory disturbance than cerebral lesion area, the close correspondance between these indices of

lesion burden makes it difficult to separate them in practical applications. As will be discussed below, this relative lack of difference between predictor variables also explains the failure of lesion laterality predictions.

A last comment about PV lesion is directed towards problems encountered in objectifying measurement -- a universal complaint in the MRI literature. Subjective ratings, alone, were used in this study by default. Originally, PV lesion area (i.e., plaque having at least some contact with a ventricle) also was to have been included in MRI scoring. Inter-rater reliability for this measure was abysmal, however, and a decision was made to drop it from the study before the final scoring protocol was completed. The most troublesome scoring problem was in differentiating the border between plaque and ventricle. Unfortunately, MRI parameters that best highlight anatomical features and MS plaque also result in comparable levels of brightness between ventricle and lesion. This imaging difficulty, the question of representational versus direct measurement, and the acute lesion fluctuation problem provide more than ample explanation for the consistent failure to demonstrate significant correlations between cognitive dysfunction and PV indices.

Uni-hemisphere Lesion Area

The data clearly did not support hypotheses that lateralized cerebral lesion area differentially correlates with modality-specific memory functioning. These negative findings may be attributed to the almost identical lesion area distribution between the left and right hemispheres (Table 6), which makes it difficult to predict to any

criterion. Equal hemispheric involvement is a consistent finding with autopsy (Lumsden, 1970) and MRI study (Marvilla, 1988) and the resulting restriction of range may be why the topic has been studied so little in MS. Previous empirical support for lateralization hypotheses was weak and only tangentially related to the issue. Brainin et al. (1988) reported a significant gradation of verbal memory deficit with medial temporal lobe lesions. Maximum severity was associated with bi-lateral involvement, uni-lateral lesion with moderate impairment, and more normal functioning was observed in subjects without medial temporal lesion area involvement. However, in four of the five "uni-lateral" patients, the lesion were on the right side rather than the left -- the reverse of what would be expected given normal lateralization of function (e.g., Walsh, 1985). Franklin et al. (1988) reported significant correlations between uni-hemisphere cerebral lesion area and verbal and nonverbal memory tests, but did not publish specific results nor comment on the relative correlation strengths of left- versus right-sided plaque. In lieu of data specific to MS, hypothesized lateralization effects were based on considerable clinical data indicating that other types of uni-lateral pathology (e.g., stroke) can result in modality-specific memory deficits (e.g., Walsh, 1987). The results published here do not disprove the hypothesis that right cerebral lesion is responsible more for nonverbal than verbal memory disturbances. However, the lack of lesion burden differences between the hemispheres makes demonstration a practical impossibility.

Other factors also may have contributed to the negative

findings. More specific localization of lesion indices, such as restricting comparisons to temporal lobe involvement, may have improved correlations with verbal and nonverbal memory. Unreliable nonverbal memory measurement may have obscured hypothesized relationships. Despite several changes from the WMS to improve the reliability and validity of nonverbal memory tasks, WMS-R Visual Index subtests have been routinely criticized. The most common complaint is that subjects use verbal strategies to augment performance on supposedly nonverbal tasks. A second potential problem is one of ceiling effects. It is not clear that the WMS-R visual memory subtests are as difficult verbal ones and, in fact, the patient sample in this study performed within normal ranges on visual memory tasks. It may be that patients did have visual memory deficits but, because of the ease of the tasks, no impairments were observed. If true, attempts to demonstrate that increased lesion burden results in decreased function would be doomed because of the resulting restriction of range.

MRI-observed Lesion: Necessary or Sufficient?

It was proposed that MRI-observed cerebral demyelination may be conceptualized as a necessary but insufficient condition for memory deficit. Comparisons of conditional probabilities -- the probability of impairment given considerable cerebral lesion versus the probability of significant cerebral lesion given memory impairment -- were in the predicted direction but were insufficient to support the hypothesis. Before rejecting either the specific results or the study technique though, some methodological issues should be addressed. A primary concern is the choice

of cut-off scores for inclusion criteria. Because no previous research could be found to guide such a decision, median splits were chosen arbitrarily as critical values for both memory functioning and cerebral lesion area. It may be that there is a critical range of plaque load, only past which does memory impairment occur. Use of more discrete cerebral lesion area groupings (e.g., quartiles) would greatly enhance the identification of any naturally occurring critical value. Unfortunately, investigations of this nature would require a relatively large sample to ensure sufficient cell size for each memory and lesion burden measure grouping. The second issue that may have resulted in a serious reduction in the power of the analyses is the aforementioned acute lesion flux problem. Future MRI investigations could exclude acute plaque area from lesion burden measures to more accurately test the conditional probability hypotheses.

Supplemental Analyses

The weaker than expected relationships between lesion burden and memory functioning led to a search for factors that might have mediated their relationship. However, the absolute and relative strength of lesion burden - memory correlations were not markedly different when disease course, length of illness, and type and degree of memory deficit were taken into consideration. Premorbid cognitive capacity, as estimated by years of education, also did not appear to moderate the relationship between MRI measures and memory test performance.

Aspects of Memory

Verbal versus visual memory. It does not appear that lesion burden is differentially sensitive to visual versus verbal memory functioning. Although MRI measure correlations with the WMS-R Visual Memory Index were significantly greater from those with the Verbal Memory Index, other factors suggest that the results are spurious. First, strong lesion - memory correlations also were seen on the CVLT, indicating that poor correlations with MRI indices were not generalized to all verbal memory impairments. Secondly, information modality was confounded with deficit severity. Subjects performed within normal limits on the WMS-R Visual Memory Index but showed significant impairments on the WMS-R Verbal Memory Index and other estimates of verbal memory functioning. Therefore, it may be that lesion burden best predicts normal-range functioning, rather than visual memory per se. A third argument against concluding that the relationship between lesion burden and memory is stronger with visual than with verbal material, is the lack of empirical and theoretical support for such an association. The only other investigation reporting verbal and nonverbal memory correlations with MRI-observed plaque involvement (Franklin et al., 1988) observed no appreciable modality differences. Certainly, no current model of memory physiology and function would lead one to posit differential sensitivity to the effects of MS plaque. Returning to the present study, correlations between lesion measures and the WMS-R Verbal Memory Index were so weak as to cause one to question whether this result is due simply to sampling artifact.

Deficit severity. Correlations between lesion burden and memory functioning were not necessarily stronger when memory was depressed. For example, tests on which the sample performed best (e.g., WMS-R Visual Memory Index) yielded the highest and most consistent correlations with lesion burden. Conversely, the weakest correlations observed were associated with the WMS-R Verbal Memory Index -- subtests on which patients performed quite poorly. These instances are not particularly good examples because, as noted above, modality is confounded with deficit severity. However, visual inspection of the correlation matrices shows that there is no reliable pattern between lesion burden and degree of deficit on memory measures other than the Visual and Verbal Memory Indices. Previous failures to observe consistent associations between memory and MRI-observed plaque have been ascribed, in part, to a lack of deficient memory performance in test samples (e.g., Callanan et al., 1989). This does not appear to be the case and, in fact, some support can be marshalled for the reverse: correlations increase with less impaired levels of performance. Investigations of cognitive functions other than memory have reported that predictions from lesion burden improve with increased test performance levels. For example, correlations between Franklin et al.'s (1988) cerebral involvement scores and measures of memory and other information processing tasks (e.g., Trails A & B; Symbol Digit Modalities) were largest on tests with more normal-range than impaired performance distributions. Similarly, Hill (1991) observed that prediction by lesion burden measures was superior on information processing tests with

less, rather than more, impairment. Because neither study specifically compared normal versus impaired cognitive performance correlations with MRI scores, their findings should be considered with caution. One interpretation for the higher lesion - dysfunction correlations with more normal performance is purely statistical. It may be that increased impairment results in a restricted range of performance, thus making prediction difficult as deficit severity increases. Whether range restriction is the sole explanation for the findings involving normal versus impaired performance, it is clear that the relationship between lesion - symptom correlations and the severity of cognitive impairment is not a simple, inverse association. The lack of deficit severity effects also indicates that observation of strong correlations between plaque and dysfunction does not mean, necessarily, that the patient is experiencing considerable dysfunction. This point is most important to clinicians and is a clear warning to avoid predictions about prognosis based solely on MRI.

Primary versus secondary memory. The strength of the association between lesion burden and memory functioning was similar across measures of primary and secondary memory. An almost identical pattern of correlations was observed between MRI scores and the WMS-R Attention/Concentration and Delayed Recall Memory Indices -- the studies' two best single measures of primary and secondary memory, respectively. Exploration of possible primary versus secondary memory differences was based on the hypothesis that increased deficit severity would result in increased lesion burden correlations with memory (e.g., Callanan et

al., 1989). Because subjects were thought to perform better on measures of PM than SM (e.g., Rao et al., 1989), it was believed that lesion burden would be more strongly related to Delayed Recall performance in comparison to scores on the subtests of the Attention/Concentration Memory Index. As discussed above, the deficit severity hypothesis did not hold up. The failure to demonstrate differential lesion burden relationships between PM and SM also may be attributed to the observation that SM was not clearly more impaired than PM in this sample. For example, group mean performance on the WMS-R Attention/Concentration and Delayed Recall was not appreciably different and the prevalence of impaired performance on the two indices was almost identical (26% and 28%, respectively).

At least two factors should be addressed, however, before rejecting the possibility that primary and secondary memory differ in their association to measures of lesion burden. First, the relatively small correlations between lesion burden and memory test performance make it difficult to tease out more subtle relationships. Even more problematic is that the memory tests used in this study may not have differed sufficiently in their PM and SM processing requirements. A chief short coming of the WMS-R and CVLT is that it is difficult to parcel out the effects of PM on later SM processing tasks. Using the prose paragraph delayed recall task of the WMS-R as an example, failure on this test may reflect intact SM in the presence of significant PM deficit. A PM impairment would prevent adequate storage of the story at input regardless of whether SM was intact or not. This problem with separating primary

from secondary memory deficit has been detailed previously and is a difficult obstacle to overcome.

Aspects of Predictor Variables

Ilness duration. The absence of a relationship between illness duration and lesion - memory correlations in this study is consistent with a similar lack of association between illness length and lesion - motor/sensory disturbance correlations (e.g., Kiel et al., 1986) and prevalence or severity of cognitive (e.g., Grant et al., 1988; Ivnik, 1978) or noncognitive impairment (e.g., Matthews et al., 1985). Whether measured as the latency since symptom onset or diagnosis, no reliable connection between illness duration and memory has been reported. Whatever pathophysiological mechanisms are responsible for memory impairment in MS, they clearly do not involve a simple accrual of effects over time.

Illness course. Memory test performance was similar across three disease courses (benign, chronic-progressive, and relapsing-remitting) and course type did not appear to change the strength or quality of the association between plaque and memory measures. For a number of reasons, however, these findings should be considered with caution. First, since no previous study has reported course relationships to lesion - memory dysfunction correlations, some replication is necessary. Also, the small sample size of course groups within this investigation greatly increases the possibility of sampling error. Finally, considerable controversy exists concerning course distinctions in memory functioning (e.g. Fischer, 1988 vs. Heaton et al., 1985) or pathoanatomical changes inferred from disease activity (e.g.

Omerod et al., 1987 vs. Grossman et al., 1986). As was highlighted in the literature review, there have been strikingly few investigations of course and clinical disease activity regardless of the research question, but especially in regards to cognitive disturbance. Future examination of lesion burden - memory associations should include some treatment of such factors as course and disease activity.

Premorbid cognitive functioning. Premorbid cognitive functioning appeared to have almost no relationship to lesion - memory correlations. Although not previously investigated, it may be that increased premorbid functioning "innoculates" the patient's susceptibility to the effects of MS lesion. These findings argue otherwise, but because only a very gross measure was used -- years of education -- the question of possible mediating effects of premorbid cognition was not addressed adequately here.

Comments Concerning Study Reliability and Validity

The quality of the relationship between memory function and structure bears some responsiblity for the continuing difficulty to characterize the association between MRI-observed lesion burden and deficit. Neural pathways involved with intact memory processing are thought to be exponentially more numerous and complex than those subserving primary sensory and motor function. By all appearances, memory lacks the one-to-one correspondence between lesion and function as is observed in the case of cervical cord or optic nerve plaque and sensory disturbance. Optimal prediction of memory impairment via MRI will require scoring methods that parallel the complexity of the neural

systems subserving memory.

We also have not begun to consider many other pathoanatomic factors that could change the nature of the relationship between MRI-observed plaque and memory function. These include but certainly are not limited to: neural pathway redundancy, neuronal plasticity of function, and the speed with which pathologic changes occur. For example, we cannot assume that two lesions -- identical in size and location but having a different course -- have the same functional effects. These issues cause one to question whether prediction of memory function from such gross indices as lesion size and lobule location will be anything approaching precise. It is more likely that successful investigation will rely on much more fine-grained levels of analysis. For example, a narrowly defined area of function (e.g., storage of information pertaining to human faces) will be matched with measurement of plaque in very circumscribed locations (e.g., left-hemisphere parieto-occipital white matter tracts).

It is not clear whether the type of MS sample used in this study contributed to the results in an unexpected fashion. The rationale for drawing subjects from support group membership was to ensure a more random sample of MS patients than has previously been described. Sampling only from those who have had contact with clinical services risked drawing from amoung those patients most likely to have memory deficits. As expected, the sample drawn in this investigation included patients both with and without memory impairments. Given the growing body of evidence that it is difficult to predict dysfunction via MRI-observed pathology,

it may be best to control for factors other than those being explicitly studied until lesion - symptom relationships are better understood. For the time being, it may be wise for experimental samples to include patients with memory deficit or patients without, but samples should not include both impaired and unimpaired patients.

A similar sampling strategy may be applied to other factors potentially mediating memory and plaque associations. While the patient and disease characteristics examined in this study did not appear to mediate lesion - dysfunction correlations, caution seems warranted given the lack of conclusive evidence to the contrary. Conservatism also should be shown with regards to other aspects of MS not addressed specifically in this study. Of those reviewed from the literature, symptom flux seems a particularly likely candidate for consideration. Changes in the quality and quantity of motor and sensory impairment over time and their relationship to MRI-observed pathology are just being described (e.g., Grossman et al., 1986). No similar investigations have been reported with memory and other cognitive capacities, in part, because of the many difficulties associated with identifying subtle temporal changes in higher cortical functioning. Yet, there is no a priori reason to dismiss the possibility that prediction from MRI data may be different across de novo versus exacerbated versus stable cognitive deficits.

MRI protocols and other issues associated with measurement of lesion burden also must be evaluated further to determine their impact on studies of lesion - function relationships. The wide variations in methodology make it

exceedingly difficult to compare results across studies or to identify which combination of measurement parameters best fit any given research question. More objective means of estimating lesion burden would be greatly beneficial on all counts. The recent development of the computerized cursor tracings is promising in this regard, although its reliability remains questionable (Franklin et al., 1988). Clinical judgement will never be removed totally from the situation since motion artifact and other scoring issues defy complete objectivity. Close communication between radiologists, neuropsychologists, and neurologists is needed to develop more reliable scoring criteria and strategies.

Sorting out the relative contribution of acute versus chronic plaque on functioning seems paramount given the findings and concerns identified in this study. Single-study measures of lesion area may be a biased estimate of disease involvement and confirmation either way is sorely needed. This issue leads to final comments pertaining to the strategy of using MRI data in understanding clinical and pathology changes in MS. The findings of this study add to a very long list indicating that cross-sectional MRI may not be sufficiently sensitive to fully identify the patho-anatomic and -physiological changes resulting in dysfunction. Previously reveiwed research suggests that centrifugal spread of plaque, incomplete myelination, remyelination, impaired neuronal transmission due to edema versus gliosis, and permanent versus temporary breakdown of neural substrates are important to changes in function. Yet, we are unable to comment on such processes using MRI alone. Even if all the MRI measurement difficulties noted

above were properly addressed, it is probably the case that a more microscopic level of analysis is needed to fully illucidate the pathological changes responsible for memory disturbance in MS.

APPENDIX

APPENDIX A

Inter-rater Correlations: MRI Data

	GN	GR	NR	AVE	ADJ
Brain Sten	.66	.68	.57	.64	.84
Cerebellum	.62	.65	.32	.53	.77
Corpus Collosum	.16	.78	.02	.32	.57
Basal Ganglia	.36	.18	.17	.24	.48
Internal Capsule	.27	.79	.09	.38	.65
Right Frontal Lobe	.69	.85	.66	.73	.89
Left Frontal Lobe	.79	.80	.78	.79	.92
Right Temporal Lobe	.60	.91	.55	.68	.87
Left Temporal Lobe	.51	.89	.52	.64	.84
Right Parietal Lobe	.80	.59	.61	.67	.86
Left Parietal Lobe	.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 raters reliability: average correlation among three raters

ADJ = composite reliability computed using Spearman-Brown formula

LIST OF REFERENCES

REFERENCES

Acheson, E. D. (1985). The epidemeology of multiple sclerosis. The pattern of the disease. In W. B. Matthews, E. D. Acheson, J. R. Batchelor, & R. O. Weller (Eds.), McAlpine's Multiple Sclerosis (pp. 301-343). Edinburgh: Churchill Livingstone.

Adams, C. W. M. (1983). The general pathology of multiple sclerosis: Morphological and chemical aspects of the lesions. In J. Hallpike, C. Adams, & W. Tourtelloutte (Eds.), Multiple sclerosis: Pathology, diagnosis, and management. (pp. 203-240). Cambridge, England: University Press.

Albert, M., Butters, N., & Brandt, J. (1981). Patterns of remote memory in amnesic and demented patients, Archives of Neurology, 36, 211-216.

Albert, M. L., Feldman, R. G., & Willis, A. L., (1974). The 'subcortical dementia' of progressive supranuclear palsy. Journal of Neurology, Neurosurgery, and Psychiatry, 37, 121-130.

Anderson, J. (1976). Language, memory, and thought. Hillsdale, NJ: Erlbaum.

Ashcraft, M. H. (1989). Human memory and cognition. Boston: Scott, Foreman and Company.

Baddeley, A. D. (1981). The concept of working memory: A view of its current state and probable future development. Cognition, 10, 17-23.

Baddeley, A. D., & Hitch, G. (1974). Working memory. In G. H. Bower (Ed.), The psychology of learning and motivation. (Vol. 8, pp. 47-89).

Barbellion, W. N. P. (1919). The journal of a disappointed man. London: Chatto and Windus.

Barnes, D., McDonald, W. I., Tofts, P. S., Johnson, G., & Landon, D. N. (1986). Nuclear magnetic resonanace imaging of experimental cerebral oedema. Journal of Neurology, Neurosurgery, and Psychiatry, 49, 1341-1347.

Baum, H. M., & Rothschild, B. B. (1981). The incidence and prevalence of reported multiple sclerosis. Annals of Neurology, 10, 420-428.

Bauer, H. J., Firnhaber, W., & Winkler, W. (1965). Prognosis criteria in multiple sclerosis. Annals of the New York Sciences, 122, 542-551.

Beatty, P. A., & Gange, J. J. (1977). Neuropsychological aspects of multiple sclerosis. The Journal of Nervous and Mental Disease, 164, 42-50.

Beatty, W. W., Goodkin, D. E., Monson, N., Beatty, P. A., & Hertzgaard, D. (1988). Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. Archives of Neurology, 45, 611-619.

Blakemore, W. F. (1982). Myelination, demyelination, and remyelination in the CNS. In W. T. Smith & J. B. Cavanagh, (Eds.), Recent advances in neuropathology 2. (pp. 53-81). Edinburgh: Churchill Livingstone.

Bofousslavsky, J., Fox, A. J., Carey, L. S., Vinitski, S., Bass, B., Noseworthy, J. H., Ebers, G. C., & Barnett, J. M. (1986). Correlates of brain-stem oculomotor disorders in multiple sclerosis. Archives of Neurology, 43, 460-463.

Brain, W. R. (1930). Critical review: disseminated sclerosis. Quarterly Journal of Medicine, 23, 343-391.

Brainin, M., Goldenberg, G., Ahlers, C., Reisner, T., Neuhold, A., & Deecke, L. (1988). Structural brain correlates of anterograde memory deficits in multiple sclerosis. Journal of Neurology, 235, 362-365.

Brorson, J., Graffman, B., Grossman, R., Silberberg, D., & Gonzalez-Scrarano, F. (1988). Repeat gadolinium MRI in a series of MS patients. Neurology, 38(supplement 1), 255.

Brown, J. (1958). Some tests of the decay theory of immediate memory. Journal of Experimental Psychology, 10, 12-21.

Brownell, B., & Hughes, J. T. (1962). The distribution of plaques in the cerebrum in multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry, 25, 315-320.

Bottomley, P. A., Hart, H. R., Edelstein, W. A., Schenck, J. F., SMith, L. S., Leue, W. M., Mueller, O. M., & Redington, R. W. (1984). Anatomy and metabolism of the normal human brain studied by magnetic resonance at 1.5 Tesla. Radiology, 150, 441-446.

Caine, E. D., Bamford, K. A., Schiffer, R. B., Shoulson, I., & Levy, S. (1986). A controlled neuropsychological comparison of Huntington's disease and multiple sclerosis. Archives of Neurology, 43, 249-254.

Cala, L. A., & Mastaglia, F. L. (1976). Computerized axial tomography in multiple sclerosis. Lancet, 1, 689.

Cala, L. A., Mastaglia, F. L., & Black, J. L. (1978). Computerized tomography of brain and optic nerve in multiple sclerosis. Journal of the Neurological Sciences, 36, 411-426.

Callanan, M. M., Logsdail, S. J., Ron, M. A., & Warrington, E. K. (1989). Cognitive impairment in patients with clinically isolated lesions of the type seen in multiple sclerosis. Brain, 112, 361-374.

Carlson, N. R. (1981). Physiology of behavior. (second ed.). Boston: Allyn and Bacon.

Carroll, M., Gates, R., & Roldan, F. (1984). Memory impairment in multiple sclerosis. Neuropsychologia, 22, 297-302.

Castaigne, R., Lhermitte, F., Escourolle, R., Hauw, J. J., Gray, F., & Lyon-Caen, O. (1981). Assymptomatic scleroses and plaques. Review of Neurology, 137, 729.

Cermak, L. S. (1982). The long and short of it in amnesia. In L. S. Cermak (Ed.), Human memory and amnesia (pp. 43-59). Hillsdale, NJ: Lawrence Erlbaum Associates.

Charcot, J. M. (1877). Lectures on the diseases of the nervous system delivered at the Salpetriere. (G. Sigerson, Trans.). London: New Syndenham Society.

Cohen, N. (1984). Preserved learning capacity in amnesia: Evidence for multiple memory systems. In L. R. Squire & N. Butters (Eds.), Neuropsychology of memory (pp. 83-103). New York: Guilford Press.

Compston, A. (1986). Genetic factors in the aetiology of multiple sclerosis. In W. I. McDonald & D. H. Silberberg (Eds.), Multiple sclerosis (Vol. 6, pp. 56-73). London: Butterworths.

Compston, A. (1988). The 150th anniversary of the first depiction of the lesions of multiple sclerosis. Journal of Neurology, 51, 1249-1252.

Confavreux, C., Aimard, G., & Devic, M. (1980). Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients. Brain, 103, 281-300.

Crisp, D. T., Kleiner, J. E., DeFillip, G. J., Greenstein, J. I., Liu, T. H., & Sommers, D. (1985). Clinical correlations with magnetic resonance imaging in multiple sclerosis. [Abstract], Neurology, 35, 137.

Cummings, J. L., & Benson, D. F. (1984). Subcortical dementia: Review of an emerging concept. Archives of Neurology, 41, 874-879.

Cummings, J. (1990). Subcortical dementia. New York: Oxford University Press.

Dawson, J. W. (1916). The history of disseminated sclerosis. Transcripts of the Royal Society of Edinburgh, 50, 517-521.

Dejong, R. N. (1970). Multiple sclerosis: history, definition, and general considerations. In P. J. Vinken & G. W. Byrun (Eds.), Handbook of clinical neurology. Multiple sclerosis and other demyelinating diseases (Vol. 9, pp. 45-62). Amsterdam: North-Holland.

Delay, J., & Brion, S. (1969). Korsakoff's syndrome. Paris: Masson.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (1983). CVLT Manual: The Califorina Verbal Learning Test. San Antonio: The Psychological Corporation.

Delouvrier, J. J., Tritschler, J. L., Desbeldes, M. T., Cambier, J., & Nahum, H. (1980). Computerized tomography in multiple sclerosis. In H. Wackenheim & G. H. du Boulay (Eds.), Choices and characteristics in computerized tomography. (pp. 81-91). Proceedings of the Eighth Congress of the European Society of Neuroradiology. Amsterdam: Kugler.

De Weerd, A. W. (1979). Computerized tomography in multiple sclerosis. Clinical Neurology and Neurosurgery, 12, 33-42.

Ebbinghaus, H. (1885/1913). Memory: A contribution to experimental psychology. (H. A. Ruger, & C. E. Bussenius, Trans.). New York: Columbia University, Teachers College.

Ebers, G. C., Paty, D. W., & Sears, E. S. (1984). Imaging in multiple sclerosis. In C. M. Poser, D. W. Paty, W. I. McDonald, L. Scheinberg, & G. C. Ebers (Eds.), The diagnosis of multiple sclerosis (pp. 185-201). New York: Thieme-Stratton.

Edwards, M., Farlow, M., & Stevens, J. (1986). Multiple sclerosis: MRI and clinical correlation. American Journal of Radiology, 147, 571-574.

Elpern, S. J., Gunderson, C. H., Kattah, J., & Kirsch, A. D. (1984, February). Cognitive and memory functioning in recently diagnosed chronic multiple sclerosis. Paper presented at the meeting of the International Neuropsychological Society, Houston, TX.

Elster, A. D. (1986). Magnetic resonance imaging: A reference guide and atlas. Philadelphia: J. B. Lippincott.

Elster, A. D. (1988). Cranial magnetic resonance imaging. New York: Churchhill Livingstone

Erickson, R. C., & Scott, M. L. (1977). Clinical memory testing: A review. Psychological Bulletin, 84, 1130-1149.

Estes, W. (1982). Learning, memory, and intelligence. In W. K. Estes (Ed.), Handbook of Human Intelligence (pp. 170-224). New York: Cambridge University Press.

Field, E. J. (1984). Multiple sclerosis: an abiotrophy with heuristic implications. In G. Scarlato & W. B. Matthews (Eds.), Multiple Sclerosis. Present and Future, New York: Plenum, pp. 119-143.

Field, E. J. (1988). Multiple sclerosis: A conceptual reappraisal with heuristic implications. Springfield, IL: Charles C. Thomas

Firth, D. (1948). The case of Augustus D'Este. Cambridge: University Press.

Fischer, J. S. (1988). Using the Wechsler Memory Scale-Revised to detect and characterize memory deficits in multiple sclerosis. The Clinical Neuropsychologist, 2, 149-172.

Franklin, G. M., Heaton, R. K., Nelson, L. M., Filley, C. M., & Seibert, C. (1988). Correlation of neuropsychological and MRI findings in chronic/ progressive multiple sclerosis. Neurology, 38, 1826-1829.

Fog, T. (1965). The topography of plaques of multiple sclerosis (with special reference to cerebral plaques). Acta Neurologica Scandinavica, 41, supplementum 15.

Gerbarski, S. S., Gabrielsen, T. O., Gilman, S., Knake, J. E., Latack, J. T., & Aisen, A. M. (1985). The initial diagnosis of multiple sclerosis: Clinical impact of magnetic resonance imaging. Annals of Neurology, 17, 469-474.

Gonzalez-Scarano, F., Spielman, R. S., & Nathanson, N. (1986). Epidemeology. In W. I. McDonald & D. H. Silberberg (Eds.), Multiple sclerosis (Vol. 6, pp. 37-55). London: Butterworths.

Grant, I. (1986). Neuropsychological and psychiatric disturbances in multiple sclerosis. In W. I. McDonald & D. H. Silberberg (Eds.), Multiple sclerosis. (pp. 134-152). London: Butterworth.

Grant, I., McDonald, W. I., Patterson T. L., & Trimble, M. R. (1986). Life events and multiple sclerosis. In G. W. Brown & T. Harris (Eds.), Life events and illness: Studies of psychiatric and physical disorders (pp. 73-90). New York: Guilford Press.

Grant, I., McDonald, W. I., Trimble, M. R., Smith, E., & Reed, R. (1984). Deficient learning and memory in early and middle phases of multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry, 47, 250-255.

Grossman, R. I., Gonzalez-Scarano, F., Atlas, S. W., Galetta, S., & Silberberg, D. H. (1986). Multiple sclerosis: Gadolinium enhancement in MR imaging. Radiology, 161, 721-725.

Gyldensted, C. (1976). Computer tomography of the cerebrum in multiple sclerosis. Neuroradiology, 12, 33-42.

Hallpike, J. (1983). Clinical aspectes of multiple sclerosis. In J. Hallpike, C. Adams, & W. Tourtelloutte (Eds.), Multiple sclerosis: Pathology, diagnosis, and management. (pp. 129-162). Cambridge, England: University Press.

Harrison, B. M., McDonald, W. I. Ochoa, J., Ohlrich, G. D. (1972). Paranodal demyelination in the central nervous system. Journal of the Neurological Sciences, 16, 489-494.

Haughton, V. M., Ho, K. C., Williams, A. L., & Eldevik, O. P. (1979). CT detection of demyelinated plaques in multiple sclerosis. American Journal of Radiology, 132, 213-215.

Heaton, R. K., Nelson, L. M., Thompson, D. S., Burks, J. S., & Franklin, G. M. (1985). Neuuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. Journal of Consulting and Clinical Psychology, 53, 103-110.

Herman, D. O. (1988). Development of the Wechlser memory scale - revised. The Clinical Neuropsychologist, 2, 102-106.

Hershey, L. A., Gado, M. H., & Trotter, J. L. (1979). Computerized tomography in the diagnostic evaluation of multiple sclerosis. Annals of Neurology, 5, 32-39.

Hill, R. S. (1990). Magnetic resonance imaging correlates of neuropsychological dysfunction in multiple sclerosis patients: A confirmatory factor analysis approach. Unpublished doctoral dissertation, Michigan State University, East Lansing, Michigan.

Hirschenfang, S., & Benton, J. G. (1966). Note on intellectual changes in multiple sclerosis. Perceptual Motor Skills, 22, 786.

Horel, J. A. (1978). The neuroanatomy of amnesia: A critique of the hippocampal memory hypothesis. Brain, 101, 403-445.

Huber, S. J., Paulson, G. W., Shuttleworth, E. C., Chakeres, D., Clapp, L. E., Pakalnis, A., Weiss, K., & Rammohan, K. (1987). Magnetic resonance imaging correlates of dementia in multiple sclerosis. Archives of Neurology, 44, 732-736.

Isaac, C., Li, D. K., Genton, M., Jardine, C., Grochowski, E., Palmer, M., Kastrukoff, L. F., Oger, J., & Paty, D. W. (1988). Multiple sclerosis: A serial study using MRI in relapsing patients. Neurology, 38, 1511-1515.

Ivnik, R. J. (1978). Neuropsychological test performance as a function of the duration of MS-related symptomology. Journal of Clinical Psychiatry, 39, 311-312.

Jacobs, L., & Kinkel, W. R. (1976). Computerized axial tomography in multiple sclerosis. Neurology, 26, 390-391.

Jacobs, L., Kinkel, W., Polachini, I., & Kinkel, R. (1986). Correlations of nuclear magnetic resonance imaging, computerized tomography, and clinical profiles in multiple sclerosis. Neurology, 36, 27-34.

Jambor, K. L. (1969). Cognitive functioning in multiple sclerosis. British Journal of Psychiatry, 115, 765-775.

James, H. (1890). The principles of psychology. New York: Dover.

Jennekens-Schinkel, A., & Sanders, E. A. (1986). Decline of cognition in multiple sclerosis: Dissociable deficits. Journal of Neurology, Neurosurgery, and Psychiatry, 49, 1354-1360.

Johnson, R. T., Katzman, R., McGeer, E., Price, D., Shooter, E. M., & Silberberg, D. (1979). Report on the panel of inflammatory, demyelinating, and degenerative disease (Report No. 79-1916). Washington, D.C.: U.S. Department of Health, Education, and Welfare.

Johnson, M. A., Li, D. K., Bryant, D. J., & Payne, J. A. (1984). Magnetic resonance imaging: serial observations in multiple sclerosis. American Journal of Neuroradiology, 5, 495-499.

Kappos, L., Stadt, D., Ratzka, M., Keil, W., Schneiderbanger-Grygier, S., Heitzer, T., Poser, S., & Nadjmi, M. (1988). Magnetic resonance imaging in the evaluation of treatment in multiple sclerosis. Neuroradiology, 30, 299-302.

Kiel, M. K., Greenspun, B., & Grossman, R. I. (1988). Magnetic resonance imaging and degree of disability in multiple sclerosis. Archives of Physical Medicine Rehabilitation, 69, 11-13.

Kirshner, H. S., Tsai, S. I., Runge, V. M., & Price, A. C. (1985). Magnetic resonance imaging and other techniques in the diagnosis of multiple sclerosis. Archives of Neurology, 42, 859-863.

Koopsman, R. A., Li, D. K. B., Grochowski, E., Cutler, P.J., & Paty, D. W. (1989). Benign versus chronic progressive multiple sclerosis: magnetic resonance imaging features. Annals of Neurology, 25, 74-81.

Kurtske, J. F. (1965). Further notes on disability evaluation in multiple sclerosis with scale modifications. Neurology, 15, 654-661.

Kurtske, J. F. (1986). Neuroepidemiology. II. Assessment of therapeutic trials. Annals of Neurology, 19, 311-319.

Kurtske, J. F., Beebe, G. W., Nagler, B., Kurland, L. T., D., Auth, T. L. (1970). Studies on the natural history of multiple sclerosis 8: early prognostic features of the later course of the illness. Journal of Chronic Diseases, 30, 819-830.

Kurtske, J. F., Beebe, G. W., Nagler, B., Nefzger, M. D., Auth, T. L., Kurland, L. T. (1970). Studies on the natural history of multiple sclerosis 5: Long term survival in young men. Archives of Neurology, 22, 215-225.

Kurtzke, J. F., Beebe, G. W., & Norman, J. E. (1979). Epidemeology of multiple sclerosis in US veterans: Race, sex, and geographic distribution. Neurology, 29, 1228-1235.

Larsson, H. B., Frederiksen, J., Kjaer, L., Henriksen, O., & Olesen, J. (1988). In vivo determination of T1 and T2 in the brain of patients with severe but stable multiple sclerosis. Magnetic resonance in medicine, 7, 43-55.

LeDoux, J. E., Risse, G., Springer, S., Wilson, D., & Gazzaniga, M. (1977). Cognition and commissurotomy. Brain, 100, 87-104.

Leibowitz, U., Kahana, E., Jacobsen, S. G., Alter, M. (1972). The cause of death in multiple sclerosis. In U. Leibowitz (Ed.), Progress in multiple sclerosis (pp. 196-209). New York: Academic Press.

Lezak, M. D. (1983). Neuropsychological assessment. (2nd ed.). New York: Oxford University Press.

Limburg, C. C. (1950). The geographic distribution of multiple sclerosis and its estimated prevalence in the United States. Proceedings of the Association for Research into Nervous and Mental Diseases, 28, 15-24.

Litvan, I., Grafman, J., Vendrell, P., & Martinez, J. M. (1988). Slowed information processing in multiple sclerosis. Archives of Neurology, 45, 281-285.

Litvan, I., Grafman, J., Vendrell, P., Martinez, J. M., Junque, C., Vendrell, J. M., & Barraquer-Bordas, L. (1988). Multiple memory deficits in patients with multiple sclerosis. Archives of Neurology, 45, 607-610.

Loftus, E. (1979). Eyewitness testimony. Cambridge, MA: Harvard University Press.

Lukes, S. A., Crooks, L. E., Aminoff, M. J., Kaufman, L., Panitch, H. S., Mills, C., & Norman, D. (1983). Nuclear magnetic resonance imaging in multiple sclerosis. Annals of Neurology, 13, 592-601.

Lumsden, C. E. (1970). The neuropathology of multiple sclerosis. In P. J. Vinken & G. W. Byrun (Eds.), Handbook of clinical neurology. Multiple sclerosis and other demyelinating diseases (Vol. 9, pp. 217-309). Amsterdam: North-Holland.

Luria, A. R. (1966). Higher Cortical Functions in Man. London: Tavistock.

Lyon-Caen, O., Jouvent, R., Hauser, S., Chaunu, M. P., Benoit, N., Widlocher, D., & Lhermitte, F. (1986). Cognitive function in recent-onset demyelinating diseases. Archives of Neurology, 43, 1138-1141.

Mack, J. L. (1986). Clinical assessment of disorders of attention and memory. Journal of Head Trauma Rehabilitation, 1(3), 22-33.

MacKay, R. P., & Hirano, A. (1967). Forms of benign multiple sclerosis: Report of two "clinically silent" cases discovered at autopsy. Archives of Neuorology, 17, 588-597.

Maravilla, K. R. (1988). Multiple sclerosis. In D. D. Stark & W. G. Bradley, Jr. (Eds.), Magnetic resonance imaging (pp. 344-358). St. Louis: C. V. Mosby.

Marsh, G. (1980). Disability and intellectual function in multiple sclerosis. Journal of Nervous and Mental Disease, 168, 758-762.

Matias-Guiu, J., Sanz, M., Molins, A., Bonaventura, I., & Capdevila, A. (1986). Correlations of MRI with the clinical status of patients with multiple sclerosis. [Abstract], Neurology, 36, (Suppl. 1), p. 177.

Matthews, W. B. (1985). Part 2: Clinical aspects. In W. Matthews, E. Acheson, J. Batchelor, & R. Weller (Eds.), McAlpine's multiple sclerosis. (pp.49-280). Edinburgh: Churchill Livingstone.

Matthews, W. B., Acheson, E. D., Batchelor, J. R., & Waller, R. O. (1985). McAlpine's multiple sclerosis. (Eds.) Edinburgh: Churchill Livingstone.

McAlpine, D. (1972). Multiple sclerosis: A reappraisal (2nd ed.). Edinburgh: Churchill Livingstone.

McAlpine, D., Compston, N. D., & Lumsden, C. E. (1955). Multiple Sclerosis. Edinburgh: Churchill Livingstone.

McDonald, W. I., & Halliday, A. M. (1977). Diagnosis and classification of multiple sclerosis. British Medical Bulletin, 33, 4-9.

McDonald, W. I., & Silberberg, D. H. (1986). Multiple Sclerosis (Eds.). Boston: Butterworths.

Medaer, R. (1979). Does the history of multiple sclerosis go back as far as the 14th century? Acta Neurologica Scandinavica, 60, 189-192.

Medaer, R., Nelissen, E., Appel, B., Swertz, M., Geutjens, J., & Callaert, H. (1987). Magnetic resonance imaging and cognitive functioning in multiple sclerosis. Journal of Neurology, 253, 86-89.

Meuller, E. (1904). Die multiple sclerose des Gehirns and Ruckenmarks. Jena, Germany: Fischer.

Miller, G. A. (1956). The magical number seven: Plus or minus two. Some limits on our capacity for processing information. Psychological Review, 9, 81-97.

Morariu, M., & Klutzow, W. F. (1976). Subclinical multiple sclerosis. Journal of Neurology, 71, 213-220.

Murdock, B., Jr. (1962). The serial position effect of free recall. Journal of Experimental Psychology, 64, 482-488.

Namerow, N. S., & Thompson, L. R. (1969). Plaques, symptoms, and the remitting course of multiple sclerosis. Neurology, 19, 765-775.

Olmos-Lau, N., Ginsberg, M., & Geller, J. (1977). Aphasia in multiple sclerosis. Neurology, 27, 623-626.

Oppenheimer, D. R. (1976). Demyelinating diseases. In W. Blackwood & J. A. N. Corsellis, (Eds.) Greenfield's neuropathology, London: Arnold.

Ormerod, I. E., Miller, D. H., McDonald, W. I., du Boulay, E. P., Rudge, P., Kendall, B. E., Moseley, I. F., Johnson, G., Tofts, P. S., Halliday, A. M., Bronstein, A. M., Scaravilli, F., Harding, A. E., Barnes, D., & Zilkha, K. J. (1987). The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: A quantitative study. Brain, 110, 1579-1616.

Ormerod, I. E., du Boulay, G. H., & McDonald, W. I. (1986). Imaging of multiple sclerosis. In W. I. McDonald & D. H. Silberberg (Eds.), Multiple sclerosis (Vol. 6, pp. 11-36). London: Butterworths.

Paty, D. W., Bergstrom, M., Palmer, M., MacFadyen, J., & Li, D. (1985). A quatitative magnetic resonance image of the multiple sclerosis brain. [Abstract], Neurology, 35(Suppl. 1), 137.

Paty, D. W., Koopsman, R., Willoughby, E., & Li, D. K. (1988). Serial MRI studies in multiple sclerosis: A new method for assessing disease activity in both chronic progressive and relapsing patients. [Abstract], Neurology, 38(Suppl. 1), 255.

Paty, D. W., Oger, J. J., Kastrukoff, L. F., Hashimoto, S. A., Hoogs, J. P., Eisen, A. A., Eisen, K. A., Purves, S. J., Low, M. D., Brandejs, V., Robertson, W. D., & Li, D. K. (1988). MRI in the diagnosis of MS: A prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology, 38, 180-185.

Penfield, W. (1958). The excitable cortex in concious man. Springfield, IL: Thomas.

Petersen, R. C., & Kokmen, E. (1989). Cognitive and psychiatric abnormalities in multiple sclerosis. Mayo Clinic Proceedings, 64, 657-663.

Peterson, L., & Peterson, M. (1959). Short-term retention and meaningfulness. Journal of Experimental Psychology, 58, 193-198.

Peyser, J. M., Edwards, K. R., Poser, C. M., & Filskov, S. B. (1980). Cognitive function in patients with multiple sclerosis. Archives of Neuorology, 37, 577-579.

Poser, C. M. (1980). Exacerbations: Activity and progression in multiple sclerosis. Archives of Neurology, 37, 471-474.

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Silberberg, D. H., & Tourtellotte, W. W. (1983). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Annals of Neurology, 13, 227-231.

Poser, S., Wikstrom, J., Bauer, H. J. (1979). Clinical data and the identification of special forms of multiple sclerosis in 1271 cases studied with a standardized documentations system. Journal of Neurological Sciences, 40, 159-168.

Prigatano, G. P. (1978). Wechsler Memory Scale: A selective review of the literature. Journal of Clinical Psychology, 34, 816-832.

Pykett, I. L., & Rosen, B. (1983). Nuclear magnetic resonance: in vivo proton chemical shift imaging. Radiology, 149, 197-201.

Rao, S. M. (1986). Neuropsychology of multiple sclerosis: A critical review. Journal of Clinical and Experimental Neuropsychology, 8, 503-542.

Rao, S. M., Glatt, S., Hammeke, T. A., McQuillen, M. P., Khatri, B. O., Rhodes, A. M., & Pollard, S. (1985). Chronic progressive multiple sclerosis: Relationship between cerebral ventricular size and neuropsychological impairment. Archives of Neurology, 42, 678-682.

Rao, S. M., Hammeke, T. A., McQuillen, M. P., Khatri, B. O., Lloyd, D. (1984). Archives of Neurology, 41, 625-631.

Rao, S., Leo, G., & St. Aubin-Faubert, P. (1989). On the nature of memory disturbance in multiple sclerosis. Journal of Clinical and Experimental Neuropsychology, 11, 699-712.

Reynolds, A., & Flagg, P. (1983). Cognitive Psychology (2nd ed.). Boston: Little, Brown, & Company.

Robertson, W. D., Li, D., Mayo, J., Genton, M., & Paty, D. W. (1985). Magnetic resonance imaging in the diagnosis of multiple sclerosis. Journal of Neurology, 232(Suppl. 1), 58.

Rose, A. S., Ellison, G. W., Myers, L. W., & Tourtelotte, W. W. (1976). Criteria for the clinical diagnosis of multiple sclerosis. Neurology, 26, 20-25.

Schacter, D. (1987). Implicit memory: History and current status. Journal of Experimental Psychology: Learning, Memory, and Cognition, 13, 501-518.

Schacter, D., & Graf, P. (1986). Effects of elaborative processing on implicit and explicit memory for new associations. Journal of Experimental Psychology: Learning, Memory, and Cognition, 12, 432-444.

Schumacher, G. A., Beebe, G., Kibler, R. F., Kurland, L. T., Kutzke, J. F., McDowell, F., Nagler, B., Sibley, W. A., Tourtelotte, W. W., & Willmon, T. F. (1965). Problems of experimental trials of therapy in multiple sclerosis; report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Annals of the New York Academy of Sciences, 122, 552-597.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bi-lateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 20, 11-21.

Sheldon, J. J., Siddharthan, R., Tobias, J., Sheremata, W. A., Soila, K., & Viamonte, M., Jr., (1985). MR imaging of multiple sclerosis: Comparison with clinical and CT examinations in 74 patients. American Journal of Radiology, 145, 957-964.

Smith, A. S., Weinstein, M. A., Modic, M. T., Pavlicek, W., Rogers, L. R., Budd, T. G., Bukowski, R. M., Purvis, J. D., Weick, J. K., & Duchesneau, P. M. (1985). Magnetic resonance with marked T2-weighted images: Improved demonstration of brain lesions, tumor, and edema. American Journal of Radiology, 145, 949-955.

Squire, L. (1987). Memory and brain. New York: Oxford University Press.

Squire, L. & Butters, N. (1984). Neuropsychology of Memory. (Eds.) New York: Guilford Press.

Squire, L. (1991, February). Memory and brain: Forms of memory and neural organization, Workshop address presented at the 19th Annual Conference of the International Neuropsychological Society, San Antonio, TX.

Springer, S. P., & Deutsch, G. (1985). Left Brain, Right Brain. New York: W. H. Freeman and Co.

Stark, D. D., & Bradley, Jr., W. (1988). Magnetic resonance imaging. St. Louis: C. V. Mosby.

Steiner, G. (1938). Multiple sclerosis: The aetiological significance of the regional and occupational incidence. Journal of Nervous and Mental Diseases, 88, 42-66.

Stevens, J. C., Farlow, M. R., Edwards, M. K., & Yu, P. (1986). Magnetic resonance imaging: Clinical correlations in 64 patients with multiple sclerosis. Archives of Neurology, 43, 1145-1148.

Stewart, W. A., Hall, L. D., Berry, K., & Paty, D. W. (1984). Correlation between NMR scan and brain slice data in multiple sclerosis. Lancet, 2, 412.

Teuber, H. L. (1959). Some alterations in behavior after cerebral lesions in man. In A. D. Bass (Ed.), Evolution of nervous control from primitive organisms to man. American Association for the Advancement of Science. Washington D. C.: C. V. Mosby & Co.

Tischler, M., & Davis, M. (1983). A visual pathway that mediates fear-conditioned enhancement of acoustic startle. Brain Research, 276, 55-71.

Tourtellotte, W., Baumhefner, R., Potvin, J., Potvin, A., & Poser, D. (1983). Comprehensive management of multiple sclerosis. In J. Hallpike, C. Adams, & W. Tourtellotte (Eds.), Multiple sclerosis: Pathology, diagnosis, and management (Chpt. 16, pp. 513-578). London: Chapman and Hall.

Tourtellotte, W. W., & Parker, J. A. (1968). Some spaces and barriers in postmortem multiple sclerosis. Progress in Brain Research, 29, 493-525.

Trimble, M., & Grant, I. (1982). Psychiatric aspects of multiple sclerosis. In D. F. Benson & D. Blumer (Eds.), Psychiatric aspects of neurologic disease. (pp. 279-299). New York: Grune & Stratton.

Tulving, E., & Donaldson, W. (Eds.). (1972). Organization of memory. New York: Academic Press.

Tulving, E. (1983). Elements of episodic memory. Oxford, England: Clarendon Press.

Uhlenbrock, D., Seidel, D., Gehlen, W., Beyer, H. K., Haan, J., Dickmann, E., Zeit, T., & Herbe, E. (1988). MR imaging in multiple sclerosis: Comparison with clinical, CSF, and visual evoked potential findings. American Journal of Neuroradiology, 9, 59-67.

van den Burg, W., van Zomeran, A. H., Minderhoud, J. M., Prangs, A. J., & Meijer, N. S. (1987). Cognitive impairment in patients with multiple sclerosis and mild physical disability. Archives of Neurology, 44, 494-501.

Victor, M., & Adams, R. (1985). The alcoholic dementias. In P. J. Vinken & G. W. Byrun (Eds.), Handbook of clinical neurology: 2nd ed. Vol. 2. Neurobehavioral disorders. Amsterdam: North-Holland.

Victor, M., Adams, R., & Collins, G. (1971). The Wernicke-Korsakoff syndrome: A clinical and pathological study of 245 patients, 82 with post-mortem examinations. Philadelphia: Davis.

Visscher, B. R., Clark, V. A., Detels, R., Malmgren, R. M., Valdiviezo, N. L., & Dudley, J. P. (1981). Two populations with multiple sclerosis. Clinical and demographic characteristics. Journal of Neurology, 225, 237-249.

Walsh, K. W. (1985). Understanding Brain Damage: A Primer of Neuropsychological Evaluation, New York: Churchill-Livingstone.

Walsh, K. W. (1987). Neuropsychology: A clinical approach. New York: Churchill Livingstone.

Wechsler, D. (1981). WAIS-R Manual: Wechsler Adult Intelligence Scale - Revised. New York: The Psychological Corportation.

Wechsler, D. (1987). WMS-R Manual: Wechsler Memory Scale - Revised. New York: The Psychological Corporation.

Weller, R. O. (1985). Pathology of multiple sclerosis. In W. B. Matthews, E. D. Acheson, J. R. Batchelor, & R. O. Weller (Eds.), McAlpine's Multiple Sclerosis (pp. 301-343). Edinburgh: Churchill Livingstone.

Whitty, C. W., & Zangwill, O. L. (1977). Amnesia: clinical psychological and medicolegal aspects. (2nd ed.). London: Butterworths.

Willoughby, E. W., Growchowski, E., Li, D. K., Oger, J., Kastrukoff, L. F., & Paty, D. W. (1989). Serial magnetic resonance scanning in multiple sclerosis: A second prospective study in relapsing patients. Annals of Neurology, 25, 43-49.

Wilson, B. (1982). Rehabilitation of memory. New York: Guilford Press.

Wuthrich, R, Gigili, H., Wiggli, U., Muller, H. R., Elke, M., Hunig, R. (1976). CT scanning in demyelinating disease. In W. Lanksh & E. Kaznen (Eds.), Cranial computerized tomography. (pp. 239-243). Berlin: Springer.

Young, S. W. (1984). Nuclear magnetic resonance imaging: Basic principles. New York: Raven Press.

Young, S. W., Hall, A., Pallis, C., Legg, N., Bydder, G., & Steiner, R. (1981). Nuclear magnetic resonance imaging of the brain in multiple sclerosis. Lancet, ii, 1063-1065.