Interhemispheric Transfer in Multiple Sclerosis

by

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Supervisor: Dr. E. Strauss

Abstract

Given previous indications of callosal damage and dysfunction in multiple sclerosis (MS; e.g., Huber et al.,1987; Jacobson, Deppe & Murray, 1983), it was hypothesized that people with the disorder would show impairment of interhemispheric transfer. People with MS (n=20) and neurologically intact control subjects (n=23) were administered six tests thought to address efficiency of interhemispheric transfer. The praxis and tactile naming tests were eliminated from statistical analyses because of ceiling effects. Univariate analyses of the remaining variables (verbal dichotic listening, visual half-field tachistoscopic reading, tactile localization and replication of hand postures) yielded results consistent with the hypothesis that MS patients would show impairment of interhemispheric communication, although a floor effect was noted on the dichotic listening measure. Clinical and empirical implications are discussed.

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Multiple sclerosis (MS) is associated with demyelination of the corpus callosum, among other regions of the central nervous system (e.g., Huber et al., 1987). Using special tests, it has been demonstrated that surgical lesions of the corpus callosum lead to decreases in interhemispheric transfer of information (e.g., Gazzaniga, 1970). In the present research, similar tests were used to examine the hypothesis that patients with MS would show impairment of interhemispheric transfer. As an introduction to the present research, background information will be provided on medical and neuropsychological aspects of MS, and on structural and functional aspects of the corpus callosum.

Multiple Sclerosis: Medical Aspects

MS is a demyelinating disorder of the central nervous system (CNS). It has been described as "the Hydra of clinical neurological disease" (Kelly, 1985, p. 49) because of the high variability in its presentation. It appears to be a disease of recent history. The first recorded cases of apparent MS date to the 14th century (Francis, Antel & Duquette, 1991; Vollmer & Waxman, 1991), but it was not until the 18th century that MS became a focus of scientific attention. Charcot (1868, cited in Francis et al., 1991; Vollmer & Waxman, 1991) is credited with the first clear description of MS as a diagnostic entity. Initial documentation of the pathology of MS appeared in the 19th

century (Vollmer & Waxman, 1991). Current data on MS will be described in the following sections.

Epidemiology

MS is the most common demyelinating disease (Waxman, 1982). Estimates of its prevalence in Canada range from 30 to 130 per 100,000 (Adams & Victor, 1993; Hader, 1982). Estimates of the gender ratio range from 1.4 to 2.2 females per male (Baum & Rothschild, 1981; Francis et al., 1991; Paty & Poser, 1984; Vollmer & Waxman, 1991).

Course

Clinical onset usually occurs between the ages of 15 and 45 years (McKhann, 1982; Weiner, Tintner & Goodkin, 1991), with a mean age at onset of approximately 30 years (Paty & Poser, 1984; Vollmer & Waxman, 1991). Symptoms typically appear abruptly (Peyser & Poser, 1986) and may subsequently follow a relapsing remitting or chronic progressive course (Paty & Poser, 1984). Approximately 15 to 30 per cent of patients show chronic decline from the outset, but the majority show initial periods of remission followed by chronic progression in the later stages of the disease (Paty & Poser, 1984; Sibley, 1990). For reasons that are not clear at this time, females are over-represented among those with early or late onset, slow disease progression, and relapsing remitting course (Francis et al., 1991).

Pathology

MS involves loss of myelin from circumscribed areas in the central nervous system (Brownell & Hughes, 1962; Francis et al., 1991; McKhann, 1982; Raine, 1990). Demyelinative or "sclerotic" plaques form in the affected areas and eventually the underlying axonal tissue may be compromised, especially in older lesions (Kolb & Whishaw, 1990; McKhann, 1982; Poser, 1984; Vollmer & Waxman, 1991). Plaques can be accompanied by high numbers of lymphocytes and microglia (Vollmer & Waxman, 1991).

Individual plaques average one to two centimetres in length, but larger demyelinative areas form when individual lesions become confluent (Francis et al., 1991). The plaques are thought to be randomly distributed throughout white matter, though clusters appear in periventricular areas and in the region of the optic nerve, brainstem and spinal cord, often close to the cerebrospinal fluid (Francis et al., 1991; Lumsden, 1970; McKhann, 1982; Poser, 1984). Myelinated fibres within cortex can also be affected (Francis et al., 1991).

Demyelination slows or blocks conduction of neural impulses by decreasing the capacity or speed with which neurons reach the firing threshold (Francis et al., 1991; Waxman, 1982). Edema and toxicity in demyelinated areas may

further impair neural transmission (Francis et al., 1991). Remission of symptoms is accompanied by a degree of remyelination and return to saltatory conduction (Adams & Victor, 1993). It has also been hypothesized that remission can be mediated by continuous propagation made possible by proliferation of sodium channels in the demyelinated internodal areas (Francis et al., 1991; McKhann, 1982). McKhann, 1982; Vollmer & Waxman, 1991). Reduction of toxicity and edema may also contribute to recovery (Francis et al., 1991; Vollmer & Waxman, 1991).

Symptoms

MS is characterized by high symptom variability (Kelly, 1985; Paty & Poser, 1984). In fact, it has been stated that MS can be associated with any classic CNS syndrome (Paty & Poser, 1984). Nonetheless, some characteristic and/or common symptoms have been identified in the visual, somesthetic and motor domains (Adams & Victor, 1993; Kolb & Whishaw, 1990).

Visual symptoms include optic neuritis (ON), which refers to inflammation of the optic nerve. It is often the first symptom of MS; approximately 50 to 75 per cent of people with ON are later diagnosed with MS (Francis et al., 1991; Paty & Poser, 1984). The possibility that ON is an especially mild or incomplete form of MS has yet to be ruled out (Francis et al., 1991). ON is usually associated with

pain, increased by eye movements, and visual loss in one eye (Francis et al., 1991; National Multiple Sclerosis Society, 1989). Internuclear ophthalmoplegia, manifest in double vision on lateral gaze, shows relatively high specificity to MS (Francis et al., 1991; Paty & Poser, 1984). Diplopia, nystagmus and blurred vision (monocular or binocular) are also seen in MS, but visual field cuts are relatively rare (Francis et al., 1991; Paty & Poser, 1984; National Multiple Sclerosis Society, 1989).

Somesthetic phenomena frequently characterize the initial presentation of MS, and arise eventually in almost all cases (Francis et al., 1991). Symptoms include general numbness, tingling, tightness, coldness and pain, as well as specific symptoms such as trigeminal neuralgia (tic douloureux), Lhermitte's symptom, and the sensory useless hand (Francis et al., 1991; Paty & Poser, 1984; Sibley, 1990). Trigeminal neuralgia involves sharp facial pain, often in response to tactile stimulation of a so-called trigger point (Paty & Poser, 1984). Lhermitte's symptom is a shock-like tingling sensation that runs down the spine and into the legs in response to flexion or a jar to the neck or spine (Paty & Poser, 1984). The sensory useless hand, though rare, is relatively specific to MS and is characterized by paraesthesia, numbness and impaired somesthetic feedback in one arm, resulting in secondary loss of motor function in

the arm in the absence of primary motor impairment (Francis et al., 1991; Paty & Poser, 1984).

Motor symptoms of MS include paresis, paralysis, spasticity, hypotonia, hyperreflexia, inability to perform complex movements, incoordination, gait disturbance, tremor and other difficulties (Francis et al., 1991; Kolb & Whishaw, 1990; Paty & Poser, 1984; Vollmer & Waxman, 1991). Truncal weakness can lead to postural and breathing disturbances (Francis et al., 1991). Motor impairments of speech include slurring and scanning (Francis et al., 1991).

In addition to the relatively common visual, somatosensory and motor symptoms, MS can be accompanied by other difficulties such as hearing impairment, either hypoacusis or hyperacusis, vertigo, seizures, urinary difficulty, constipation and sexual dysfunction (Francis et al., 1991; Kolb & Whishaw, 1990; Paty & Poser, 1984).

Diagnosis

MS can be difficult to diagnose, particularly in the early stages of the disease (Baum & Rothschild, 1981), owing to the high variability in symptoms (Poser, 1984) and to the existence of other disorders of similar presentation (Francis et al., 1991; Vollmer & Waxman, 1991). Specific

guidelines for the diagnosis of MS have been developed. According to the Schumacher committee (1965), the diagnosis requires objective demonstration of CNS dysfunction related to at least two separate, predominantly demyelinative lesions of the CNS. Poser et al. (1983) elaborated the Schumacher criteria to yield diagnostic categories which are, in order of decreasing certainty, clinically definite MS, laboratory-supported definite MS, clinically probable MS, laboratory-supported probable MS, and possible MS (Poser et al., 1983; Vollmer & Waxman, 1991).

The process of diagnosing MS typically involves obtaining a neurological history and examination, as well as laboratory tests, the most common of which are evoked potentials, cerebrospinal fluid (CSF) analysis, and neuroimaging (Francis et al., 1991; Harmony, 1984; McKhann, 1982; Peyser & Poser, 1986). Goals of CSF analysis include detection of elevations of lymphocytes and immunoglobulins, and of oligoclonal banding. Elevations of immunoglobulin G are common in MS and are relatively rare in other disorders, but are not specific enough to be used alone to rule MS in or out (Francis et al., 1991; Weiner et al., 1991). Distinct oligoclonal bands (OCBs), which appear on electrophoresis of CSF, represent excess production of selected antibodies. The specific antigen(s), against which production of these antibodies is targeted, have not been identified. OCB

abnormalities are present in 85 to 95 per cent of clinically definite MS cases, 40 to 50 per cent of probable MS cases, and 25 to 30 per cent of possible MS cases (Francis et al., 1991).

Evoked potentials represent the electrical CNS activity caused by sensory stimulation, and abnormal readings indicate CNS damage (Francis et al., 1991). Evoked potentials are particularly useful in demonstrating subclinical lesions, and can be used to support the diagnosis of a multifocal disorder. Evoked potential abnormalities are observed in 50 to 85 per cent of clinically definite MS cases, 30 to 70 per cent of probable MS cases, and 25 to 45 per cent of possible MS cases. The three most common forms of sensory stimulation used in evoked potential testing are visual, somatosensory and auditory, the first two of which are the most sensitive to MS (Francis et al., 1991).

Neuroimaging techniques used in the diagnosis of MS include computerized tomography (CT) and magnetic resonance imaging (MRI) (Peyser & Poser, 1986; Rao, 1986; Reischies, Baum, Brau, Hedde & Schwindt, 1988; Reisner & Maida, 1980; Vollmer & Waxman, 1991; Weiner et al., 1991; Willoughby & Paty, 1990). MRI is approximately ten times more sensitive than CT to the lesions in MS (Lukes et al., 1983; Young et

al., 1981). MRI can be used to detect from 80 to 100 per cent of lesions, relative to postmortem analysis, and allows visualization of areas of the CNS that cannot be captured with CT (Francis et al., 1991; Willoughby & Paty, 1990). Abnormalities can be detected on MRI in 90 to 97 per cent of clinically definite MS cases, but data are not available for probable or possible cases. Despite the importance of MRI in the diagnostic process, other measures are required to differentiate MS from other multifocal disorders which have a similar appearance on MRI (Francis et al., 1991; Willoughby & Paty, 1990).

Additional tests employed in the diagnostic process include neuropsychological evaluation, electroencephalogram and thermal sensitivity testing (Peyser & Poser, 1986; Vollmer & Waxman, 1991). Despite the recent refinements in the diagnostic criteria and procedures for MS, premorbid diagnosis remains difficult (McNamara, 1991).

Etiology

The cause or causes of MS are currently unknown, but genetic, viral and immunological hypotheses have been proposed (Francis et al., 1991; Johnson, 1985; Kolb & Whishaw, 1990; McKhann, 1982; Reder & Arnason, 1985; Stevens, 1988). The genetic hypothesis receives support from racial, familial and twin data (Francis et al., 1991). For

example, risk factors for MS include northern European racial heritage (Paty & Poser, 1984) and a family history of the disease (Sibley, Bamford & Clark, 1984). Concordance for MS parallels degree of gene sharing among family members (Francis et al., 1991), and is accordingly higher among monozygotic than dizygotic twins (McKhann, 1982). Candidate genes for MS reside on chromosomes 6 and 18 (McKhann, 1982; Tienari, Wikstrom, Sajantila, Palo & Peltonen, 1992). Available data support either a recessive form of transmission, or a dominant form with low penetration (Francis et al., 1991).

An as yet unidentified exogenous factor may precipitate development of the disease in genetically susceptible individuals (Francis et al., 1991; McKhann, 1982). High risk for MS is associated with residence in regions of greater latitude in both northern and southern hemispheres (Vollmer & Waxman, 1991), including northern and central Europe, northern United States, and southern Canada (Francis et al., 1991; McKhann, 1982). People who emigrate from high risk regions before adolescence acquire the lower risk of the area to which they move, whereas those who emigrate later carry with them the risk associated with their former home (Francis et al., 1991; Vollmer & Waxman, 1991). These considerations and other geographic and migration data suggest the involvement of an exogenous factor or factors,

possibly a slow virus, acquired before adolescence and not expressed until adulthood (Sibley et al., 1984; Vollmer & Waxman, 1991).

Although epidemiological data provide only circumstantial support for the viral hypothesis, other supportive evidence derives from immunological research (Francis et al., 1991), and the viral and immunological hypotheses are not mutually exclusive (Vollmer & Waxman, 1991). For example, antibodies directed against measles and other viruses occur at relatively high levels in MS patients. Whether this reflects a viral cause for MS or nonspecific hyperfunctioning of the immune system is debatable (Francis et al., 1991; Johnson, 1985; Reder & Arnason, 1985; Vollmer & Waxman, 1991). Nonetheless, personal histories of viral infections such as measles, herpes simplex, influenza A, mumps, rubella or Epstein Barr virus are considered risk factors for MS (Johnson, 1985).

Factors no longer considered relevant to either the onset or exacerbation of MS include bacterial infection, vaccination, physical trauma and physical overexertion (Sibley et al., 1984). One possible synthesis of available data is that in genetically susceptible individuals, an exogenous agent, such as a virus, is acquired before or during adolescence and expressed in adulthood when it

attacks myelin either directly or indirectly, possibly via immunological mechanisms (Francis et al., 1991; McKhann, 1982).

Intervention

There is no known cure for MS but a number of potential interventions have been proposed (Francis et al., 1991; Kolb & Whishaw, 1985; McKhann, 1982; Peyser & Poser, 1986; Vollmer & Waxman, 1991). Of the interventions directed against immunological factors, corticosteroids, such as adrenocorticotrophic hormones and prednisone, are widely used despite disagreement as to their effectiveness (Francis et al., 1991; Vollmer & Waxman, 1991). Beta-interferon has recently been shown to decrease the frequency and severity of relapses in relapsing-remitting MS (Arnason, 1993). Other immunotherapies that may prove effective include cyclophosphamide and total lymphoid irradiation (Francis et al., 1991; Vollmer & Waxman, 1991). Nonimmune therapies, including administration of antibacterial and antiviral agents, have no demonstrated effectiveness in the treatment of MS (Francis et al., 1991). Other interventions have been designed to decrease discomfort and disability through management of motor, sensory, psychological and other symptoms of the disease (Noseworthy, 1991; Vollmer & Waxman, 1991).

In summary, MS is a highly variable demyelinating disease of unclear etiology. It is difficult to diagnose or treat effectively. As a disease of the CNS, it is associated with neuropsychological impairment, which will be described in the following section.

Multiple Sclerosis: Neuropsychological Aspects

In one of the earliest accounts of the characteristics of multiple sclerosis, Charcot (1877; cited in Peyser & Poser, 1986) underscored the prominence of impaired memory, conceptualization and regulation of emotion. In contrast, subsequent researchers emphasized the importance of motor impairment, but recent research tends to corroborate Charcot's impression that neuropsychological dysfunction is also among the key features of MS (Minden & Schiffer, 1990a; Peyser, Rao, LaRocca & Kaplan, 1990; Peyser & Poser, 1986; Ron & Feinstein, 1992). A contemporary examination of the characteristics and correlates of neuropsychological dysfunction in MS will be provided in this section.

General Intellectual Ability

Tests of intellectual ability, including but not limited to the Wechsler tests of intelligence, have been employed in both cross-sectional and longitudinal research with MS samples. Cross-sectional research has revealed lower

overall IQ scores among MS patients than among healthy controls (Ivnik, 1978a; Ron, Callanan & Warrington, 1991; van den Burg, van Zomeren, Minderhoud, Prange & Meijer, 1987), but clear and consistent group differences have not been obtained on comparison of MS patients to neurological (Goldstein & Shelly, 1974; Ivnik, 1978b; Jambor, 1969) or psychiatric patients (Goldstein & Shelly, 1974; Jambor, 1969). Longitudinal research has yielded conflicting results due probably to sampling differences. Decreases in intellectual functioning have been observed among patients with MS but not among healthy controls (Ivnik, 1978b), with test-retest intervals as short as six months (Canter, 1951). In one study, recent-onset patients' Verbal IQ was not found to decline over a one-year period, but Performance IQ was not evaluated (Fink & Houser, 1966). Finally, significant increases, due presumably to practice, have been observed even with inter-test intervals of approximately 18 months in patients not experiencing recent exacerbations (Filley, Heaton, Thompson, Nelson & Franklin, 1990).

Verbal IQ has not typically been observed to differ between MS patients and healthy control subjects (Jambor, 1969; Litvan, Grafman, Vendrell & Martinez, 1988a; Rao, Leo, Bernardin & Unverzagt, 1991; Reitan, Reed & Dyken, 1971; Staples & Lincoln, 1979). MS patients have generally obtained lower Performance than Verbal IQs, though in a

number of relevant studies the differences have not been evaluated statistically (Canter, 1951; Goldstein & Shelly, 1974; Heaton, Nelson, Thompson, Burks & Franklin, 1985; Ivnik, 1978a,b; Klonoff, Clark, Oger, Paty & Li, 1991; Marsh, 1980; Matthews, Cleeland & Hopper, 1970; Reitan et al., 1971; for review, see Fennel & Smith, 1990). Observed discrepancies or "splits" between scores on the Verbal and Performance Scales have ranged from approximately 4 to 12 points in MS samples, but it should be noted that discrepancies of up to 12 points have been reported in approximately 75 per cent of the general population (Matarazzo & Herman, 1984). Few studies have addressed the possible impact of sensory and motor deficits on test performance. If the Verbal/Performance split is to be interpreted as evidence of impairment of nonverbal intellectual ability in MS, its specificity to MS must be examined, and the relative impact of alternate forms of neuropsychological dysfunction must be addressed (Klonoff et al., 1991; Rao, 1986).

Sensory and Motor Abilities

Sensory and motor deficits are common in MS. Even when clinical tests of visual acuity are normal, visual deficits have been demonstrated on experimental tests of double-flash resolution (Galvin, Heron & Regan, 1977), contrast-sensitivity (Regan, Silver & Murray, 1977), and orientation-

specific contrast sensitivity (Whitlock, Murray & Beverly, 1980). Performance on tactile and auditory tests has been variable (Ivnik, 1978b), but standardized motor tests, such as the Finger Tapping Test, the Dynamometer, the Purdue Pegboard, and the Static Steadiness Test, have generally yielded consistent evidence of impairment among MS patients relative to healthy controls (Beatty & Gange, 1977; Caine, Bamford, Schiffer, Shoulson & Levy, 1986; Goldstein & Shelly, 1974; Klonoff et al., 1991; Matthews et al., 1970; Reitan et al., 1971). In one study, patients with MS were impaired relative to healthy controls on both unimanual and bimanual conditions of the Grooved Pegboard, but the possibility of excessive impairment on the bimanual condition, which could be consistent with decreased intermanual coordination and callosal disconnection, was apparently not addressed (Klonoff et al., 1991).

Speech and Language

The prevailing view has been that MS patients are free from language impairment except in the moderate to severe stages of the disease, but that impression has recently been challenged (Beatty & Monson, 1989; for reviews, see Fennel & Smith, 1990; Rao, 1986). Whereas performance on relatively cursory tests of speech comprehension and repetition has typically been normal among MS patients in various stages of the disease (Caltagirone, Carlesimo, Fadda & Roncacci, 1991;

Goldstein & Shelly, 1974; Heaton et al., 1985; Jambor, 1969; Rao et al., 1991; but see Beatty & Monson, 1989; Klonoff et al., 1991), expressive deficits have been observed on tests of naming (Beatty & Monson, 1989; Caine et al., 1986; Jambor, 1969; Pozzilli et al., 1991, but see Beatty, Goodkin, Monson & Beatty, 1989; Caltagirone et al., 1991; Rao et al., 1991) and controlled oral word association (Beatty et al., 1989; Beatty & Monson, 1989; Caine et al., 1986; Heaton et al., 1985; Klonoff et al., 1991; Pozzilli et al., 1991; van den Burg et al., 1987). It has been noted that the observed difficulties may be part of more general, perhaps executive, cognitive dysfunction (Fennell & Smith, 1990).

Despite the appearance of deficits on tests of expressive language, classic aphasias have rarely been reported in the MS literature (Olmos-Lau, Ginsberg & Geller, 1977). In contrast, speech disturbances, characterized by intention tremor, dysmetria and ataxia, have been reported (Babkina, 1988). In addition, it has been suggested that given the prevalence of white matter lesions in MS, intrahemispheric disconnection syndromes, such as alexia without agraphia, may be present (Rao, 1986). In general, the nature of language impairment in MS has yet to be fully elucidated (Fennell & Smith, 1990).

Visuoperceptual, Visuospatial and Visuoconstructional Abilities

Observed discrepancies between Verbal and Performance IQs in MS (see above) suggest the presence of impairment in one or more of the visuoperceptual, visuospatial or visuoconstructional domains, and this has been supported on the basis of other measures of these abilities (Caine et al., 1986; Franklin, Heaton, Nelson, Filly & Siebert, 1988; Rao et al., 1991, but see Caltagirone et al., 1991; Pozzilli et al., 1991). Nonetheless, no clear consensus exists as to whether the observed impairments are due to primary deficits in the measured domains or are secondary to sensory, motor, problem-solving or other difficulties (Fennell & Smith, 1990; Knudsen, Elbol, Stenager, Jensen & Work, 1988; Rao, 1986).

Attention, Executive Ability and Conceptualization

Attentional and executive dysfunction has been demonstrated among MS patients on simple and continuous reaction time tasks, the Paced Auditory Serial Additions Test, the Stroop Test (Elsass & Zeeberg, 1983; Filley, Heaton, Nelson, Burks & Franklin, 1989; Litvan et al., 1988a; Rao, St. Aubin-Faubert & Leo, 1989; Ron et al., 1991; van den Burg et al., 1987; Vleugels, Bosters, Fasotti, van Greyt, Troost & Ketalaer, 1988), and on measures of perseveration (Beatty et al., 1989; Caltagirone et al.,

1991; Heaton et al., 1985; Rao & Hammeke, 1984; Rao, Hammeke & Speech, 1987; Rao et al., 1991, but see Pozzilli et al., 1991). In addition, impairment has been noted in conceptualization on measures such as the Halstead Category Test and the Wisconsin Card Sorting Test (Beatty et al., 1989; Caltagirone et al., 1991; Elpern, Gunderson, Kattah & Kirsch, 1984; Heaton et al., 1985; Jambor, 1969; Parsons, Stewart & Arenberg, 1957; Peyser, Edwards, Poser & Filskov, 1980; Rao & Hammeke, 1984; Rao, Hammeke & Speech, 1987; Rao et al., 1991; Ron et al., 1991; , but see Goldstein & Shelly, 1974; Klonoff et al., 1991; for review, see Rao & Hammeke, 1984). In general, disturbances of attention, executive ability and conceptualization are apparently quite common in MS (Rao, 1986). Approximately one-third of subjects in a population-based study showed impairment on a small number of selected measures of these abilities (McIntosh-Michaelis et al., 1991).

Learning and Memory

Learning and memory are among the more thoroughly examined neuropsychological domains in MS research, and impairment of aspects of these functions has been demonstrated across methodologically diverse studies (Minden, Moes, Orav, Kaplan & Reich, 1990; Rao, 1986 for reviews). On learning tasks, MS patients have shown impairment of overall performance, but the learning curve,

or relative increment in recall per trial, has been preserved (Rao, 1986). An exception occurred among patients with chronic progressive MS and severe memory impairment, who showed little incremental learning (Rao, Hammeke, McQuillen, Khatri & Lloyd, 1984).

Deficits have been reported among MS patients on delayed recall of verbal and nonverbal material in auditory and visual modalities (Beatty & Gange, 1977; Beatty, Goodkin, Monson, Beatty & Hertsgaard, 1988; Caine et al., 1986; Canter, 1951; Carroll, Gates & Roldan, 1984; Grant, McDonald, Trimble, Smith & Reed, 1984; Heaton et al., 1985; Huber et al., 1987; Jambor, 1969; Klonoff et al., 1991; Litvan et al., 1988a; Mann, Staedt, Kappos, Wense & Haubitz, 1989; Minden et al., 1990; Pozzilli et al., 1991; Rao et al., 1984, 1991; Schiffer, Caine, Bamford & Levy, 1983; Staples & Lincoln, 1979; van den Berg et al., 1987; but see Rao et al., 1984). In contrast to the documented deficits in delayed memory, relative preservation of immediate memory span has been observed on measures such as the Digit Span Test (Digits Forward) (Elpern et al., 1984; Grant et al., 1984; Heaton et al., 1985; Jambor, 1969; Litvan et al., 1988b; Pozzilli et al., 1991; Rao et al., 1984; Rao et al., 1991; Vowels, 1979; but see DePaulo & Folstein, 1980; Hirschenfang & Benton, 1966) and the Corsi Block Span Test (Pozzilli et al., 1991). Relative sparing of recognition

(Carroll et al., 1984; Elpern et al., 1984; Rao et al., 1984), remote memory (Rao et al., 1991), implicit memory (Beatty, Goodkin, Monson & Beatty, 1990b) and incidental memory (Grafman, Rao, Bernardin & Leo, 1991) has also been reported. Based on the observed discrepancy between recall and recognition, it has been suggested that MS may be characterized by relative preservation of processing and storage of information, with relative impairment of retrieval (Rao, 1986). In general, aspects of memory and learning are often compromised in MS.

Affect and Emotion

A number of affective and emotional disturbances have been described in MS, including euphoria, unipolar and bipolar mood disorders, and pathological laughing and crying (Minden & Schiffer, 1990a; Rao, Huber & Bornstein, 1992; Trimble & Grant, 1982 for reviews). At one time, euphoria was considered a cardinal feature of MS, but this is no longer the case because of high variability regarding its definition and prevalence in MS (Boyle, Clark, Klonoff, Paty & Oger, 1991; McNamara, 1991; Minden & Schiffer, 1990a; Peyser & Poser, 1986; Rabins, 1990). In the past, patients reported as euphoric may actually have had pseudobulbar palsy or other conditions (Minden & Schiffer, 1990a). Pathological laughing and crying related to the pseudobulbar state have been reported in the MS literature with variable

frequency (Minden & Schiffer, 1990a). Heightened affect following corticosteroid treatment may also have contributed to the impression of euphoria (Minden & Schiffer, 1990a).

Unipolar depression has a point prevalence of approximately 25 to 50 per cent in MS, and is typically of moderate severity (Arias-Bal, Vazquez-Barquerro, Pena, Miro & Berciano, 1991; Minden & Schiffer, 1990a,b; Schiffer, Caine, Bamford & Levy, 1983). Bipolar mood disorder and MS have been found to co-occur at a rate of 13 per cent, which is approximately twice the level expected on the basis of population rates for each disorder (Joffe, Lippert, Gray, Sawa & Horvath, 1987; Minden & Schiffer, 1990a,b), and it has been suggested that they share a genetic vulnerability factor (Minden & Schiffer, 1990). Schizophrenia and related psychotic disorders appear to be relatively rare in MS (Peyser & Poser, 1986).

The potential contribution of both reactive and organic factors to the development of emotional and affective difficulties in MS has been recognized (Boyle et al., 1991; Peyser & Poser, 1986; Rao, 1990; Rao et al., 1992). MS is associated with a number of significant stressors that may contribute to the genesis of some emotional difficulties, including an often lengthy diagnostic process (Minden & Schiffer, 1990a,b; Stenager, Knudson & Jensen, 1991),

disruption of short-term and long-term life planning (Minden & Schiffer, 1990a), and disruption of occupational, family and social activities (for reviews: Minden & Schiffer, 1990a; Rao et al., 1992; Stenager, Knudsen & Jensen, 1991). In general, affective and emotional disturbances occur in MS with greater frequency than in other disabling neurological conditions with similar reactive factors (e.g., Peyser & Poser, 1986; Schiffer & Babigan, 1984; Surridge, 1969; Whitlock & Siskind, 1980; for review see Schiffer, 1990). With this in mind, it is noteworthy that neuroimaging research has shown relations between various indices of brain degeneration and degree of emotional disturbance, which suggests that emotional difficulties in MS are at least in part related to neuropathology (Honer et al., 1987; for review, see Rao et al., 1992).

Dementia

Controversy surrounds the idea that dementias can usefully be classified according to whether the predominant site of neuropathology is cortical or subcortical, and the idea that dementias so classified are associated with characteristic patterns of neuropsychological dysfunction (Albert, Feldman & Willis, 1974; Mayeux, Stern, Rosen & Benson, 1983). Because MS primarily involves degeneration of subcortical white matter, it has been classified with the subcortical dementias (Mahler & Benson, 1990). Examination

of the neuropsychological literature on MS indicates at least partial adherence to the pattern of findings thought to characterize subcortical dementia (Beatty & Monson, 1989; Beatty et al., 1988; Bracco et al., 1988; Caltagirone et al., 1991; Filley, Franklin, Heaton & Rosenberg, 1988; Filley et al., 1989; Mahler & Benson, 1990; Rao, 1986; White, 1990). For example, MS is associated with the expected impairment of psychomotor speed, conceptual and executive ability, visuospatial ability and mood, and by relative preservation of encoding and storage in a context of poor retrieval (Cummings & Benson, 1988; Mahler & Benson, 1990; Rao, 1986). However, growing evidence of apparent language impairment in MS (and Parkinson's Disease) may necessitate reconceptualization of the subcortical dementia concept and/or its application in certain diseases (Beatty et al., 1988; Beatty & Monson, 1989; Mahler & Benson, 1990).

Filley and colleagues (1988; 1989) have proposed that subcortical dementias be subdivided according to whether the pathology primarily involves deep grey matter, as in Parkinson's Disease, or white matter, as in MS. White matter dementias are thought to be characterized by less profound movement disorder and greater attentional disturbance than subcortical grey matter dementias (Filley et al., 1988). The validity of the proposed dementia classifications for MS has yet to be fully examined.

Correlates of Neuropsychological Dysfunction

Attempts have been made to identify correlates of cognitive and affective dysfunction in MS. Target variables include disease course (e.g., chronic progressive versus relapsing remitting), disease status during testing (e.g., exacerbation or remission), disease duration, physical disability, disease severity, use of psychoactive medications, and extent and site of neuropathology (for reviews, see Peyser & Poser, 1986; Rao, 1986). Findings are summarized in the following paragraphs according to whether the weight of evidence shows no relation, a possible relation, or a clear relation between the various target variables and degree of cognitive dysfunction.

No consistent relation has been found between disease duration and cognitive dysfunction (Beatty, Goodkin, Hertsgaard & Monson, 1990a; Blesa, Pares, Boget & Bofill, 1988; Ivnik, 1978a; Grant et al., 1984; Rao et al., 1984, 1985; van den Burg et al., 1987; Peyser & Poser, 1986 for review) which may partly reflect the inherent difficulties in establishing the diagnosis and onset of the disease (e.g., Rao, 1986), and partly the fact that cognitive impairment can occur early in the course of the disease as well as late (Klonoff et al., 1991; Young, Saunders & Ponsford, 1976; for review see Peyser & Poser, 1986). Despite the presence of some positive findings, no clear

relation has been established between cognitive dysfunction and use of psychoactive medications (Beatty & Gange, 1977; Grant et al., 1984; Heaton et al., 1985; Rao et al., 1984; van den Berg et al., 1987; Minden & Schiffer, 1990a for review) nor to presence of depression in MS (Blesa et al., 1988; Jambor, 1969; Lyon-Caen et al., 1986; Rao et al., 1984; Van den Berg et al., 1987), which suggests that the cognitive dysfunction in MS is not secondary to these factors.

Conflicting findings on the relation of physical disability and disease severity to cognitive dysfunction may reflect the fact that demyelination limited to the spinal cord can cause severe physical disability without affecting cognition (Peyser & Poser, 1986; Stenager, Knudsen & Jensen, 1988; White, 1990). In addition, despite findings that cognitive dysfunction is more severe in chronic-progressive than relapsing-remitting MS (Beatty et al., 1989; Caltagirone et al., 1991; Heaton et al., 1985; Rao et al., 1987), disconfirmatory evidence has also been found (Beatty et al., 1990a; Cutajar, Stecchi, Piperno & Miccoli, 1988; White, 1990).

The combined results of computerized tomography and nuclear magnetic resonance studies indicate that extent of neuropathology, particularly on indices of periventricular,

callosal and total lesion area, is positively related to severity of neuropsychological dysfunction in MS (Anzola et al., 1988, 1990; Franklin et al., 1988; Hohl, Regard & Landis, 1988; Huber et al., 1987, 1992; Huber et al., 1992; Mann et al., 1989; Pozzilli et al., 1991; Rao, 1990; Rao et al., 1985, 1989; Reischies et al., 1988; Ron et al., 1991). In long-term patients, the presence of an exacerbation during testing is associated with greater cognitive dysfunction (Grant et al., 1984). Overall, examination of the correlates of cognitive dysfunction in MS indicate that the most important factors are extent and location of neuropathology, and presence of an exacerbation.

To summarize, despite early impressions that MS was not associated with cognitive dysfunction, recent research clearly indicates that MS is characterized by a wide variety of cognitive and affective difficulties. The neuropsychological profile emerging from the present review of the literature is one of relative impairment of sensory, motor, attentional, executive and conceptualization abilities, in addition to aspects of learning and memory. These deficits appear together with, but not due to, depression and anxiety. As expected, given the high variability that is so characteristic of MS, individual patients do not necessarily conform to the general pattern. It is in this context of diverse and variable

neuropsychological dysfunction that interhemispheric transfer was examined in the present study. Before reviewing the literature on interhemispheric transfer in MS, a synopsis of the related literature on structural and functional aspects of the corpus callosum will be presented.

Structural and Functional Aspects of the Corpus Callosum

Structure of the Corpus Callosum

The corpus callosum is the largest commissural structure in the cerebrum, containing an estimated 200 to 800 million axons, about half of which are myelinated (Kolb & Whishaw, 1990). Most callosal fibres connect homologous association areas of the cerebral hemispheres (Gilman & Newman, 1987; Gordon, 1990; Kolb & Whishaw, 1990). From anterior to posterior, the corpus callosum is divided into four sections, namely the rostrum, genu, body and splenium (Gazzaniga and LeDoux, 1978; Kolb & Whishaw, 1990; Walsh, 1978). In general, fibres originating in prefrontal cortex pass through the rostrum and genu. Fibres from the rest of the frontal lobe and from the parietal lobe pass through the body of the corpus callosum. Temporal and occipital fibres pass through the splenium (DeLacoste, Kirkpatrick & Ross, 1985; Kolb & Whishaw, 1990). Structural variations in the corpus callosum have been related to gender, age,

handedness, speech dominance and intelligence (e.g., Doraiswamy et al., 1991; Habib, Gayraud, Oliva, Salamon & Khalil, 1991; Lacoste-Utamsing & Holloway, 1982; O'Kusky et al., 1988; Strauss, Wada & Hunter, in press; Witelson, 1985, 1986; Witelson & Goldsmith, 1991).

In addition to the corpus callosum, the forebrain commissures include the anterior commissure and the hippocampal commissure (Kolb & Whishaw, 1990). Some brains also contain a grey matter structure of unknown functional significance, called the massa intermedia, which connects the thalami (Kolb & Whishaw, 1990). Other smaller forebrain and brainstem commissures also exist (Gazzaniga, 1970).

The Functional Significance of the Corpus Callosum

Early speculations on the functional significance of the corpus callosum include Vesalius' (1543, cited in Bogen, 1993) hypothesis that the structure provided mechanical support for the two hemispheres, and de la Peyronnie's (1741, cited in Colonnier, 1986) hypothesis that it housed the soul. Viq d'Azur (1784, cited in Bogen, 1993) is credited with first proposing that the corpus callosum provided a communication link between the hemispheres. At the turn of the century, two apparent cases of decreased interhemispheric communication were reported following callosal disconnection. Dejerine (1892, cited in Walsh,

1987) attributed alexia without agraphia to a combination of left occipital and callosal damage. Liepmann (1906, cited in Walsh, 1987) attributed unilateral left apraxia to anterior callosal dysfunction.

More subjects became available for research on the functional significance of the corpus callosum with the advent of split-brain surgery (Bogen, 1993; Reeves, 1991; Walsh, 1987). Beginning in 1939, severe, intractable epilepsy was treated with surgical disconnection of the cerebral commissures in attempt to reduce the interhemispheric spread of seizure activity (van Wagenen & Herren, 1940, cited in Reeves, 1991; Walsh, 1987). The operation decreased seizure frequency, but was initially reported to cause little or no disturbance in human cognition or behaviour (Akelaitis, 1941, cited in Gazzaniga, 1985; Reeves, 1991; Van Wagenen & Herren, 1940, cited in Reeves, 1991).

In the 1950s and 1960s, Sperry and Myers showed that under special conditions, independent functioning of the cerebral hemispheres could be demonstrated after disconnection of the corpus callosum and optic chiasm in monkeys and cats (Bogen, 1993; Myers, 1956; Sperry, 1961; Kolb & Whishaw, 1990). In addition, decreased interhemispheric transfer was demonstrated in two case

studies of humans with callosal damage (Gazzaniga, Bogen & Sperry, 1962; Geschwind & Kaplan, 1962). These findings renewed interest in the effects of split-brain surgery in humans. Beginning in the 1960s, Sperry and colleagues investigated interhemispheric transfer in people who had undergone the split-brain operation (e.g., Bogen & Gazzaniga, 1965; Gazzaniga, 1970; Gazzaniga & LeDoux, 1978; Gazzaniga, 1985). They developed specialized tests on which the neuropsychological effects of the operation could be reliably demonstrated.

Over the years, the split-brain operation has been refined from the relatively extensive commissurotomy to the more conservative callosotomy (Bogen, 1993). Whereas commissurotomy involves extensive disconnection of cerebral commissures, including the anterior and hippocampal commissures as well as the corpus callosum, callosotomy involves section of the corpus callosum alone, though with unavoidable damage to the adjacent hippocampal commissure (Bogen, 1993). Most current callosotomies are partial rather than complete, and are performed in stages (Bogen, 1993). The refinements in the operation have lead to decreased morbidity, accompanied by continued success in decreasing the frequency and severity of seizures (Nordgren, Reeves, Viguera & Roberts, 1991; Oguni, Olivier, Andermann & Comair, 1991).

Research involving patients who have undergone commissurotomy or callosotomy for severe, intractable epilepsy has contributed greatly to the current understanding of the functional significance of the corpus callosum in humans (e.g., Bogen, 1993; Gazzaniga, 1967, 1970; Gordon, 1990, for reviews). The neuropsychological effects of commissurotomy and callosotomy are very similar and are typically discussed together (Bogen, 1993), as will be done in the present paper. Most of the research, including that which will be reviewed here, has involved dextrals (Bogen, 1993). The neuropsychological effects of split-brain surgery can be divided into neighbourhood signs and disconnection symptoms (Bogen, 1993). These effects will be reviewed in this section, supplemented where appropriate with findings from a smaller body of research on the effects of other surgical and pathological conditions involving the corpus callosum (Bogen, 1993).

Neighbourhood signs. Neighbourhood signs following callosal damage include, but are not limited to, confusion, decreased concentration, memory problems, emergence of infantile reflexes, akinesia, mutism, apathy and disinhibition (Bogen, 1993; Sperry, 1974). These symptoms may be due at least in part to extra-callosal brain damage acquired during surgery. For example, apathy arising after anterior callosotomy has been attributed to medial frontal

damage (Bogen, 1993; Sperry, 1974). Memory deficits have been attributed to fornix and/or frontal damage (e.g., Gordon, 1990) or to callosal damage per se (Bentin, Sahar & Moscovitch, 1984; Geffen, Nilsson, Quinn & Teng, 1985; Scarpa & Sorgato, 1990; Zaidel, 1990; Zaidel & Sperry, 1977).

Disconnection symptoms. One of the striking characteristics of split-brain patients is the usual absence of appreciable long-term symptoms in everyday behaviour, though effects of callosal disconnection can be demonstrated on special tests (Bogen, 1993; Sperry, 1986; Sperry, Gazzaniga & Bogen, 1969; Trevarthen, 1990). Six specific tests of callosal disconnection, pertaining to visual, auditory, somesthetic, kinesthetic and complex motor functions (Risse, Gates, Lund, Maxwell & Rubens, 1989), were chosen for examination in the present study and will be described here. For reviews of other specific disconnection tests and symptoms, the reader is referred to Bogen (1993), Gazzaniga (1970), Gordon (1990), Reeves (1991) and Trevarthen (1990).

Impairment of cross-integration following callosal disconnection can be demonstrated on tests of localization of tactile stimulation. When different fingers of one of the patient's hands are touched by the examiner, patients can

adequately identify the location of the stimulation with the same (unseen) hand, but not with the other (Galin, Diamond & Herron, 1977; Risse et al., 1989; Sperry et al., 1969). Cross-integration deficits can also be demonstrated on tests of cross-replication of hand postures, on which patients can replicate hand postures with the same (unseen) hand but not the opposite one (Bogen, 1993; Chen, Campbell, Marshall & Zaidel, 1990; Risse et al., 1989; Trevarthen, 1990; Sperry et al., 1969; Sperry, 1974). These findings occur regardless of the direction of stimulation and response, that is, left hand to right hand or vice versa (Bogen, 1993; Chen et al., 1990).

The neurological basis of cross-integration deficits on the tactile localization and posture replication measures lies in the decussation and relatively separate hemispheric representation of the human sensory and motor systems (Bogen, 1993; Kolb & Whishaw, 1990). In an intact brain, information regarding each side of the body is thought to be integrated at the cortical level via callosal transfer. In the absence of a functional corpus callosum, each hemisphere maintains control over the opposite side of the body, but in isolation from the other hemisphere (Bogen, 1993; Kolb & Whishaw, 1990).

In split-brain patients, impairments of linguistic and praxic functions occur on left-sided but not right-sided trials. Linguistic deficits can be demonstrated in the auditory, visual and tactile modalities. In the auditory modality, split-brain patients typically show relative preservation of reporting from the right ear channel on verbal dichotic listening, with relative impairment of reporting from the left ear channel, termed left ear suppression (Springer, Sidtis, Wilson & Gazzaniga, 1978; Trevarthen, 1990). In some studies, enhanced right ear performance is observed on verbal dichotic listening (Bogen, 1993; Risse, LeDoux, Springer, Wilson & Gazzaniga, 1978; Springer & Gazzaniga, 1975), although the possibility is often not specifically addressed, for example, when difference scores or laterality indices are used (Milner, Taylor & Sperry, 1968; Springer, 1986). In the visual modality, patients have difficulty reading aloud verbal stimuli such as words or letters presented briefly to the left visual field on tachistoscope, but they read relatively well from the right visual field (Beaumont, 1982; Bogen, 1993; Sidtis, Volpe, Holtzmann, Wilson & Gazzaniga, 1981; Trevarthen, 1990). The possibility of right visual field enhancement is often not addressed (Bogen, 1993; Sperry, Gazzaniga & Bogen, 1969; Trevarthen, 1990). In the tactile modality, deficits are observed in naming objects palpated in the left hand but not the right, although the object can

be retrieved from among a set of distractors with either hand. Thus, patients can identify the object on the basis of sensory input, but have relative difficulty naming it when palpated with the left hand as compared to the right (Diamond, Scammel, Brouwers & Weeks, 1977; Gazzaniga, 1967; Risse et al., 1989; Sperry et al., 1969; Trevarthen, 1990). In addition to their linguistic symptoms, split-brain patients show left manual apraxia. That is, they can make gestures and other complex voluntary movements with the right hand but not the left, despite intact primary motor functions in both hands (Gazzaniga, Bogen & Sperry, 1967; Risse et al., 1989; Sperry et al., 1969; Trevarthen, 1990, but see Milner & Kolb, 1985). The linguistic and praxic symptoms thus include impairment of left verbal dichotic listening, left tachistoscopic reading, left tactile naming and left manual praxis, with relative preservation (or enhancement, in some cases) of performance on right-sided trials. Neurologically intact control subjects generally show no or less discrepancy in performance between left- and right-sided trials (Gazzaniga, 1970; Springer & Deutsch, 1981).

One widely accepted explanation of the neurological basis of linguistic and praxic effects of split-brain surgery lies in the contralateral organization of human sensory and motor systems, discussed above, combined with

left hemispheric functional specialization (Heilman & Rothi, 1993; Gazzaniga et al., 1967; McKeever, 1986; Springer, 1986). Sensory information transmitted from right-sided sensory receptors to the left hemisphere has relatively direct access to areas of the left hemisphere necessary for certain linguistic functions, whereas that is not the case for information transmitted from left-sided sensory receptors to the right hemisphere. In an intact brain, the information from the right hemisphere is thought to be transmitted via the corpus callosum to the left hemisphere. In the split-brain patient, this transfer is interrupted, resulting in the symptoms described above. Similarly, left hemispheric praxic control can be exerted relatively directly over the right side of the body, resulting in normal praxis of the right hand following surgery. However, with anterior callosal section, interruption of transfer of the necessary information to right motor cortex results in left manual apraxia. It should be noted that split-brain symptoms arise despite the existence of ipsilateral tracts in the majority of sensory and motor systems, and despite the presence of noncallosal interhemispheric commissures in the brain (McKeever, 1986; Springer, 1986).

Effects of partial callosotomy. Although the functional organization of the corpus callosum is not completely understood, it seems that the anteroposterior arrangement of

callosal connections parallels the arrangement of the cortical areas from which they originate (Pandya & Selzer, 1986). Therefore it has been speculated that in general anterior callosal section should disrupt motor function, section of the middle and posterior body should disrupt transfer of somesthetic and kinesthetic information, and section of the splenium should disrupt transfer of auditory and visual information (Reeves, 1991; Risse et al., 1989). Partial callosotomy evidence supports these basic distinctions, but in some studies also indicates sparing of interhemispheric transfer despite disconnection of the seemingly relevant callosal fibres (Bogen, 1993; Gazzaniga & LeDoux, 1978; Gordon, 1990; Reeves, 1991; Risse et al., 1989; Trevarthen, 1990).

Callosal Disconnection and Multiple Sclerosis

According to MRI research, the demyelinative plaques in MS show a predilection for the corpus callosum, among other areas of the central nervous system (Huber et al., 1987, 1992; Simon, Schiffer, Rudick & Herndon, 1989). Earlier microscopic and macroscopic post-morbid investigations yielded inconsistent results, due probably to technical differences among the studies (Barnard & Triggs, 1974; Brownell & Hughes, 1962; Lumsden, 1970), but the weight of

available evidence indicates that some degree of callosal demyelination is common in patients with MS.

Given the prevalence of plaques in the corpus callosum in MS, patients would be expected to show left ear suppression on verbal dichotic listening tests, and this has in fact been demonstrated in several studies using consonant-vowel and number stimuli (Jacobson, Deppe & Murray, 1983; Lindeboom & Horst, 1988; Rao et al., 1989; Rubens, Froehling, Slater & Anderson, 1985). In addition, on comparison with healthy control subjects, MS patients showed a greater discrepancy between latencies on left and right visual field presentations on a tachistoscopic object naming task (Rao et al., 1989). Excessive left ear and left visual field suppression are consistent not only with callosal damage, but also with asymmetric cerebral lesions among other factors (Jacobson et al., 1983; Rubens et al., 1988). Of the possible explanations, data available at the inception of the present study lent at least partial support to the callosal disconnection hypothesis. First, although they had access to computerized tomography data for only four subjects, Rubens and colleagues suggested that left ear suppression effects in MS were usually due to callosal damage. Secondly, Lindeboom & Horst (1988) found that degree of left ear suppression on verbal dichotic listening in their MS group correlated with impairment on a visual-verbal

association learning task, a finding which they interpreted as supporting the callosal disconnection hypothesis. Finally, Rao and colleagues (1989) demonstrated a relation of callosal atrophy with ear and visual field discrepancies on dichotic listening and tachistoscopic tasks respectively.

Enhanced right ear performance on dichotic listening was reported in two of the studies with MS samples (Jacobson et al., 1983; Lindeboom & Horst, 1988), but was not present in the third (Rubens et al., 1985) and was not addressed in the fourth (Rao et al., 1989). Because the first two studies did not appear to differ systematically from the third, the reason for the discrepancy in findings was not clear. The possibility of enhanced right visual field performance was not addressed in the available tachistoscopic study (Rao et al., 1989). Jacobson and colleagues (1983) did not offer an explanation for the finding of enhanced right ear performance, but Lindeboom & Horst (1988) attributed it to decreased interference secondary to decreased input from the left ear channel (Lindeboom & Horst, 1988). However they suggested this explanation was not entirely satisfactory because some subjects in the MS group showed enhanced right ear performance while still showing normal left ear performance.

A number of classic callosal disconnection symptoms, such as unilateral left apraxia and impaired tactile cross-localization, had not previously been tested in patients with MS. Although Barnard & Triggs (1974) reported no disconnection symptoms on post-mortem review of 20 patients with known callosal atrophy, they also noted that no specific testing for disconnection symptoms had been done in these patients. Previous research indicates that split-brain symptoms can go undetected without specialized measurement (Sperry, 1986).

The purpose of the present study was to replicate previous dichotic listening and tachistoscopic findings using different test versions, and to test for a number of classic callosal disconnection symptoms in patients with MS. The specific hypotheses are described in the following section.

Hypotheses

Verbal Dichotic Listening

On the basis of previous findings of left ear suppression on verbal dichotic listening in neurologically intact, right-handed subjects (e.g., Beaumont, 1982a,b; Spreen & Strauss, 1991), it was hypothesized that our control subjects would show a degree of left ear

suppression. On the basis of previous findings in split-brain patients and MS patients (Gazzaniga, 1970; Jacobson et al., 1983; Lindeboom & Horst, 1988; Rao et al., 1989; Rubens et al., 1985; Springer & Deutsch, 1981; Trevarthen, 1990), it was hypothesized that the MS patients in our sample would show excessive left ear suppression. Although previous MS research had yielded ambiguous results, it was also decided to investigate the possibility of right ear enhancement on verbal dichotic listening.

Visual Half-Field Tachistoscopic Reading

Given previous findings that neurologically intact, right-handed subjects typically read verbal stimuli better on right visual field presentations than on left visual field presentations (e.g, Beaumont, 1982a,b), we expected our control subjects to show the same pattern of results. On the basis of the MS and split-brain literature (e.g., Gazzaniga, 1981; Rao et al., 1989; Trevarthen, 1990), we expected the MS subjects to show poorer left visual field performance than control subjects on tachistoscopic reading. Given previous dichotic listening findings of right ear enhancement in MS, it was also decided to investigate the possibility of right visual field enhancement on tachistoscopic reading in this sample.

Localization of Tactile Stimulation

On the basis of the split-brain literature on the localization of tactile stimulation (e.g., Galin et al., 1977; Sperry et al., 1969), we expected that control and MS subjects would perform well on the ipsilateral conditions, but that the MS patients would show impairment on the contralateral conditions.

Replication of Hand Postures

On the basis of previous findings among split-brain patients (e.g., Bogen, 1985; Sperry et al., 1969; Trevarthen, 1990), we expected that the control and MS subjects would perform well on the ipsilateral conditions, but that the MS patients would show impairment on the contralateral conditions.

Tactile Naming

On the basis of previous split-brain findings (e.g., Sperry et al., 1969; Trevarthen, 1990), we hypothesized that control and MS subjects would be able to name objects palpated in the right hand, but that MS patients would have difficulty in naming objects felt with the left hand.

Manual Praxis

On the basis of the existing split-brain literature (e.g., Sperry et al., 1969; Trevarthen, 1990), we hypothesized that control and MS subjects would be able to

make gestures with the right hand, but that MS patients would show impairment on left-sided trials.

It should be noted that no hypotheses of enhanced performance were made for the latter four measures, on which stimulation (or response, in the case of praxis) was unilateral rather than bilateral. It was felt that a performance advantage would not likely result from callosal degeneration in MS because these tests did not involve presentation of simultaneous, conflicting, contralateral stimuli (or responses), and because enhancement had not been reported on similar measures in split-brain patients.

Methods

Subjects

Patients with MS (n=25) and control subjects without neurological disorder (n=25) participated in the study. MS patients were contacted by mail through the auspices of the Vancouver Island Multiple Sclerosis Society. At first, contact was made only with patients attending the local neurologist who had agreed to participate in the research. Eventually, to access the necessary number of subjects, patients attending other neurologists were also contacted. Members of local service and interest groups, and staff at a nearby high school volunteered as control subjects.

Exclusionary criteria included non-right-handedness, age less than 18 years, mental incompetence to give informed consent, and presence of a neurological condition other than MS. For control subjects, additional exclusionary criteria included presence of MS or a family history of MS. For the purpose of the present study, subjects were considered right-handed if they performed the six primary items of the Annett Handedness Inventory (Annett, 1972; Appendix A) with the right hand. Two members of the MS group and one member of the control group were considered non-dextral according to this criterion and were therefore excluded from the study. Two MS patients were excluded because they had

neurological disorders other than MS. In addition, one MS patient, diagnosed with Bipolar Mood Disorder, was in a manic phase at the time of the study and was too confused to give informed consent. One control subject was excluded because his mother had MS. After satisfying the exclusionary criteria, subjects remaining in the study numbered 23 in the control group and 20 in the MS group.

MS patients had clinically-definite (n=5) or laboratory-definite diagnoses (n=14), according to their neurologists' evaluations based on the criteria developed by Poser and colleagues (1983). One neurologist did not provide a rating of certainty, but stated that the diagnosis was certain in his opinion. Scores on the Extended Disability Status Scale (Kurtzke, 1983), provided for each patient by his or her neurologist, indicated a moderate overall level of disability in the MS group (mean = 6.1 $\pm$ 2.16; range 2 - 8). According to patient report, the time since initial diagnosis ranged from 1 to 22 years (mean = 8.3 $\pm$ 6.11 years). The time since patients experienced their first symptom of MS ranged from 6 to 38 years (mean = 14.9 $\pm$ 8.83 years).

Control and MS subjects' demographic, cognitive and selected medical characteristics are presented in Table 1. The groups did not differ in relative number of males and

females (ϕ = .23, p > .05), nor age (r = .05, p > .05), but the control group had attended school longer than the MS group (r = -.39, p < .01). The groups did not differ in age-specific scaled scores on the Wechsler Adult Intelligence Scale - Revised Vocabulary test (r = -.21, p > .05; Wechsler, 1981), but the control group outperformed the MS group on the Block Design test (r = -.38, p < .05). It should be noted that one control subject and three MS subjects did not complete the Block Design subtest, because of dislike for the test (n=1 control, 1 MS) or severe motor disturbance (n=2 MS). Four control subjects, but no MS subjects, reported having had a psychiatric disorder in the past. Three MS subjects, but no control subjects, reported having a current psychiatric disorder. It was not possible to apply correlational statistical analyses to self-reported psychiatric history and status because of cells containing zeros. Of the small number of subjects in each group who admitted to having a past or present psychiatric disorder, all identified their difficulty as depression. Fewer control than MS subjects were taking medication at the time of the study (ϕ = .49, p < .001). Control subjects reported taking the following: antihypertensive medication (n=2), thyroid hormone replacement (n=2), antihistamines (n=1), insulin (n=1) and oral hypoglycaemia (n=1). MS patients reported taking medications to regulate immunological functioning (n=3), improve motor control (n=4), and reduce symptoms

associated with trigeminal neuralgia (n=1), anxiety (n=1), depression (n=1), ulcerative colitis (n=1), arthritis (n=1) and hypertension (n=1). In addition, two MS patients were taking Vitamin B.

Patients in the MS group were classified by their neurologists as having chronic progressive (n=13) or relapsing remitting (n=7) forms of the disease. Characteristics of the two MS subgroups are presented in Table 2. Because of the small number of subjects in each MS subgroup, tests of group differences had low power. No significant relations were found between MS type and any of the demographic, cognitive or medical variables with the exception of disease activity and extent of disability. All subjects in the chronic progressive group were, by definition, experiencing symptoms of MS at the time of the study, whereas only three relapsing remitting patients were experiencing symptoms (ϕ = .68, $p < .005$). On the Extended Disability Status Scale (Kurtzke, 1983), neurologists rated their chronic progressive patients as having a greater disability than their relapsing remitting patients (ϕ = -.69, $p < .005$).

Complete neurological data were not available for each MS subject. It is particularly important to note that MRI data were available for twelve of the subjects in the

present study. However, only five scans were examined specifically for the presence or absence of callosal damage and, of those, three were positive for callosal lesions. The remaining scans showed periventricular abnormalities, but were not specifically performed nor examined to detect callosal lesions.

Measures and Procedures

After obtaining informed consent (Appendix B) and administering the handedness questionnaire, all subjects were administered the following measures in the following order.

1. Audiometer. Each subject's auditory acuity was measured with an audiometer. Subjects with inter-ear discrepancies of more than 20 decibels in the 500 to 6000 Hertz range were not administered the dichotic listening test, because their results would have been invalid (Spreen & Strauss, 1991). The dichotic listening test is robust to milder discrepancies (Spreen & Strauss, 1991). It was necessary to exclude only one subject, an MS patient, from the dichotic listening procedure on the basis of audiometer findings.

2. Verbal dichotic listening. The dichotic listening test employed in the present study was developed at the

University of Victoria (Allison version; Spreen & Strauss, 1991). It consisted of a tape presented in stereo on headphones. The tape contained 22 sets of stimuli. In each set there were three trials, each trial consisting of a pair of one-syllable words (e.g., hat, port, cow) presented simultaneously, one to each ear. Stimulus onset and loudness were equal for each ear. After each set of three trials, the subject was to say immediately as many of the six words as possible. A demonstration set was given, and the instructions were repeated if necessary to ensure that each subject understood the task. Accuracy scores were calculated out of 66 for each ear (Spreen & Strauss, 1991).

3. Double simultaneous visual stimulation. A procedure based on the one developed by Reitan (Reitan & Davison, 1974) was used to screen for visual neglect. The examiner placed her hands at the periphery of the subject's visual fields, and moved the left index finger, the right index finger or both. Twelve trials were administered at the top, middle and bottom of the subject's visual fields. The subject was asked to respond by indicating on which side the finger had been moved. Subjects with more than one error in either visual field were not administered the visual half-field tachistoscopic reading task, because of concern regarding the validity of their results. It was necessary to

exclude only one subject, an MS patient, on the basis of this measure.

4. Visual half-field tachistoscopic reading. The tachistoscopic procedures employed in the present study were based on descriptions by Bradshaw & Nettleton (1983), Hardyck & Dronkers (1985), McKeever (1986) and Young (1982). Visual stimuli consisting of pairs four-letter words and pronounceable nonwords (Appendix C) were back-projected onto an opaque screen located 63.5 cm in front of the subject. Nonwords were created by rearranging the letters of the "word" stimuli. After administration of ten practice trials, a set of 64 stimuli was presented twice, with a brief rest for subjects between sets. Thus a total of 128 test trials were presented.

Each stimulus pair contained a word and a nonword on a random selection of half of the trials, or two nonwords on the rest of the trials.[1] The stimuli were printed horizontally in black typescript, with one word or nonword on each side of the slide. Bilateral presentation was chosen because it is thought to yield larger asymmetries than unilateral presentation (Young, 1982).

Subjects were asked to read aloud all the words they saw, and to say "no word" when both members of the stimulus

pair were nonwords. Instructions were repeated if necessary to ensure that each subject understood the task. Accuracy of word reading was computed out of 32 for each visual field. Tachistoscopic data were transformed to percentage correct to adjust for the fact that subjects failed to respond on approximately 2.5 per cent of trials, usually because they blinked or momentarily looked away during a trial, or because they reported being unable to see the stimulus on a trial. Reading accuracy was chosen as the sole dependent variable because it was felt that measures of reaction time among MS patients might prove difficult to interpret, given the prevalence and variability of motor dysfunction in MS.

The medial edge of each stimulus fell at 2 degrees to the left or right of centre. The stimuli subtended a visual angle of 2.57 to 2.86 degrees, depending on the length of the word or nonword. Thus, the stimuli were within the recommended visual angle of 2 to 6 degrees to the left or right of centre, which is thought to allow each lateralized stimulus to fall in one visual field (Young, 1982). In addition, this recommended visual angle of presentation was used to avoid interference with central fixation, which may occur at smaller visual angles, and to avoid excessively lateral presentation, in view of the fact that visual acuity declines rapidly at the lateral edges in the horizontal plane (Young, 1982).

Stimuli were presented for 30 ms. This duration was chosen on the basis of empirical evidence that durations between 20 and 150 ms yield the expected visual field differences among control subjects (Young, 1982). Exposure durations of 120 ms or less are considered brief enough to prevent the subject from being able to move the eyes to look directly at the stimulus (Hardyck & Dronkers, 1985; Young, 1982). In addition to the above considerations, pilot data suggested that exposures of 30 ms yielded a moderate overall accuracy rate of about 65 to 70 per cent. It was felt that this level of difficulty would be sufficient to prevent both ceiling and floor effects. More specifically, it was chosen to allow for detection of right sided enhancement, were such enhancement to occur.

Throughout the tachistoscopic task, subjects were asked to maintain central fixation. The hope was that they would not move their eyes, either deliberately or otherwise, to look directly at one visual field or the other, which would obviate the purpose of the lateralized presentations. According to some researchers, randomized unilateral presentation of target stimuli provides its own protection against the effects of eye movements, because the subject cannot predict the side to which eye movements will be useful on any given presentation (McKeever & Van Eys, 1986). The spirit of this reasoning was carried through in the

present study in the use of bilateral presentations in which target (word) stimuli were pseudorandomly assigned to each visual field. Nonetheless, central fixation was tested by presenting a single letter in the centre of the visual field on a random selection of 20 trials, replacing the expected lateralized presentation. The subject was asked to read aloud the central letter. Accuracy of at least 80 per cent on these central fixation trials was required for the subject's tachistoscopic data to remain in the study. Tachistoscopic data from three control subjects and four MS subjects were eliminated because of failure to meet this criterion.

5. Localization of tactile stimulation. In this test, adapted from procedures described, for example, by Sperry and colleagues (1969) and Galin and colleagues (1977), the subject commenced by placing one hand at a time, palm up, behind a screen. The examiner lightly touched each of the subject's fingertips with the sharpened tip of a pencil. The subject responded by indicating the stimulated finger with the thumb of the same hand (ipsilateral condition) or by indicating the corresponding finger of the other hand with the thumb of that hand (contralateral condition). Subjects were required to respond immediately in an effort to prevent an opportunity for cross-cuing by sub-vocalization (Lassonde, Sauerwein, Geoffroy & Ptito, 1988). In addition,

subjects were asked not to move the stimulated finger, to prevent enhancement of stimulation through kinesthetic feedback. The task was demonstrated in full view of the subject and instructions were repeated as necessary to ensure that the subject understood. Sixteen ipsilateral trials and 16 contralateral trials were administered on each hand, for a total of 64 trials. Stimulations were presented in a pseudorandom order within each set of 16, with the proviso that each finger was stimulated four times per set. The ipsilateral conditions were always given first, so that it would be difficult to attribute potential errors on the subsequent contralateral trials, which were of greater empirical interest, to unfamiliarity with or lack of comprehension of the task. The left hand was stimulated first in a random selection of half of the subjects, and the right hand was stimulated first in the other half. Subjects were pseudorandomly assigned to one of ten stimulus order - hand order conditions with the proviso that there were an approximately equal number of patient and control subjects in each combination. Accuracy scores were obtained out of 16 for each hand in each of the ipsilateral and contralateral conditions, with higher scores representing better performance. Scores were also collapsed over the hand variable to yield scores out of 32 for each of the ipsilateral and contralateral conditions.

6. Replication of hand postures. In this test, adapted from descriptions provided in the split-brain literature (e.g., Chen al., 1990; Risse et al., 1989; Sperry et al., 1969; Sperry, 1974; Trevarthen, 1990), the subject placed one hand at a time behind a screen. The examiner molded the subject's hand into one of ten postures. The subject held the hand in the posture for two seconds and then released it. Then the subject was required to recreate the posture with either the same hand (ipsilateral condition) or the other hand (contralateral condition). The task was demonstrated in full view of the subject, and the instructions were repeated if necessary to ensure the subjects' understanding of the task. Ten ipsilateral and ten contralateral trials were administered to each hand for a total of four conditions and 40 trials. The same ten hand postures were given in a different order in each of the four conditions. The ipsilateral conditions were always administered first. The left hand was manipulated first in a random selection of half of the subjects, and the right hand was manipulated first in the other half. Subjects were pseudorandomly assigned to one of ten stimulus order - condition order combinations, with the proviso that there were an approximately equal number of patient and control subjects in each combination. Responses were scored as correct or incorrect. Scores were totalled for the ten postures performed with each hand in each of the ipsilateral

and contralateral conditions, with higher scores representing better performance. Scores were also collapsed over the hand variable to yield scores out of 20 for each of the ipsilateral and contralateral conditions.

7. Tactile naming. In the tactile naming test, which was based on descriptions provided, for example, by Dimond et al. (1977), Risse et al. (1989), Sperry et al. (1969) and Trevarthen (1990), the examiner placed one of ten common objects in one of the subject's hands at a time. The objects, chosen from Spreen and Benton's (1969) Neurosensory Center Comprehensive Examination for Aphasia, were a comb, ring, key, cup, ashtray, thimble, padlock, paper clip, knife and fork. The subject was allowed to hold and palpate each object for up to 20 seconds, and was asked to name the objects within that time. Attempts were made to prevent subjects from cross-cuing, for example by making noises with the object. Nonetheless, a number of subjects in both groups made a noise with the comb by running their thumb along its teeth.

After any failure to correctly name an object within the time limit, the subject was asked to retrieve the object from among a set of three objects placed behind a screen. The subject used the same hand to retrieve the object that he or she had just used to palpate the object. This was done

to demonstrate the person was able to palpate the object well enough to know its identity and retrieve it, and that the problem lay in naming rather than tactile sensation or palpation.

Instructions were repeated if necessary to ensure that the subjects understood. The same ten objects were used in a different order with the left and right hands. Subjects were pseudorandomly assigned to one of ten stimulus order - hand order combinations, with the proviso that there were an approximately equal number of patient and control subjects in each of the ten combinations. Accuracy of naming was scored correct or incorrect on each of the ten trials for each hand, with higher scores representing better performance. The percentage of correct retrievals following incorrect naming was also computed.

8. Manual praxis The manual praxis test was adapted from the procedures described, for example, by Risse et al. (1989), Trevarthen (1990) and Zaidel & Sperry (1977). With eyes closed, subjects were asked to perform ten different gestures with the left and right hands separately. Five of the gestures were transitive, and five were intransitive. Subjects were instructed to demonstrate to the examiner how they would brush their teeth, shave, comb their hair, clip their fingernails, eat with a spoon, salute, throw a kiss,

wave goodbye, beckon, and hitchhike. Instructions were repeated if necessary to ensure each subject understood the task, but no demonstrations were given. The same commands were administered in a different order for each hand. The left hand was tested first in a random selection of half of the subjects, and the right hand was tested first in the other half. Subjects were pseudorandomly assigned to one of ten stimulus order - hand order combinations, with the proviso that an approximately equal number of patient and control subjects were in each combination. Responses were scored as correct or incorrect. Accuracy scores were totalled for the ten gestures performed with each hand, and higher scores represented better performance. The number of instances in which subjects used their body part as the intended object (BPO errors) was also recorded.

9. Revised Wechsler Adult Intelligence Scale Subtests. Vocabulary and Block Design scales were administered to obtain brief estimates of verbal and nonverbal intellectual ability (Spreen & Strauss, 1991; Wechsler, 1981).

10. Demographic and medical questionnaire. Subjects were asked to complete the questionnaire shown in Appendix D.

Analyses and Results

The six test variables were tachistoscopic reading, verbal dichotic listening, tactile localization, posture replication, tactile naming and praxis. Descriptive data are presented in Table 3.

Manual Praxis and Tactile Naming

The manual praxis and tactile naming tasks were performed with high accuracy by members of each group. With the exception of one right-sided error, made by an MS patient, all subjects performed the manual praxis test with 100 per cent accuracy (Table 3). Body-part-as-object (BPO) responses, which were recorded separately from other errors on the praxis task, were made by four control subjects and one MS subject. Each subject who gave a BPO response made the same error with each hand, such that no asymmetry of BPO responses occurred. Control subjects made no errors in tactile naming, whereas six MS subjects made one or more errors on this task. Only one subject, an MS patient, showed more than a one-point difference between the hands. She made one error with the right hand and four with the left, but was able to retrieve all the stimuli from among a set of distractors. In general, all but one subject were able to correctly retrieve objects they were unable to name. The tactile naming and praxis tests were eliminated from further

analyses because of the above-mentioned findings, which were interpreted as consistent with ceiling effects.

Tachistoscopic Reading, Dichotic Listening, Localization of Tactile Stimulation and Replication of Hand Postures

Data from the four remaining experimental measures were submitted to analysis of variance (ANOVA) [2] and classification analysis using SPSS/PC (Norusis, 1990). When outlier and covariate analyses were employed, the results did not substantively differ from those reported here. [3,4]

Tachistoscopic reading. The tachistoscopic reading task proved problematic. It was necessary to eliminate subjects because of failure to meet central fixation standards (n=3 control and n=4 MS subjects), inability to see the briefly-presented stimuli (n=1 control and n=4 MS subjects), presence of more than one error on visual neglect testing (n=1 MS subject), equipment failure (n=1 control and n=1 MS subject), or lack of time on the part of the subject to complete this relatively time-consuming procedure (n=1 control subject). Older subjects with less education were over-represented among those not completing the tachistoscope task. Because of the difficulties associated with the tachistoscopic data, they were entered into separate analyses for the 17 control subjects and 10 MS subjects with available data.

A 2 X 2 repeated measures ANOVA was performed. The between-subjects factor was group (MS, control). The within-subjects factor was visual field of stimulus presentation (left, right). The group main effect was not significant ($F(1, 25) = 0.0$, $p > .05$), but there was a significant main effect of visual field ($F(1,25) = 20.19$, $p < .0001$). As expected, there was a significant group by visual field interaction ($F(1,25) = 8.81$, $p < .01$). Data are presented in Figure 1 and Table 3.

T-tests were used to examine group effects for left and right visual field presentations separately. As expected, a one-tailed t-test indicated that the accuracy of the MS group was significantly lower than that of the control group on left visual field presentations ($t(25) = 1.86$, $p < .05$; Table 3). As a follow-up to the analyses of group differences, a classification analysis was performed. Using left visual field tachistoscopic reading accuracy, twelve (70.6 %) of the control subjects and six (60.0%) of the MS subjects were accurately classified into their respective groups. Overall classification accuracy was 66.7 per cent.

Given the tentative nature of the hypothesis regarding enhancement on right visual field presentations, these data were subjected to a more conservative two-tailed t-test. Nonetheless, the MS group performed significantly better

than the control group on right visual field presentations ($t(24.8) = 2.69$, $p < .01$). Given the significant group difference, right visual field tachistoscopic reading data were also submitted to classification analysis. Eleven (64.7 %) of the control subjects and eight (80.0 %) of the MS subjects were correctly classified. Overall classification accuracy was 70.4 per cent.

Dichotic listening. One control subject showed an inter-ear discrepancy of greater than 20 decibels on audiometry, and therefore was not administered the dichotic listening test. One subject in the MS group declined to complete the dichotic listening test, but could only explain that she did not like it. Dichotic listening data from the remaining 41 subjects were entered into a 2 X 2 repeated measures ANOVA. The between-subjects factor was group (MS, control). The within-subjects factor was condition of stimulus presentation (left ear, right ear). The main effect of group was not significant ($F(1,40) = 0.61$, $p > .05$), but the main effect of condition was significant ($F(1,40) = 226.44$, $p < .0001$). As predicted, there was a significant group by condition interaction ($F(1,40) = 10.74$, $p < .005$). Data are presented in Figure 2 and Table 3.

T-tests were performed to elucidate the interaction. A one-tailed t-test was used to evaluate expected group

differences on left ear dichotic listening scores. Contrary to expectations, the MS group did not show significantly lower accuracy than the control group on left ear presentations ($t(40) = .70$, $p > .05$) although the mean difference was in the expected direction (Table 3). As mentioned in the Introduction, previous findings regarding enhanced right ear performance on verbal dichotic listening among MS subjects were inconsistent across studies, and a two-tailed test was therefore used to examine for a group difference on right ear presentations in the present study. The MS group performed significantly better than the control group on right ear presentations ($t(40) = 2.84$, $p < .01$; Table 3).

Localization of tactile stimulation. One MS patient was not administered the tactile stimulation test because of a severe somatosensory deficit. Data from the remaining 42 subjects were entered into a 2 X 2 repeated measures ANOVA. The between-subjects factor was group (MS, control). The within-subjects factor was condition (ipsilateral, contralateral). The group main effect was significant ($F(1,40) = 11.44$, $p < .005$), as was the main effect of condition ($F(1,40) = 30.11$, $p < .0001$). As predicted, the group by condition interaction was significant ($F(1,40) = 11.79$, $p < .001$). Data are presented in Table 3.

A one-tailed t-test revealed the expected group difference in the contralateral condition ($t(40) = 3.24$, $p < .005$), such that control subjects performed better than MS subjects. As expected, two-tailed t-tests revealed no group differences in the ipsilateral condition ($t(40) = .51$, $p > .05$; Table 3). [5]

Replication of hand postures. Two MS patients were not administered the hand postures test because of severe somatosensory and/or motor deficit. One of these patients was the same person who was not administered the test of localization of tactile stimulation. Data from the remaining 41 subjects were entered into a 2 X 2 repeated measures ANOVA. The between-subjects factor was group (MS, control). The within-subjects factor was condition (ipsilateral, contralateral). The main effect of group was significant ($F(1,39) = 4.50$, $p < .05$), as was the main effect of condition ($F(1,39) = 5.40$, $p < .05$). As expected, the group by condition interaction was significant ($F(1,39) = 4.06$, $p < .05$). Data are presented in Table 3.

A one-tailed t-test revealed the expected group difference in the contralateral condition ($t(39) = 2.12$, $p < .05$), such that control subjects performed better than MS subjects. As expected, a two-tailed t-test revealed no group

difference in the ipsilateral condition ($t(39) = 1.26$, $p > .05$; Table 3).[5,6]

Classification analysis. Results of the classification analysis using tachistoscopic reading data, done for the relatively small number of subjects who completed the task, were presented previously. The remaining variables that were hypothesized to differ between groups (left dichotic listening, contralateral tactile localization, contralateral posture replication) were entered together into a classification analysis for the 22 control and 18 MS subjects who completed all three tasks. Twenty-one (95.5 %) of the control subjects and ten (55.6 %) of the MS subjects were accurately classified into their respective groups, and the overall rate of correct classification was 77.5 per cent. According to the canonical discriminant function structure coefficients, the variables which contributed most to the analysis were tactile localization and posture replication (Table 4). When left verbal dichotic listening test scores were replaced with right ear scores, which had been associated with a group difference in previous analyses, 22 (100 %) of the control subjects and 11 (61.1 %) of the MS subjects were accurately classified. The overall rate of correct classification was 82.5 per cent. The contribution of the right ear scores to the discrimination was relatively substantial (Table 4).

Exploratory Analyses: Classification by Type of MS

Exploratory analyses were conducted to determine accuracy of classification of MS patients into chronic progressive (CP) and relapsing remitting (RR) subgroups, though analyses were hampered by the very small number of subjects in each subgroup. [7] Descriptive data on the test variables are presented in Table 5. It should be noted that when comparing the performance of CP and RR groups on the test variables, no group by condition interactions were significant (all $p > .05$). Tachistoscopic data were examined separately for the six CP and four RR subjects who completed the task. Using left visual field scores, four (66.7 %) of the CP patients and three (75.0 %) of the RR patients were accurately classified, and overall accuracy of classification was 80 per cent. Using right visual field tachistoscopic reading scores, three (50.0 %) of the CP patients and four (100.0%) of the RR patients were accurately classified, and overall accuracy of classification was 70 per cent.

Left verbal dichotic listening, contralateral tactile localization and contralateral posture replication test scores were entered together into a classification analysis for the eleven CP and eight RR subjects with complete data. Seven (63.9 %) of the CP patients and seven (100.0 %) of the RR patients were accurately classified. Overall

classification accuracy was 77.8 per cent. According to the canonical discriminant function structure coefficients, tactile localization scores contributed most to the analysis (Table 6). When left ear scores on the verbal dichotic listening test were replaced with right ear scores, six (54.5 %) of the CP patients and seven (100.0 %) of the RR patients were accurately classified. The overall level of classification accuracy was 72.2 per cent, but the right ear scores made a very modest contribution to the analysis (Table 6).

Discussion

As hypothesized, MS subjects in the present study demonstrate deficits consistent with decreased interhemispheric transfer. In previous studies, MS patients demonstrate excessive left auditory suppression on verbal dichotic listening tests using consonant-vowel and number pair stimuli (Jacobson et al., 1983; Lindeboom & Horst, 1988; Rao et al., 1989; Rubens et al., 1985). In the present study, on a verbal dichotic listening test using word stimuli, MS patients score lower than control subjects on left ear presentations, but the difference is not statistically significant. Previous findings consistent with decreased interhemispheric transfer on a tachistoscopic object naming task (Rao et al., 1989) are replicated in the present study using visual half-field reading accuracy as the dependent variable. Furthermore, the present study yields results consistent with impairment of interhemispheric transfer on other measures used in split-brain research, including tests of localization of tactile stimulation and replication of hand postures. In the present research, there are too few MRI scans, evaluated for callosal involvement, to allow meaningful investigation of relations between callosal atrophy and performance on tests of interhemispheric transfer in MS patients. In previous research, Rao and colleagues (1989) demonstrate that

callosal atrophy in MS is positively related to the size of the left-right visual field discrepancy on a verbal tachistoscopic task. Since the present study was carried out, an inverse relation has been demonstrated between left ear performance on verbal dichotic listening and MRI indices of posterior callosal atrophy in MS (Reinvang, Bakke, Hugdahl & Karlsen, 1993). In other subsequent research, a callosal disconnection syndrome, consisting of left tactile anomia, left agraphia and left apraxia, has been described in an MS patient with callosal and bilateral white matter degeneration on MRI, although other MS patients show no difficulty on the relatively crude measures of interhemispheric transfer employed in the study (Schnider, Benson & Rosner, 1993). The present findings, together with those of other related studies, support the hypothesis that functional callosal disconnection occurs in MS.

In the relevant studies to date (Jacobson et al., 1983; Lindeboom & Horst, 1988; Rao et al., 1989; Reinvang et al., 1993; Rubens et al., 1985; Schnider et al., 1993), including the present one, performance on a number of purported indices of interhemispheric transfer (e.g., left ear performance on verbal dichotic listening, left visual field tachistoscopic reading) has been significantly poorer in MS subjects than in neurologically healthy control subjects. However, the performance of MS subjects on these indices

appears better than that of many split-brain patients, at least on comparison with previously published data. For example, in all studies using verbal dichotic listening tests, MS patients have been able to accurately report a percentage of left ear stimuli (Jacobson et al., 1983; Lindeboom & Horst, 1988; Rao et al., 1989; Reinvang et al., 1993; Rubens et al., 1985), whereas split-brain patients perform at less-than-chance level on this measure, and may even deny the presence of stimuli in the left ear channel (Springer, 1986). This difference may reflect the fact that surgical lesions in split-brain patients are relatively complete, affecting both white and grey matter within the corpus callosum or sections thereof, whereas the lesions in MS are relatively circumscribed and predominantly affect white matter. In addition, split-brain patients probably have more extensive brain damage of longer duration.

In the present research, as in two previous studies, MS subjects demonstrate right ear enhancement on verbal dichotic listening tests relative to healthy control subjects (Jacobson et al., 1983; Lindeboom & Horst, 1988). No systematic procedural variations can be invoked to account for the fact that Rubens and colleagues (1985) fail to replicate this finding, although their study contains a relatively small number of subjects (11 MS and 10 control subjects). Reinvang and colleagues (1993) do not

statistically evaluate the possibility of right ear enhancement, but show a four per cent right ear advantage in accuracy among MS subjects relative to neurologically intact control subjects. Using a visual field difference score (left versus right) on tachistoscope as their dependent variable, Rao and colleagues (1989) do not address whether their observed group difference is due to impairment of left visual field performance, enhancement of right visual field performance, or both. In the present study, the finding of enhanced right ear performance on verbal dichotic listening is accompanied by impairment of left visual field performance and enhanced right visual field performance on tachistoscopic reading.

Decreased interference from attenuated left-sided input could explain the observed right-sided enhancement on verbal dichotic listening and tachistoscopic tests. Decreased left-sided input would lead to decreased competition for access to left hemispheric processing resources. In general, when integration of hemispheric activity would hamper cognitive performance, for example when the inputs to each hemisphere differ, callosal damage may be associated with better performance because of decreased conflict between the different activities of the two hemispheres (Trevarthen, 1990). In the present study, most individual MS subjects who show enhanced right-sided performance on either the dichotic

listening or tachistoscopic tasks also show relatively poor left-sided performance, which supports the idea that attenuation of left-sided input is associated with right-sided enhancement.

However, in the present study, right ear enhancement on dichotic listening appears in the absence of statistically significant left ear impairment. In addition, in the study by Lindeboom & Horst (1988), some of the MS subjects who show right ear enhancement on verbal dichotic listening perform normally on the left ear channel. Therefore, those authors argue that decreased competition from left-sided input cannot account for the right-sided enhancement in their study, but they do not offer another explanation. One possibility is that the corpus callosum normally mediates tonic or other inhibition of left hemispheric verbal processing. Such inhibition might normally allow left-sided input to "catch up" to right-sided input, thereby allowing more parsimonious simultaneous processing of information that may differ between the ears in relative external location, but not in content. As such, one role of the corpus callosum would be to enable "optimal integration of cortical activity" (Lassonde, 1986, p. 386). If the corpus callosum normally mediates both an excitatory and an inhibitory influence, and if these two functions are independent, selective impairment of callosal inhibition due

to circumscribed plaques in MS could lead to right-sided enhancement regardless of the strength or weakness of left-sided performance. The possibility that the corpus callosum has an inhibitory as well as excitatory role is supported by behavioral research (Clark, Zaidel & Lufkin, 1990; Liederman, 1986a,b; Liederman & Meehan, 1986; Liederman, Merola & Hoffman, 1986; Liederman, Merola & Martinez, 1985; Merola & Liederman, 1985; Zaidel, Clark & Lufkin, 1990), but not necessarily by neurophysiological data which, to date, indicate that the corpus callosum contains only excitatory fibres (Lassonde, 1986; LePoré, 1993; but see Pribram, 1986).

Although the suggestion that the corpus callosum mediates inhibition of left hemisphere verbal processing would explain the present dichotic listening and tachistoscopic findings, its relevance to the tactile localization and posture replication findings is less apparent. It is possible that callosal inhibition, if it occurs, is specific to the processing of verbal information or other relatively lateralized tasks. Alternatively, the inhibition may not be task- or material-specific, in which case, one might expect that in a test with sufficient sensitivity and different simultaneous bilateral inputs, MS patients would show enhanced performance on ipsilateral

trials on tactile localization and posture replication tasks relative to neurologically intact control subjects.

Alternate Explanations and Methodological Considerations

Although the performance of MS patients in the present and related studies is consistent with decreased interhemispheric communication due to callosal lesions, other possible explanations, both anatomical and behavioural, can and should be considered. For example, the obtained results may be due to extra-callosal lesions, or may be secondary to other cognitive or affective abnormalities.

At least four possible explanations based on extra-callosal lesions can be advanced. First, the dichotic listening and tachistoscopic results could be secondary to an asymmetrical distribution of lesions within the auditory and visual systems. Considerations which render this explanation unlikely include the fact that lesions are thought to be randomly not asymmetrically distributed in MS (Brownell & Hughes, 1962; Francis et al., 1991; Rubens et al., 1985). Although an asymmetrical lesion distribution could occur in one or two MS samples, this seems unlikely to account for the findings in the numerous separate samples which have been examined to date. In addition, with an asymmetry of lesions in the CNS, one might expect to obtain

lateralized findings on the ipsilateral conditions in tactile localization and posture replication tasks and on the visual neglect screening test and the audiometer, but that is not the case in the present study.

Secondly, bilateral lesions could account for the obtained findings. For example, as suggested by Rubens and colleagues (1985), right ear input, traversing the shorter pathway to the left hemisphere, would encounter fewer areas of demyelination and hence less degradation on average than stimuli traversing the longer pathway from the left ear to the right hemisphere and then to the left hemisphere. It should be noted however, that this explanation is not incompatible with the callosal disconnection hypothesis. In other words, a callosal lesion, perhaps situated at the roots of corpus callosum in either hemisphere (Geschwind, 1985), could provide one source of extra degradation. Although the bilateral lesion hypothesis could account for left-sided suppression on verbal dichotic listening and tachistoscopic reading, and for the tactile localization and posture replication findings, its ability to account for the right-sided enhancement on the former tasks is tenuous.

Third, bilateral lesions could account for the results in another manner. Because the right hemisphere contains more white matter than the left (Kolb & Whishaw, 1990), it

might also contain relatively more plaques in MS patients. Thus, impulses originating at the left ear and left visual field would encounter greater potential degradation when traversing the right hemisphere than those originating at the right ear and right visual field, which would not necessarily traverse the right hemisphere. Although this possibility would account for left-sided impairment and right-sided enhancement on dichotic listening and tachistoscopic findings, it cannot readily explain the audiometry, visual neglect, tactile localization and posture replication results, in which lateralized findings were not obtained. More sensitive versions of the latter two tests would better address the issue.

Fourth, extra-callosal lesions in some of the other forebrain and/or brainstem commissures could be invoked to account for the findings. However, other researchers have ruled out the possibility that abnormalities of auditory brainstem responses could account for dichotic listening findings in their studies (Jacobson et al., 1983; Rao et al., 1989; Rubens et al., 1985), and this decreases the likelihood that brainstem lesions account for the present findings. In addition, it would be difficult to explain why the randomly distributed lesions of MS would selectively affect noncallosal forebrain commissures.

The functional callosal disconnection hypothesis is supported by MRI research in MS, which demonstrates a positive relation between callosal atrophy and impairment of interhemispheric transfer (Rao et al., 1989; Reinvang et al., 1993). In fact, Reinvang and colleagues (1993) demonstrate a specific positive relation between left ear suppression on verbal dichotic listening and atrophy of callosal auditory fibres. Further research of this nature is currently under way, and preliminary findings agree with those reported here (Habib, 1993). Despite the support these findings lend to the callosal disconnection hypothesis in MS, it would be useful in future to further examine the specificity of the relation, for example, by addressing relations between measures of interhemispheric transfer and the extent of lesions elsewhere in the brain. This may be particularly important because callosal atrophy is highly related to degree of extra-callosal brain atrophy in MS, and because the location of lesions within the corpus callosum is likely to be specifically related to the location of extra-callosal lesions (Huber et al., 1992; Swirsky-Sacchetti, 1992). In addition, degree of callosal atrophy is related to degree of cognitive impairment in MS (Huber et al., 1985; Rao, Leo, Haughton, St. Aubin-Faubert & Bernardin 1989); the possibility should be ruled out that the observed relation between callosal atrophy and impairment of interhemispheric transfer in MS is a nonspecific

manifestation of the overall relation between callosal atrophy and cognitive impairment. In general, the specificity of the observed relation between callosal atrophy on MRI and performance on tests of interhemispheric transfer has yet to be fully established in MS samples.

In the present research, procedures have been employed to help determine whether the apparent callosal disconnection effects could be secondary to cognitive or behavioural impairments. For example, all subjects undergoing the dichotic listening procedure are free from substantial inter-ear discrepancies in auditory acuity that could invalidate the results of the test (Spreen & Strauss, 1991). Control procedures have also been incorporated into the other tests. This, together with the fact that Jacobson and colleagues (1983) screened subjects for abnormal auditory brainstem responses, suggests that findings consistent with impairment of interhemispheric transfer in MS are not secondary to other cognitive or behavioural factors.

Nonetheless, MS patients are prone to attentional dysfunction (e.g., Rao, 1986) and one criticism of the dichotic listening test pertains to its susceptibility to attentional effects. For example, subjects may report more words from the right than left channel on verbal dichotic

listening measures simply because they are paying more attention to the right channel, not necessarily because of requirements for interhemispheric transfer nor because of hemispheric asymmetry in linguistic processing. As part of the directed attention technique, which has been developed to help address this criticism, subjects are instructed to report the stimuli from either the right or left channel first. Excessive left ear suppression, though slightly attenuated, is still observed in MS patients even when the directed attention technique is employed (Lindeboom & Horst, 1988; Reinvang et al., 1993), which decreases the probability that the findings are due to a disturbance in directing attention.

A second attentional factor should be addressed. It has been suggested that in addition to its role in transferring information between the hemispheres, the corpus callosum is involved in directing attention and behavioural activation to the appropriate (more specialized) hemisphere, depending on the task at hand (Kinsbourne, 1974; Trevarthen, 1990). For example, on the verbal dichotic listening task, the corpus callosum might play a role in directing attentional resources to the left hemisphere. However, this would not readily explain findings of excessive left ear suppression and right ear enhancement obtained across studies using MS samples, which suggest that the most advantageous pattern of

hemispheric arousal for this verbal task is exaggerated rather than diminished in MS.

In future research, nonverbal dichotic listening tests might be employed in conjunction with verbal versions to further address the question of attentional effects on test performance. If the expected dissociation of verbal and nonverbal test results occurred (Springer, 1986), it would help rule out the attentional hypothesis, particularly if employed in conjunction with the directed attention technique.

Procedures intended to address alternate behavioural explanations of the tactile localization and posture replication results have been employed in the present study. On these tests, MS patients demonstrate the sensory, motor and cognitive capacity to localize tactile stimulation and replicate hand postures on ipsilateral trials with each hand. This suggests that the impairment observed on contralateral trials is not secondary to such extraneous factors, but rather to impairment of interhemispheric transfer.

MS is associated with affective difficulties (e.g., Minden & Schiffer, 1990a), which raises the possibility that the observed deficiencies on tests of callosal dysfunction

in MS could be secondary to affective or motivational factors rather than to impairment of interhemispheric transfer. However, this interpretation is unlikely because, first, efforts were made to ensure that subjects were motivated to perform to the best of their ability. Secondly, group differences were observed in the left-right pattern of results, but not in the overall level of performance on dichotic listening and tachistoscopic tests. The observed enhancement of performance on selected measures would be difficult to attribute to motivational deficiency or affective disturbance.

In summary, although the findings of the present and related studies are consistent with the hypothesis that the MS patients show decreased interhemispheric transfer due to callosal lesions, other possible explanations exist. In future research, it would be useful to investigate the specificity of MRI correlates of test performance and to employ strenuous control procedures to help eliminate alternate cognitive and behavioural explanations for the findings.

Manual Praxis and Tactile Naming

The expected left praxic and left tactile naming deficits are not observed in the present study. This may be due to test insensitivity as most subjects obtained perfect

or near-perfect scores on these measures. In future research, sensitivity of the tactile naming test could be improved by using lower-frequency nouns and by employing a dichaptic procedure (Witelson, 1974). Sensitivity of the praxis test could be increased by using more complex, compound, infrequent, and fine finger movements (Gazzaniga et al., 1967; Kimura & Archibald, 1974; Kolb & Milner, 1981; L. Taylor, personal communication; Zaidel & Sperry, 1977), and both tests should contain more items to increase reliability.

Although it seems likely that the absence of praxic and tactile naming deficits in the present research is due to test insensitivity, it is possible that the deficits would not have been observed on more sensitive tests. Two observations decrease the likelihood of this explanation. First, the only observed tactile naming deficit occurred in an MS patient with the expected (left) hand, and the patient was able to correctly retrieve the objects using the sense of touch. Her performance is consistent with impairment of interhemispheric transfer. Secondly, lesions are thought to be randomly distributed in MS. Therefore, there is no reason to suspect that the callosal fibres involved in tactile naming and praxis would be spared if callosal fibres thought to be involved in the other four tests are not. It is possible, though it has not been empirically demonstrated,

that the fibres involved in tactile naming and manual praxis are more diffusely distributed within the corpus callosum, and therefore less susceptible to appreciable destruction by circumscribed lesions.

In future, along with increasing the sensitivity of the manual praxis test, it would be useful to include a procedure to help determine whether patients could visually recognize a correct gesture from a set of distractors, even when unable to perform that gesture with the left hand. This would help rule out the possibility that any observed deficits were due to lack of verbal comprehension. In addition, future research would benefit from the addition of tests of motor speed, strength and dexterity, to help rule out the possibility that any observed deficits on praxis testing are secondary to motor impairment.

Implications

The existence of apparent callosal disconnection symptoms in MS carries potential clinical and empirical implications. Tests of interhemispheric transfer might usefully supplement other neuropsychological measures in the diagnostic evaluation of people with suspected MS. Impairment of interhemispheric transfer could be used as behavioural evidence to support the diagnosis of a multifocal disorder. Further research is needed to determine

the specificity of callosal disconnection symptoms to MS relative to other disorders involved in the differential diagnosis. In addition, research is needed to determine whether impairment of interhemispheric transfer can be detected early enough in the course of the disease to provide useful diagnostic assistance. The author is currently investigating whether tests of interhemispheric transfer can be used to predict which patients with optic neuritis will go on to develop MS, or to detect those who already show evidence of a mild form of the disease.

The existence of apparent callosal disconnection symptoms in MS has potential implications for split-brain research. At present most hemispheric disconnection research is conducted with patients who have undergone a split-brain operation for intractable epilepsy, but this population carries certain disadvantages. For example, subject groups are quite small in number, and available subjects vary in demographic and disease-related factors, such as age and severity of illness. Chronic epilepsy is often associated with early brain insult, functional brain reorganization and cortical dysfunction, and the surgery itself can be associated with extra-callosal damage (Trevarthen, 1990). Patients with MS would provide a more readily available population for split-brain research, since their numbers are relatively large. In addition, because MS is quite common,

it would be possible to select subjects with relatively homogeneous demographic and disease-related characteristics when appropriate. Nonetheless, certain difficulties would be connected with this direction of research, such as the fact that MS is associated with extra-callosal plaques.

Research with MS patients may afford the opportunity to address some empirical issues not encountered with surgical patients. In fact, MS patients may provide an interesting empirical contrast to split-brain subjects, since they provide a sample in which it may be possible to examine the effects of relatively circumscribed callosal lesions.

Geschwind (1985) suggests that the number of disconnection syndromes, including callosal disconnection syndromes, is probably commonly underestimated in clinical practice in favour of an over-reliance on cortical explanations of cognitive deficits. This may be the case in clinical and empirical work with MS patients. For example, the suggested neuropsychological battery for MS research does not include tests of interhemispheric transfer (Rao et al., 1991). Further study of interhemispheric transfer may prove interesting and useful in clinical and empirical neuropsychological investigations of MS.

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Footnotes

1. The use of trials with two nonwords originated in pilot research, in which subjects were asked to state whether or not they had seen a word. During the pilot research, it became apparent that word reading was a more sensitive test. It was therefore not necessary to include the trials on which two nonwords appeared, but they were retained by mistake.

2. Although MANOVA might have been considered appropriate for the present study, it was decided to use separate ANOVAs for each dependent variable. It has been argued that multiple univariate analyses are appropriate when the individual tests variables are of greater interest than is their multivariate combination, especially in a study of an exploratory nature such as the present one (Huberty & Morris, 1989).

3. Given the small sample sizes in the present study, it was felt that the validity of outlier analyses could not be assured and they were therefore not included in the text of the paper. Procedures related to detection and handling of outliers are presented here for the reader's information.

MS and control groups were examined separately for univariate outliers. Using normal probability plots and detrended normal plots from the SPSSPC MANOVA package, three outliers were detected in the control group, and two were detected in the MS group on the tachistoscopic reading task. Two of the control subjects showed reversed dominance on the tachistoscopic task. That is, they performed better on left than right visual field stimulation. Three outliers were detected among MS subjects on dichotic listening, but no outliers were present among control subjects. No cases of reversed dominance were present in the dichotic listening data. No other outliers were detected on the test variables. No subject obtained an outlying score on more than one variable. In each group, some of the outliers performed above average in accuracy, whereas others scored below. Visual inspection indicated that outlying cases performed slightly better than the rest of the subjects on the Block Design subtest, but no other differences were observed on cognitive, medical or demographic variables.

As mentioned, exclusion of outliers did not result in any substantive differences from the results of the analyses reported in the text of the paper. In summary, after outliers were removed, the group by condition interactions were still significant on tachistoscopic reading ($F(1,20) = 11.53$, $p < .005$) and dichotic listening ($F(1,37) = 17.77$, $p < .0001$), as were the t-tests of expected groups differences on each of the individual test variables (all $p < .05$), with

the exception of left dichotic listening scores, which were not significant in the original analyses either.

4. Because previous analyses indicated that the control and MS groups differed on education, Block Design test scores and presence or absence of medications, these variables were considered potential confounds and were therefore entered as covariates in analyses of group differences. Analyses of covariance (ANCOVA) resulted in only one difference from the results of analyses not employing covariates. That is, on posture replication, the interaction of group and condition was no longer significant at the .05 alpha level ($F(1,35) = 3.01$, $p = .092$). It should be noted, however, that the group difference was still in the expected direction, and the change in the level of significance may be at least partly attributable to the loss of degrees of freedom to the three covariates. For these reasons, the single discrepant result of the ANCOVA was not considered a threat to the interpretation of the ANOVA presented in the text of the paper.

5. When the contralateral and ipsilateral scores on the tactile localization and posture replication tasks were further analyzed according to hand of stimulus presentation, no substantive departures from the original analyses were observed. That is, no group differences were observed on ipsilateral trials, regardless of whether the left or right hand was used (all $p > .05$). As expected, the groups differed in the contralateral conditions, regardless of whether the left or right hands were used to respond (all $p < .05$).

6. Because there was little variability in scores on the tactile localization and posture replication tests, analyses were performed using dichotomized versions of these variables. That is, performance was coded as perfect (all correct) or imperfect (with one or more errors), and the measures were thus treated as screening tests. As would be expected, significantly fewer subjects from the MS group than from the control group gave perfect performances in the contralateral conditions of the tactile localization and posture replication tasks ($\chi^2(1) = 5.54$, $p < .05$; $\chi^2(1) = 8.32$, $p < .005$ respectively), but the groups did not differ in the ipsilateral conditions ($\chi^2(1) = 2.33$, $p > .05$; $\chi^2(1) = 1.39$, $p > .05$ respectively).

7. Additional exploratory analyses were performed to evaluate potential relations between the test variables and other medical, demographic and cognitive variables. Because a large number of correlations was performed, the results can only be interpreted as suggestive at most. In fact, with

Bonferroni correction, none of the results were significant. Using a critical alpha level of .01 in an attempt to impose a degree of conservatism, the following significant relations were observed. Within the MS group, presence of current self-reported psychiatric disorder was negatively related to accuracy of finger localization on ipsilateral trials ($r_{pb} = -.57$, $p < .01$), but no other relations of medical, demographic or cognitive variables with test variables were observed. Within the control group, the only significant finding was a positive correlation between Vocabulary scores on the Wechsler Adult Intelligence Scale - Revised and accuracy of posture replication on ipsilateral trials ($r = .52$, $p < .01$).

Table 1

Demographic, Cognitive and Medical Characteristics of Control and Multiple Sclerosis (MS) Subjects

	Control (n=23)		MS (n=20)	
	M	SD	M	SD
Age (years)	43.0	14.6	45.0	9.1
Education (years)**	15.2	2.5	13.4	2.3
Vocabulary [a]	12.5	2.5	11.5	2.6
Block Design [a,b] *	12.3	2.8	10.0	2.8
	n		n	
Gender: # Males	8		3	
# Females	15		17	
Medications [c] ***	6		15	

[a] Wechsler Adult Intelligence Scale - Revised age-specific scaled scores [b] n=22 control, 17 MS [c] Number of subjects who were taking prescription medications at the time of the study.

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

Table 2

Demographic, Cognitive and Medical Characteristics of Subjects with Chronic Progressive (CP) and Relapsing Remitting (RR) MS

	CP (n=13)		RR (n=7)		
	M	SD	M	SD	r
Age (years)	45.9	10.4	43.1	6.1	-.15
Education (years)	13.2	2.5	13.6	2.1	.07
Vocabulary [a]	11.6	2.6	11.1	2.7	-.09
Block Design [a,b]	9.7	3.1	10.6	2.5	.16
EDSS Score [c]	7.0	1.6	3.8	1.6	-.69*
Duration of Disorder					
Since Diagnosis [d]	7.3	5.4	10.1	7.3	.23
Since First Symptom	13.3	7.4	17.9	11.0	.25
	n		n		ϕ
Gender					
Females	11		6		.01
Males	2		1		
Certainty of Diagnosis [e]					
Clinically Definite	3		2		.04
Laboratory Definite	9		5		
Active Disease [f]	13		3		.68 *
Taking Medication [g]	11		4		.30
Psychiatric Disorder					
Present	2		1		.01
Past	0		0		NA

Table 2 (Continued)

[a] Wechsler Adult Intelligence Scale - Revised age-specific scaled scores [b] n=10 CP, 5 RR [c] Extended Disability Status Scale (Kurtzke, 1983), n=12 CP, 5 RR [d] Durations are in years. [e] n=12 CP [f] Number of patients whose symptoms were evident on the day of the study [g] Number of patients who were taking prescription medications at the time of the study

* $p < .005$

Table 3

Mean Accuracy on Test Variables by Control and Multiple Sclerosis (MS) Subjects

	Control (n=23)		MS (n=20)	
	M	SD	M	SD
Manual Praxis				
Left Hand (10) [a]	10.0	0.0	10.0	0.0
Right Hand (10)	10.0	0.0	9.9	0.2
Tactile Naming				
Left Hand (10)	10.0	0.0	9.6	1.0
Right Hand (10)	10.0	0.0	9.6	0.6
Tachistoscopic Reading [b]				
Left Visual Field (100) [c] *	59.3	20.1	41.6	29.2
Right Visual Field (100) †	68.3	22.2	85.9	11.6
Dichotic Listening [d]				
Left Ear Channel (66)	17.1	7.2	13.5	21.8
Right Ear Channel (66) ††	40.2	6.1	49.5	13.4
Tactile Localization [e]				
Contralateral (32) **	31.1	1.1	28.5	3.3
Ipsilateral (32)	32.8	0.6	31.7	0.5
Posture Replication [f]				
Contralateral (20) *	19.7	0.6	18.8	1.7
Ipsilateral (20)	19.8	0.5	19.4	1.0

Table 3 (Continued)

[a] Numbers in parentheses indicate maximum scores. [b] n=17 control, 10 MS [c] Tachistoscopic reading scores are reported as percentage accuracy. [d] n=22 control, 19 MS [e] n=19 MS [f] n=18 MS

* $p < .05$, 1-tailed test. ** $p < .005$, 1-tailed test.
† $p < .05$, 2-tailed test. †† $p < .01$, 2-tailed test.

Table 4

Canonical Discriminant Function Structure Coefficients (r) for Group Classification Analyses (Control, MS)

Analysis 1.	
Left Dichotic Listening	0.14
Contralateral Tactile Localization	0.96
Contralateral Posture Replication	0.66
Analysis 2.	
Right Dichotic Listening	-0.63
Contralateral Tactile Localization	0.77
Contralateral Posture Replication	0.53

Table 5

Mean Accuracy on Test Variables by Subjects with Chronic Progressive (CP) and Relapsing-Remitting (RR) Multiple Sclerosis

	CP (n=13)		RR (n=7)	
	M	SD	M	SD
Tachistoscopic Reading [a,b]				
Left Visual Field (100)	33.0	27.5	54.6	30.6
Right Visual Field (100)	82.3	13.8	91.3	4.8
Dichotic Listening				
Left Ear Channel (66) [c]	13.6	26.5	13.3	10.0
Right Ear Channel (66)	50.5	16.5	47.4	3.1
Tactile Localization [d]				
Contralateral (32)	27.6	3.8	30.1	0.9
Ipsilateral (32)	31.8	0.5	31.7	0.5
Posture Replication [e]				
Contralateral (20)	18.6	2.1	19.1	1.1
Ipsilateral (20)	19.3	1.3	19.7	0.5

[a] n=6 CP, 4 RR [b] Tachistoscopic reading accuracy scores are expressed as percentages [c] Numbers in parentheses indicate maximum raw scores [d] n=12 CP [e] n=11 CP

Table 6

Canonical Discriminant Function Structure Coefficients (r) for MS Type Classification Analysis (Chronic-Progressive, Relapsing-Remitting)

Analysis 1.	
Left Dichotic Listening	-0.07
Contralateral Tactile Localization	0.85
Contralateral Posture Replication	0.28
Analysis 2.	
Right Dichotic Listening	-0.30
Contralateral Tactile Localization	0.86
Contralateral Posture Replication	0.28

Figure 1. Tachistoscopic reading accuracy by visual field of stimulus presentation in control and MS groups.

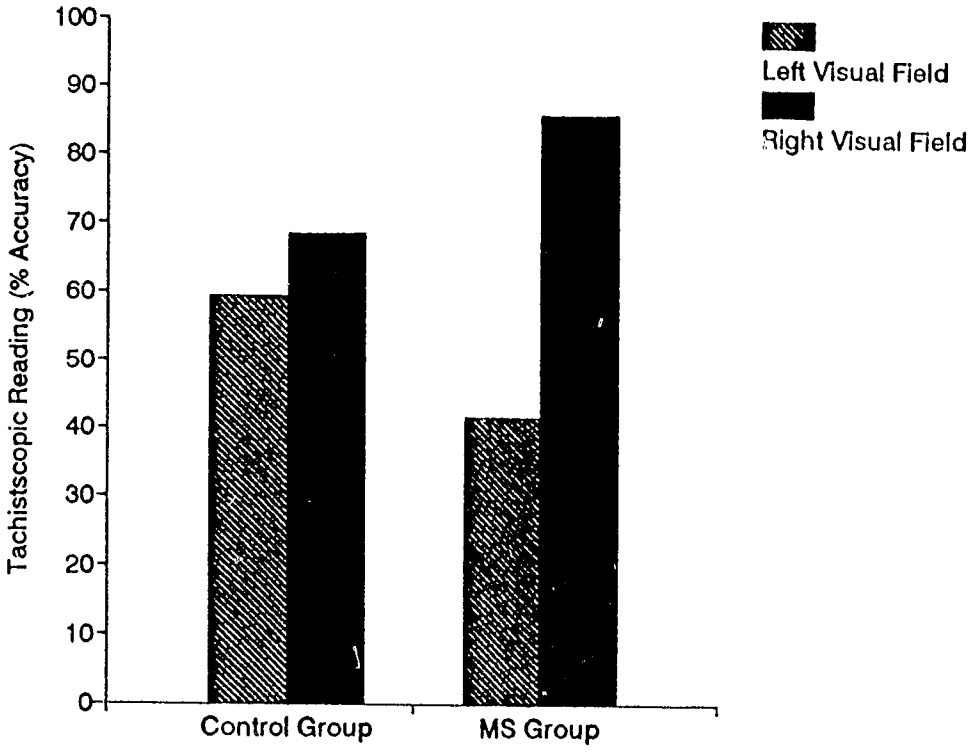
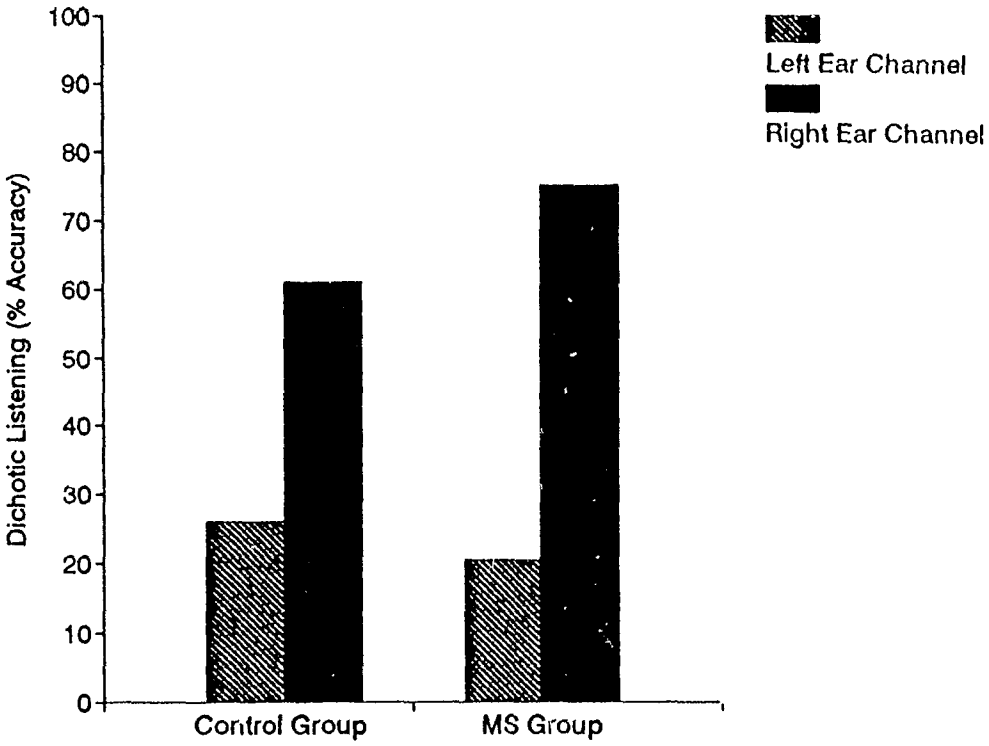

Tachistscopic Reading (% Accuracy)
100
90
80
70
60
50
40
30
20
10
0
Control Group
MS Group
Left Visual Field
Right Visual Field

Figure 2. Verbal dichotic listening accuracy by ear channel in control and MS groups.


100
90
80
70
60
50
40
30
20
10
0
Dichotic Listening (% Accuracy)
Control Group
MS Group
Left Ear Channel
Right Ear Channel

Appendices

Appendix A

Annett Handednesss Questionnaire (1972):

Primary Items

The subject is asked to demonstrate how they would:

1. write a letter legibly
2. throw a ball to hit a target
3. hold a tennis racket
4. hammer a nail into wood
5. hold a match while striking it
6. hold a toothbrush while brushing

Appendix B

Consent Forms

Consent Form (Control Version)

I agree to participate in Dr. Strauss' and Ms. Wishart's study. I understand that my participation in this study will involve psychological testing of sensory, motor and naming abilities. I agree to participate in this study on the condition that my anonymity will be maintained, and the information will be used only for research purposes.

I understand that participation in this project is voluntary, and that I may withdraw without penalty from this project at any time.

_____

signature

_____

date

Consent Form (Patient Version)

I agree to participate in Dr. Strauss' and Ms. Wishart's study on multiple sclerosis. I understand that my participation in this study will involve psychological testing of sensory, motor and naming abilities. I consent to Ms. Wishart obtaining medical information that is necessary for her research from my medical files. I agree to participate in this study on the condition that my anonymity will be maintained, and the information will be used only for research purposes.

I understand that participation in this project is voluntary, and that whether I participate or not will have no bearing on my treatment. I understand that may withdraw without penalty from this project at any time.

_____

signature

_____

date

Appendix C

Visual Half-Field Tachistoscopic Reading

1.	that	lero	W-L	31.	t		CFC
2.	reve	fact	W-R	32.	lemi	leru	
3	open	wevi	W-L	33.	half	tath	W-L
4	mert	nefi		34.	tesi	mert	
5.	lemi	ceap		35.	wram	view	W-R
6.	main	nasp	W-L	36.	w		CFC
7.	a		CFC	37.	tath	span	W-R
8.	leab	mert		38.	romf	open	W-R
9.	warm	stig	W-L	39.	temi	role	W-R
10.	fahl	form	W-R	40.	stoc	neto	
11.	nepo	pile	W-R	41.	pile	mani	W-L
12.	neno	leab		42.	ceha	oloc	
13.	n		CFC	43.	f		CFC
14.	nefi	atad		44.	fact	epil	W-L
15.	neth	ceha		45.	nefi	ceha	
16.	neto	slup		46.	ocer	main	W-R
17.	mani	unit	W-R	47.	leab	neto	
18.	tesi	lemi		48.	stig	that	W-R
19.	tuni	gist	W-R	49.	r		CFC
20.	epil	warm	W-R	50.	resu	leab	
21.	slup	nefi		51.	gist	romp	W-L
22.	form	temi	W-L	52.	resu	stoc	
23.	d		CFC	53.	i		CFC
24.	ceap	stoc		54.	slup	neno	
25.	span	ocer	W-L	55.	ceha	tesi	
26.	core	wram	W-L	56.	view	tuni	W-L
27.	ceap	neth		57.	atad	resu	
28.	ever	nepo	W-L	58.	role	reve	W-L
29.	caft	time	W-R	59.	lero	core	W-R
30.	leru	tesi		60.	neno	atad	

61. unit caft W-L
62. p CFC
63. netu lero
64. nasp ever W-R
65. neth neno
66. e CFC
67. cloc slup
68. mert neth
69. sloc oloc
70. oloc resu

71. wevi half W-R
72. atad lemi
73. leru ceap
74. time fahl W-L

Accuracy:

W-R _____

W-L _____

CFC _____

Appendix D
Demographic and Medical Questionnaires

Questionnaire (Control Version)

Demographic Information

1. Gender: Male ____ Female ____

2. Date of Birth (Year, Month, Date):

3. Age (years):

4. Education:

5. Current employment (title, nature of work, dates of employment):

6. Past employment (title, nature of work, dates of employment):

7. Current recreational activities (nature of activity, number of times per month):

Medical Information

1. Do you have any medical condition(s)? _____ If so, please specify the type(s):

2. Have you had any medical condition(s) in the past? _____ If so, please specify the dates and type(s):

3. Do you have any psychiatric condition(s)? _____ If so, please specify the type(s):

4. Have you had any psychiatric conditions in the past? _____ If so, please specify the dates and type(s).

5. Are you currently taking any prescription medications, nonprescription medications or other drugs of any kind? _____ If so, please specify the type(s) and dosage(s):

6. Please estimate the number of alcoholic drinks you consume in an average week:

7. Have you ever used alcohol or drugs to excess on a regular basis? _____ If so, please specify the substance and estimate the average number of excessive uses per week and the longest period of regular excessive use (e.g., 2 months, 2 years):

8. Do you have any hearing difficulties? _____ If so, do you wear a hearing aid? _____

Questionnaire (Patient Version)

Demographic Information

1. Gender: Male ____ Female ____

2. Date of Birth (Year, Month, Date):

3. Age (years):

4. Education:

5. Current employment (title, nature of work, dates of employment):

6. Past employment (title, nature of work, dates of employment):

7. Current recreational activities (nature of activity, number of times per month):

Medical Information

1. Do you have any medical condition(s) other than MS (e.g., epilepsy)? _____ If so, please specify the type(s):

2. Have you had any medical condition(s) in the past other than MS? _____ If so, please specify the dates and type(s):

3. Do you have any psychiatric condition(s)? _____ If so, please specify the type(s):

4. Have you had any psychiatric conditions in the past? _____ If so, please specify the dates and type(s).

5. Are you currently taking any prescription medications, nonprescription medications or other drugs of any kind? _____ If so, please specify the type(s) and dosage(s):

6. Please estimate the number of alcoholic drinks you consume in an average week:

7. Have you ever used alcohol or drugs to excess on a regular basis? _____ If so, please specify the substance and estimate the average number of excessive uses per week, and the longest period of regular excessive use (e.g., 2 months, 2 years):

8. Do you have any hearing difficulties? _____ If so, do you wear a hearing aid? _____

9. How many years has it been since you were first formally diagnoses with multiple sclerosis?

10. How many years has it been since you experienced your first symptom of multiple sclerosis?

11. Have you ever had a remission of symptoms since the beginning of your MS? _____ If so, please specify when your last remission began and ended.

Began: _____

Ended: _____

12. Are your MS symptoms active or in remission today?

13. What medications were you taking six months ago?

14. Did/does anyone else in your family have multiple sclerosis? _____ If so, please specify the relationship of that person to you (e.g., sister, father):