Cognitive Deficits in Multiple Sclerosis as Measured with the Computerized Tests of Information Processing and Adjusting-Paced Auditory Serial Addition Test

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Abstract

The ability of two newly developed measures of information processing to detect deficits in cognitive functioning associated with Multiple Sclerosis (MS) was investigated. The Computerized Tests of Information Processing (CTIP) and the Adjusting-Paced Auditory Serial Addition Test (Adjusting-PASAT) were administered to 60 clinically definite MS patients and 60 control participants. A repeated measures analysis of variance revealed the MS patients responded significantly slower than controls on the reaction time tests composing the CTIP. As the CTIP tests became more difficult, reaction times of the MS patients became increasingly longer than that of the controls. However, an analysis of variance showed the groups performed comparably on the Adjusting-PASAT. These results suggest the CTIP is sensitive to the cognitive deficits observed in MS and that the CTIP shows the potential to serve as a viable alternative to the traditional measures of information processing.

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Cognitive Deficits in Multiple Sclerosis as Measured with the Computerized Tests of Information Processing and Adjusting-Paced Auditory Serial Addition Test

The purpose of this study was to evaluate the utility of two newly developed tests of information processing to detect cognitive deficits in Multiple Sclerosis (MS) patients. Early research indicated that MS patients experienced only physical impairments. However, more recent evidence has shown that MS may also produce cognitive deficits, particularly a reduction in the speed at which information can be processed (Bobholz & Rao, 2003; Denney, Lynch, Parmenter, & Horne, 2004; Zakzanis, 2000). Unfortunately, relatively few neuropsychological tests effectively assess this type of impairment. However, two newly developed measures, the Computerized Tests of Information Processing (CTIP: Tombaugh & Rees, 1999) and the Adjusting-Paced Auditory Serial Addition Test (Adjusting-PASAT: Tombaugh, 1999), have been found to be sensitive to deficits in processing speed associated with traumatic brain injury (TBI: Tombaugh et al., in press). These tests also show the potential to be sensitive to the reduction in information processing speed (IPS) found with MS patients. The present study was undertaken to determine if these two tests can provide valid and reliable measures of cognitive decline in MS patients. In the following sections, a description of the disease and how it affects patients will be described as well as an overview of the neuropsychological findings with MS patients. The construct of information processing and the tests used to assess this function will also be examined. Finally, the rationale behind the development of both the CTIP and Adjusting-PASAT, and their relevance to IPS deficits found in MS will be presented.

What is MS?

MS is thought to be an immunological, or autoimmune, disorder in which the body attacks the myelin or myelin-producing cells (oligodendrocytes) because they have been incorrectly identified as foreign agents. The demyelination process results in lesions, or sclerotic plaques, that are randomly distributed throughout the central nervous system. These plaques reach grossly visible diameters, sometimes two to three centimetres wide and several centimetres long (Rao, 1990). Myelin is vital to the normal transmission of neural impulses, the loss of myelin initially results in the "scrambling" of these impulses so neuronal information slows or never reaches its target. The etiology of the disease is unknown. However, because MS is found more frequently in some geographic areas (the extreme south and north) than others (near the equator), an environmental agent may be involved in the contraction of the disease, possibly a slow virus (Zillmer & Spiers, 2001). Genetic factors also appear to contribute to the risk of developing the disease, evidence of which comes from findings that one in five patients have a family member with the disease and a higher concordance rate occurs in monozygotic twins (20-30%) than in dizygotic twins (2-5%) (Banich, 2004). Prevalence rates estimate that MS occurs in approximately 85 out of every 100,000 individuals and almost twice as many females acquire the disease as males (Banich, 2004). MS is the most common cause of neurologic disability affecting young and middle-aged adults (Banich, 2004; Rao, 1990; Feinstein, 2004; Staffen et al., 2002). For most patients, symptoms emerge between the ages of 15- to 50 years with the average age of onset being twenty-nine to thirty years old (Rao, 1990).

Patients commonly present with weak, stiff arms and legs often accompanied by decreased coordination. Some patients must rely on the use of an aid, such as a cane or wheelchair, to remain mobile. Individuals with MS often possess a gait disturbance as well as visual impairments ranging from blurry vision to blindness. Taken together, these symptoms explain why MS patients are prone to falls and bumping into objects. Individuals with the disease also often experience hesitancy and retention or urgency and incontinence of the bladder and bowels. Sexual dysfunction is not uncommon. Sensory changes range from sensations of numbness or tingling to feelings of electric shock. A major symptom reported by nearly all MS patients is fatigue. The presence of fatigue often prevents individuals from carrying out their usual daily activities and may require them to take short breaks or naps in order to complete a task. Less common symptoms include dysarthria "characterized by thickened sluggish sounding speech or by spasmodically spaced – scanning speech" (Lezak, 2004, p. 244), difficulty swallowing (dsyphagia), and tremor. These symptoms are quite variable in their nature, a product of the lesions being diffuse and variable in their location. The variety of motor and sensory symptoms is not unexpected given that the randomness in the location of lesions dictates that the longest white matter tracts will be lesioned most frequently. Sensory and motor tracts are often myelinated, as information must travel long distances from the peripheral receptor to the brain or from the brain to the muscle. Because these are some of the longest myelinated tracts found in the central nervous system it is likely that these functions will be affected.

There are no specific laboratory tests to identify the disease and the path to a definitive diagnosis is often a lengthy one. The diagnosis of MS is predominantly an

exclusionary one where all other possible illnesses must be eliminated or excluded first. Physicians have several methods available to help corroborate or reject the presence of the disease. These include the patient's history, neurological exam, MRI scan, evoked potential testing, and examination of the cerebrospinal fluid (CSF). Diagnostic criteria have been created to guide in the diagnosis of the disease. These criteria were recently revised to include results available from new technology; this revision is known as the McDonald criteria and includes the following (McDonald, Compston, & Edan, 2001, p. 124):

- Two or more attacks; objective clinical evidence of 2 or more lesions
- Two or more attacks; objective clinical evidence of 1 lesion + Dissemination in space, demonstrated by MRI *or* Two or more MRI-detected lesions consistent with MS and positive CSF *or* Await further clinical attack implicating a different site
- One attack; objective clinical evidence of 2 or more lesions + Dissemination in time, demonstrated by MRI *or* Second clinical attack
- One attack; objective clinical evidence of 1 lesion + Dissemination in space, demonstrated by MRI *or* Two or more MRI-detected lesions consistent with MS and positive CSF with dissemination in time, demonstrated by MRI *or* Second clinical attack
- Insidious neurological progression suggestive of MS + Positive CSF and dissemination in space, demonstrated by MRI evidence of specific numbers of brain or spinal cord lesions *or* Abnormal visual evoked potentials with specific numbers of brain and spinal cord lesions

demonstrated by MRI *and* dissemination in time, demonstrated by MRI

or Continued progression for 1 year

If these criteria are met and no alternative explanation can be reached, a diagnosis of either MS or possible MS is assigned, based on how well the criteria are fulfilled.

The course of the disease is highly variable; some patients may experience few or no unexpected relapses (i.e., exacerbations) in their lifetime while others may have frequent attacks resulting in permanent impairments and sometimes death. Most individuals fall somewhere in between. Approximately 25 percent of MS patients do not become seriously disabled and may continue to work productively 20- to 25 years following onset (Rao, 1990). While most patients experience various combinations of symptoms, three distinct patterns of disease course have been categorized: Relapsing-Remitting (RR), Secondary Progressive (SP) and Primary Progressive (PP). The RR form of MS is characterized by unpredictable relapses, or exacerbations, during which time new symptoms appear or existing symptoms become more severe. The duration of these relapses varies from days to months. Relapses are followed by periods of remission during which there may be partial or full recovery followed by disease stability until the next attack. It is estimated that 85% of patients are initially diagnosed with this subtype (Lublin & Reingold, 1996). When a patient initially diagnosed with RR-MS fails to exhibit a period of stability the diagnosis is changed to SP-MS. Patients with this form of the disease may have relapses but symptoms progressively increase between relapses. Fifty percent of RR patients will be re-diagnosed as SP (Lublin & Reingold, 1996). PP-MS is characterized by symptoms that begin gradually but then slowly worsen over time and may or may not include periods of stability. This form is often difficult to diagnose

and has limited treatment options. The PP subtype occurs in 15% of patients (Lublin & Reingold, 1996).

Severity of the disease is typically assessed using a clinical measure known as the Expanded Disability Status Scale (EDSS: Kurtzke, 1983). Scores on the EDSS are based on the neurological examination of eight functional systems. These systems are the pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and other. Scores on the EDSS can range from 0 to 10, with 0 indicating a normal neurological examination for all systems and 10 indicating death due to MS. In the past, the EDSS was the primary outcome measure employed in clinical drug trials. However, problems with standardization, sensitivity, reliability, and rater-to-rater variability were documented and motivated the development of an improved outcome measure [the Multiple Sclerosis Functional Composite (MSFC)], though the EDSS remains a useful tool for classifying MS patients by disease severity (Cutter et al., 1999).

The previously described motor and sensory symptoms of MS are well defined. However, this is not the case for cognitive deficits which have only been the focus of research over the past two decades. The frequency of cognitive dysfunction is high with prevalence rates estimated to be between 40% and 60% of patients (Banich, 2004; Heaton, Nelson, Thompson, Burks & Franklin, 1985; McIntosh-Michaelis & Roberts, 1991; Peyser et al., 1990; Rao, Leo, Bernardin & Unverzagt, 1991). Like other symptoms, the presence and nature of cognitive deficits show great variability among individuals. Some patients may exhibit little to no cognitive decline while others may show clear compromise in their functional abilities. General intellectual ability is typically found to remain intact (McIntosh-Michaelis & Roberts, 1991; Rao, 1990;

Zakzanis, 2000). Cognitive dysfunction may occur independently of physical disability and is not directly related to disease duration (Audoin et al, 2003; Feinstein, 2004; Staffen et al., 2002). The relation between cognitive disturbances and severity of the disease remains unclear. Correlational studies comparing cognitive impairment with either disability status scores or the degree of cerebral demyelination have yielded conflicting results (Maurelli et al., 1992). It also remains unclear as to how disease type and MRI relate to cognitive functioning (Swirsky-Sacchetti et al., 1992). Although it is accepted that MS does impact cognitive functioning, clinical investigators still debate about the magnitude and pattern of deficits and disagree on whether these deficits are indicative of clinical course and subtype classification. The pattern of cognitive abnormalities observed has been compared to that of the subcortical dementias (Rao, 1986). The cardinal features of the subcortical dementias are cognitive slowing and impaired memory

Neuropsychological Findings

Motor. It is likely not surprising that MS patients have a tendency to perform poorly on tests of motor functioning. In fact, most 'comprehensive' neuropsychological studies of the disease do not include measures of motor ability, presumably because it is intuitive that patients would be impaired on such tasks. Those studies that have included assessments of motor skills confirm that MS patients encounter difficulties within this domain. Zakzanis (2000) conducted an effect size analysis to review the neuropsychological literature of MS. Neuropsychological test results from 1845 MS patients and 1265 cognitively intact controls were synthesized using meta-analytic principles. The largest effect sizes existed for tests of manual dexterity and motor speed.

The effect sizes ranged from d = –1.76 for the Purdue Pegboard[1] (left hand) to d = -.74 for the Grooved Pegboard (left hand). All effect sizes within this range are considered to be large (Cohen, 1988). It was also reported that motor speed was more impaired than manual dexterity, as effect sizes were larger for Purdue Pegboard performance and Finger Tapping Test speed than Grooved Pegboard performance. Other studies have also found MS patients to differ significantly from controls on motor speed as measured by finger tapping tasks (Beatty & Gange, 1977; Jennekens-Schinkel, Laboyrie, Lanser, & Van der Velde, 1990). In the only study found to include an examination of grip strength, performances of MS patients and controls were comparable (Beatty & Gange, 1977). Thus, aside from grip strength, motor functions are often impaired in individuals with MS.

Memory. Memory, the most intensely studied cognitive function in individuals with MS, has been found to be consistently impaired. However, much disagreement exists as to which components of memory are affected by the disease.

Many researchers have reported that short-term memory (STM), a limited capacity temporary store, is not diminished by the effects of the disease (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Landro, Sletvold, & Gulowsen Celius, 1999; Litvan, 1988a; Maurelli et al., 1992; Rao, 1986; Rao, Leo, & St. Aubin-Faubert, 1989a; Rao et al., 1991; Swirsky-Sacchetti et al, 1992). In the neuropsychological literature of MS, STM was most often assessed using the Digit Span subtest found in both the Wechsler Adult Intelligence Test (WAIS) and the Wechsler Memory Test (WMS). For example, in Zakzanis' (2000) review, the WAIS-Revised

[1] See Appendix A for descriptions of common neuropsychological tests referred to throughout the document.

(WAIS-R: Wechsler, 1981) Digit Span Forward subtest was reported to have a mean effect size of d= –.37 (SD=.40). This effect size is considered to be small (Cohen, 1988) and the author noted that it was less substantial than those obtained for other neuropsychological tests examined. In addition, a significant difference in the magnitude of the effect size for this measure was found between the RR and chronic progressive types (SP and PP combined) of the disease. The difference in the effect sizes indicated the test was more sensitive for discriminating chronic progressive patients, who often exhibit increased severity of symptoms, from controls compared with the RR subtype.

In contrast to the studies cited above, Staffen et al. (2002) reported that an MS group scored significantly lower than a control group on Digit Span, suggesting that STM store may be impaired in patients with the MS. However, the MS group received a mean scaled score of 10.1 (SD=2.3) compared with a score of 11.7 (SD=1.6) for the control group. The average scaled score obtained by the MS patients is well within the average range and therefore, even though they may have obtained lower scores than controls, these patients would not be considered as impaired. An examination of the demographic variables reported for the patient group yielded surprising findings. The 21 patients tested were between 16 and 43 years of age, and all were classified as RR with a disease duration of less than three years. In addition, no patient was experiencing an exacerbation at the time of the study. Such characteristics could lead one to assume it unlikely that these individuals would experience cognitive difficulties. Indeed, some of the previously cited studies reporting MS patients performed as well as controls on Digit Span assessed patient groups possessing demographic characteristics that would make them far more likely to perform poorly on this task. The authors stated that the patient

and control groups were matched for age, years of education, and sex and there was nothing unusual regarding the methods used. In spite of Staffen et al.'s (2002) findings, it still appears that STM storage is not significantly affected in the majority of MS patients. Although, STM storage appears to be spared, individuals diagnosed with MS do exhibit relatively more susceptibility to STM interference than cognitively intact participants as revealed by poorer performances on conditions where distracters are present compared to when they are not (Coolidge, Middleton, Griego, & Schmidt, 1996; Denney et al., 2004; Grant, McDonald, Trimble, Smith, & Reed, 1984; Landro et al., 1999; Thornton & Raz, 1997).

Retrieval and recall appear to be susceptible to the adverse effects of MS (Banich, 2004; Coolidge, et al., 1996; Feinstein, 2004; Grant et al. 1984; Landro et al., 1999; Litvan et al., 1988a; Maurelli et al., 1992; Rao, 1986, 1990; Rao et al. 1989a; Thornton & Raz, 1997; Zakzanis, 2000). Evidence for faulty retrieval is derived from studies showing patients to be impaired in free recall but not in recognition memory (Brassington & Marsh, 1998; Rao et al., 1989a). In comparison with free recall, recognition is assumed to exert less demand on retrieval while still employing encoding and storage operations. The inconsistency in free recall of items over multiple trials has also been interpreted as evidence of successful memory encoding in the context of a retrieval component. Taken together, these results suggest that MS patients are able to initially register information into memory but retrieve information less consistently than controls. However, DeLuca and colleagues (1998) found verbal retrieval and recall to be intact. The authors allowed participants as many learning trials as was necessary to learn a ten-item word list in its entirety to control for differences in information *acquisition* between

groups. They found that the MS group required significantly more trials to learn the word-list than controls. The groups did not differ in recall or recognition of the words following a 30-minute, 90-minute, and 1-week delay. These findings led the authors to conclude that verbal retrieval and recall remain intact while a deficit in the acquisition of information is responsible for long-term memory dysfunction. In contrast to verbal memory, the MS group still required a significantly greater number of learning trials to reach criterion but they performed significantly worse on both recall and recognition of the visual information.

In summary, aside from increased susceptibility to interference, STM appears to be spared in the majority of MS patients. The status of acquisition and encoding/storage of information in patients with MS remain ambiguous. While some studies have yielded results similar to those reported by DeLuca et al.(1998) (e.g., Rao, 1990; Zakzanis, 2000), other researchers have found retrieval and recall to be impaired (Feinstein, 2004; Landro et al., 1999; Rao et al., 1989a; Thornton et al., 2002). In contrast, recognition is consistently unaffected in individuals diagnosed with MS (Banich, 2004; Rao, 1986; Swirsky-Sacchetti et al., 1992). Thus, the individual components of memory are differentially affected by the disease.

Executive Functions. In terms of executive functioning, deficits in concept formation, abstract reasoning, planning, cognitive flexibility, and problem solving have been reported (Banich, 2004; Brassington & Marsh; 1998; Bobholz & Rao, 2003; Feinstein, 2004; Rao, 1990). MacIntosh-Michaelis et al. (1991) studied the incidence of cognitive impairment in a community-based sample of MS patients compared with a group of individuals having rheumatoid arthritis. Thirty-three percent of the MS patients

were impaired on tests of frontal lobe function [modified-Wisconsin Card Sorting Test (m-WCST: Nelson, 1978), Controlled Oral Word Association Test (COWAT: Benton & Hamsher, 1976)] as compared to none of the individuals with rheumatoid arthritis.

In Zakzanis' (2000) meta-analytic effect size analysis, MS patients were moderately impaired on tests of conceptual function. The most sensitive tasks of conceptual function in MS were Raven's Progressive Matrices (Raven, 1960), followed by the Stroop test (Stroop, 1935), and the Wisconsin Card Sorting Test (WCST: Heaton, 1981). In an investigation of the frequency and patterns of cognitive dysfunction in a sample of community-based MS patients, Rao et al. (1991) also found MS patients to perform significantly worse on measures of conceptual reasoning (WCST and Raven's Progressive Matrices) compared to controls. An investigation of problem solving in MS patients carried out by Beatty and Monson (1996) compared the performance of patients with controls on the WCST and California Card Sorting Test (CCST: Delis, Squire, Bihrle & Massman, 1992).

On the WCST, the MS group achieved fewer categories than controls and made significantly more perseverative responses and errors. These findings support patterns observed in previous studies (Beatty et al., 1989; Heaton et al., 1985; Rao, Hammeke & Speech, 1987). However, the patients did not commit more non-perseverative errors or require a greater number of trials to recognize the first category, nor did they fail to maintain set more often than the controls. The CCST requires sorting of three sets of stimulus cards, each containing six cards, into two groups of three cards based on eight different sorting rules (either regarding verbal properties of words printed on the cards or physical properties of the cards themselves). The CCST involves three conditions, one of

which is 'free sorting' where participants are asked to sort a set of cards in as many different ways as possible. Another condition is 'structured sorting' where the examiner sorts the set of cards and participants are asked to describe the rule following each sort. Finally, there is 'cued sorting' where participants are again asked to sort the cards into two piles while the examiner provides an abstract description of the rule by which the cards are to be sorted, followed by explicit description if a subject does not sort the cards correctly. The CCST enables differentiation between impairment in concept formation and perseverative response. On the CCST, MS patients were impaired in generating and identifying concepts, as they attained fewer correct sorts than did controls, but increased scores on measures of perseveration did not occur. The differences in perseverations between the two measures may be due to how they were calculated for the individual tests. The authors also noted that measures of concept achievement and perseveration are not statistically independent on the WCST while they are much less strongly related on the CCST.

Rao and colleagues (1987) also examined performance on the WCST in RR and chronic progressive (SP and PP) MS patients. Their performances were compared to control groups composed of chronic back pain patients. A significant difference in the number of categories completed between chronic progressive patients and controls was observed. The chronic progressive group also exhibited significant perseverative tendencies relative to controls. These results suggest that MS patients with a chronic progressive course exhibit deficits on some conceptual learning tasks due to an impaired ability to shift cognitive set in response to negative feedback. The RR group was found to be unimpaired on the WCST relative to controls.

In a study comparing MS patients with cognitively intact controls on various measures of executive skills (Foong et al., 1997), MS patients were found to exhibit less usage of strategy on a task requiring a search for a blue token hidden within a number of boxes shown on a screen. Foong et al. (1997) also found that MS patients required increased time for initiation and execution of moves on a planning test based on the Tower of London (TOL) task. Additionally, they reported that the control group solved a significantly greater number of problems with the minimum number of moves allowed than the patient group and at each level of difficulty patients required more moves in solving the problems (i.e., made more unnecessary moves) than controls. These results indicate that the MS patients were less efficient in their performance than controls. However, Denney and colleagues (2004) found that when fatigue and depression were controlled for, the only differences remaining between patients and controls on the TOL task were for measures involving speed of information processing, such as increased planning times. Thus, various executive abilities such as conceptual reasoning, problem solving, and planning may be affected in patients with MS. Further research is necessary to determine the contributions of variables such as fatigue, depression, and processing speed to these deficits.

Visuospatial Abilities. The status of visuospatial abilities in MS patients is unclear (Rao, 1990). Even when deficits on visuospatial tasks are observed, they may be confounded by sensory and motor symptoms since tasks that assess this domain often require speeded manual performance and/or manual dexterity (Banich, 2004). With this in mind, a review of recent developments in the cognitive dysfunction of MS (Bobholz & Rao, 2003) reported controlled neuropsychological studies consistently showed a decline

on tasks of viuospatial abilities. Impairment of visuospatial perception has been reported in a community-based sample of MS patients (Rao et al., 1991) and a study assessing perceptual integration/organization using the Hooper Visual Organization Test (HVOT: Hooper, 1958) found 45 % of patients recruited from a clinical centre to be impaired (Swirsky-Sacchetti et al., 1992). Thus, keeping in mind the possibility of sensory and motor confounds, visual spatial abilities have often been reported to be impaired in MS patients.

Language. When language functioning in MS has been studied, it has been found to be largely intact (Bobholz & Rao, 2003; Jennekens-Schinkel et al., 1990; MacIntosh-Michaelis et al., 1991; Rao, 1990; Rao et al., 1991). However, a few studies have observed some type of language dysfunction in patients. The conflicting evidence regarding this domain is, at least in part, due to (a) the use of abbreviated tests resulting in a mostly superficial assessment and (b) the diversity of measures employed in different investigations. Rao et al. (1991) found approximately 25% of their MS sample to be impaired on verbal fluency (COWAT) whereas patients and controls were not significantly different on measures of naming [Boston Naming Test: BNT (Kaplan, Goodglass, & Weintraub, 1983)] and comprehension [Oral Comprehension (Bayles, Kaszniak, & Tomoeda, 1987)]. In an investigation of patients recruited from a clinical centre, 34- and 41% were observed to be impaired on the BNT and COWAT, respectively (Swirsky-Sacchetti et al., 1992). In his review, Feinstein (2004) also noted that patients have difficulty with verbal fluency as measured by the COWAT. On the Verbal Fluency Test, Foong and colleagues (1997) found an MS group to generate significantly fewer words than controls for both conditions (words beginning with 'S' and

animal naming). Beatty and Monson (1996) compared patients with controls on the FAS fluency test and also found the MS group generated fewer words. Friend and colleagues (1999) conducted an in-depth investigation of language functioning in MS. They compared the performance of an MS group on measures of naming, comprehension, and fluency to that of controls. Patients significantly differed from controls on a visual naming test and the letter and category fluency tests. They also obtained significantly lower scores on the Token Test (Benton & Hamsher, 1978), a measure of comprehension.

In sum, the findings regarding language functions have been inconsistent and further investigations are necessary to determine whether language is impacted in MS and whether individual components are differentially affected. With regards to measures of fluency it is important to recognize that, although these measures are related to language abilities, they are also commonly identified as tests of executive functioning. Performances on tests such as the COWAT involve a systematic search through semantic memory, which is likely directed by some component(s) of the executive system. Therefore, poor performance on these types of tests may not be indicative of language dysfunction but may be taken as further evidence for diminished executive functioning.

Attention and Concentration. Attentional processes have been studied far less systematically in MS than, for example, memory (McCarthy, Beaumont, Thompson, & Peacock, 2005). In general, a review of recent neuropsychological studies on MS reported a decline on tasks of attention (Bobholz & Rao, 2003). This finding is supported by the results of a study including MS patients and control participants that reported a significant impairment of attention in the MS group as measured by the Mental Control subtest of the WMS (Maurelli et al., 1992). In an investigation of both visual and

auditory attention, MS patients were found to be impaired on measures of both modalities (Brassington & Marsh, 1998). An attempt will be made to present the results of the few studies which have investigated different aspects of attention.

Sustained attention has been reported to be impaired in MS patients (Cohen & Fisher, 1989; Filley, Heaton, Nelson, Burks, & Franklin, 1989; Janculjak et al., 2002; Rao et al., 1991). For example, Filley et al. (1989) compared the performance of MS patients to a cohort of patients with dementia of the Alzheimer's type. The MS group was found to be more impaired on measures of both visual and auditory sustained attention. With regards to selective or divided attention, Swirsky-Sacchetti et al. (1992) found that 35% of their MS sample was impaired on Digit Span Backward and 32% on the Symbol Digit Modalities Test (SDMT: Smith, 1982). D'Esposito et al. (1996) found MS patients showed a greater decrement than controls in performance on a dual task compared with a single task. In an attempt to increase the knowledge base on the aspects of attention differentially affected by MS, McCarthy et al. (2005) conducted a study including measures of both sustained and divided attention. The sustained attention task required participants to attend to a series of numbers presented on a computer screen and to respond when a specific target number appeared; the target numbers changed over the course of the task. The divided attention task presented participants with pairs of numbers and required them to respond when target pairs, which were defined as any pair of numbers where the members were consecutive in either an ascending or descending order, appeared. MS patients showed consistently poorer performances than controls on both tests -- they obtained a lower percentage of correct responses and higher response times across the tasks. Thus, deficits in attention are consistently reported for MS

patients and the few studies attempting to study individual components of attention have reported poorer performances on tasks of sustained and divided attention, however, further research should be conducted to clarify these findings.

Summary. Motor skills are clearly disturbed in MS. Memory is also frequently affected by the disease, however, there is still much debate with regards to which aspects of memory are differentially affected. Executive functioning also appears to be adversely impacted by the pathology of the disease. Specifically, studies have shown concept formation, abstract reasoning, and planning skills to be deficient. The effect on visuospatial abilities is unclear as assessments of this domain are often confounded by motor and sensory symptoms. Language has been thought to remain largely intact; however deficits in verbal fluency, naming, and comprehension have been observed. Attention has been found to be frequently impaired and the evidence available suggests both auditory and visual as well as sustained and selective attention are all negatively impacted. It should be noted that the cognitive difficulties resulting from MS will depend upon the areas of the central nervous system affected by the disease. Because MS patients do not present with a common pattern of lesion distribution, instead of the observance of a 'cognitive profile' characteristic of other neurologic populations, cognitive symptoms can vary from individual to individual. The speed at which information can be processed has yet to be discussed. IPS is of primary interest in the present study, thus the neuropsychological findings regarding this function in patients with MS will now be described, as well as the process of working memory and its relationship with processing speed.

Information Processing Speed

The speed at which information can be processed is a critical function to study in MS for a number of reasons. For one, processing speed may be an important contributor to cognitive dysfunction associated with the disease (this premise will be discussed in more detail below). Cognitive dysfunction in MS is associated with a significant impact on activities of daily living (Bobholz & Rao, 2003; DeSousa, Albert & Kalaman, 2002; Feinstein, 2004). Rao et al. (1991) investigated how cognitive deficits affect the ability of MS patients to perform certain tasks as well as their quality of life. Patients were classified as either cognitively intact or cognitively impaired based on the results of a comprehensive neuropsychological test battery. Based on the results of a neurologic examination, self-report questionnaire, occupational therapy evaluation, and personality ratings by a close relative or friend, it became apparent that cognitive dysfunction significantly impacts patients' quality of life. In comparison to cognitively intact patients, those experiencing impairment were less likely to be working, participated in fewer social activities, experienced greater sexual dysfunction, had increased difficulty performing routine household tasks, and were more likely to exhibit psychopathology.

Secondly, slowed processing speed is one of the most common cognitive impairments in MS and may be the earliest cognitive manifestation of the disease (Archibald & Fisk, 2000; DeLuca et al., 2004). Therefore, IPS represents an important early indicator of cognitive dysfunction. If changes in the rate of processing speed can be accurately detected, such evidence can be used as a tool to determine the relative risk of the occurrence and progression of cognitive dysfunction in individuals diagnosed with MS. If at-risk patients can be identified they may benefit from early treatment

interventions (Feinstein, 2004). For example, interferon beta-1a has been found to have a significant beneficial effect on cognitive performance in early MS (Fisher et al., 2000).

Thirdly, if processing speed represents the primary cognitive deficit in MS, it is possible patients could benefit from being taught remediation techniques designed to provide additional processing time. Such rehabilitation efforts have been launched (e.g., Lengenfelder et al., 2006). These efforts have focused on helping patients to use additional time when confronted with challenging tasks and to identify which every-day tasks may be improved by taking additional time to complete them. By optimizing the time allotted to process information, working memory accuracy may be improved, enhancing stimulus acquisition abilities and thus improving learning. Therefore, by functionally restoring impaired skills or providing compensatory strategies to enhance learning, cognitive rehabilitation can help patients better perform tasks and activities essential to daily living.

The construct of IPS can be conceptualized as how quickly many different types of processing operations can be carried out (Salthouse, 1996). Slowed information processing has been frequently documented as a predominant deficit in the cognitive functioning of individuals diagnosed with MS (Archibald & Fisk, 2000; Audoin et al., 2003; Brassington & Marsh, 1998; D'Esposito et al., 1996; DeLuca, Johnson, & Natelson, 1993; Demaree et al., 1999; Diamond et al., 1997; Feinstein, 2004; Kail, 1997, 1998; Kujala et al., 1995; Lengenfelder, Chiaravalloti, & DeLuca, 2003; Lengenfelder et al., 2006; Litvan, Grafman, Vendrell, & Martinez, 1988b; Rao, St. Aubin-Faubert, & Leo, 1989b; Ruchkin et al., 1994; Sailer, Heinze, Schoenfield, Hauser & Smid, 2000). IPS has been measured using various methods throughout the MS literature. Kail (1997)

reviewed 12 studies involving measures of speeded performance that included tasks of counting letters, simple reaction time, moving pegs, and naming pictures. The results indicated that individuals with MS tended to require approximately 36% more time to respond than those not affected by MS. As a follow-up to this review, Kail (1998) investigated the performances of 11 MS patients and 11 controls on two psychometric measures of processing speed -- the Visual Matching and Cross-Out tasks from the Woodcock-Johnson Tests of Cognitive Ability (Woodcock & Johnson, 1989), a visual choice reaction time test, and on a visual search task. Results revealed that, across all tasks, the MS group performed approximately 46% more slowly than controls. In contrast with Kail's (1997) review, his 1998 investigation indicated that patients responded more slowly than controls by an amount that increased gradually as a function of the responses of the control group, as opposed to increasing linearly. That is, the difference in response time was relatively small when controls responded rapidly but greater in conditions when controls responded more slowly. This observation suggests the presence of a complexity effect -- as task difficulty increases response latencies become increasingly slower. Thus deficits in processing speed generally become more apparent on tasks involving greater cognitive demand.

Reaction time (RT) is a sensitive measure of processing efficiency (Milner, 1986) and has frequently been used to assess MS patients' ability to process information. Elsass and Zeeberg (1983) proposed that simple RT could discriminate MS patients from controls. They compared the performance of individuals with MS to patients hospitalized for non-neurologic conditions on a task that required participants to attend to a series of auditory signals occurring at random intervals from two to six seconds. Subjects

responded to each signal by pressing a button as quickly as possible. The MS group had significantly delayed RTs in comparison with controls, and 72% of the MS group and 80% of controls were correctly identified using a cut-off score of .165-seconds (10^{th} percentile score). In 1986, Arena and colleagues also investigated RTs of MS patients in comparison to control patients. However, they used visual stimuli (the illumination of two spatially separated coloured lights), and required participants to respond with a button press. RTs involving ipsilateral presentation and response were found to be longer for patients with MS compared to those of the control group. Jennekens-Schinkel and colleagues (1988) measured simple and go-no-go RT before and after four hours of neuropsychological testing requiring prolonged cognitive effort. They hoped to induce mental fatigue in order to assess the affects of such fatigue on RT for both visual (coloured lights) and auditory (signal) modalities. Mean RTs of the MS group were longer in comparison to controls both before and after the prolonged effort for all but the auditory simple RT condition. The groups could not be discriminated by the amount of pre- post change in RTs (RT after effort minus RT before effort).

Kujala et al. (1994) incorporated simple RT and choice RT in a study examining controlled processing (that which demands conscious attention) and automatic processing (that which does not demand conscious attention). MS patients classified as mildly cognitively deteriorated were found to perform more slowly on tasks of controlled processing while automatic processing was found to be affected in both the cognitively deteriorated and cognitively preserved patients. This finding was supported by the results of Janculjak et al. (2002) but is contradicted by results of other studies finding effortful processing to be more greatly affected in MS (e.g., De Sonneville et al., 2002; Grafman et

al., 1991). The variety of procedures used between these studies makes it difficult, if not impossible, to determine why the disparity in findings occurred. Janculjak et al. (2002) also measured both simple RT and choice RT. The simple RT task required participants to press a key when a randomly appearing visual stimulus was presented on a computer screen. For the choice RT task, participants were asked to press a key with one hand in response to a visually presented stimulus and to use their other hand to press a different key in response to another stimulus. The results showed that both simple and choice RTs were longer in the MS group compared with controls. The investigators went on to calculate decision reaction time (DRT) by subtracting simple RT from choice RT. They found that DRT did not significantly differ between groups.

In addition to RT, investigators have also used the Sternberg Memory Scanning test to examine speed of information processing. This test assesses the rate at which information held in STM can be scanned. The Sternberg test requires subjects to memorize a set of 1, 2, or 4 digits for each block of 16 trials. On each trial the participant is shown a digit on a computer screen and must decide whether it belongs to the set of digits held in memory. The slope of the reaction time function is assumed to represent the mean time a subject takes to compare the test stimulus to the representation of that stimulus in memory. This variable is purported to measure 'pure' cognitive speed, as it is not influenced by any existing motor impairment. Contradictory results have been found using this instrument. For example, Rao and colleagues (1989b) found significant differences between MS patients and controls. This finding is supported by the results of Archibald and Fisk (2000) and Janculjak et al. (2002). In contrast, Litvan et al. (1988b) found patients' performance not to be significantly different from that of controls. The

discrepancy between the results may be due in part to the demographic differences between patients tested in the Litvan et al. study and the others.

Another measure that has been used in the study of processing speed is the Paced Auditory Serial Addition Task (PASAT: Gronwall, 1977). This task requires individuals to add each number presented (ranging from 1 to 9) to the number immediately preceding it, so that the second number is added to the first, the third to the second and so on, and to say the sum aloud. Traditionally four trials are used, each with different time intervals between digits [i.e., inter-stimulus intervals (ISI)] of 2.4, 2.0, 1.6, and 1.2 seconds. DeLuca et al. (1993) found MS patients differed from controls on both fast and slow ISI rates. DeLuca and colleagues (1998) used a modified, computerized version of the PASAT called the Auditory Threshold - Serial Addition Test (AT-SAT). The AT-SAT was used so that speed of processing could be measured while the groups were equated on accuracy. Accuracy was controlled for by employing a method of limits procedure that increased or decreased the ISIs contingent upon the correctness of the response in order to obtain the optimum ISI, or threshold, at which each subject was able to correctly respond to 50% of the items. By holding accuracy constant, the authors hoped to isolate the speed component of this mental processing task. Results showed that the MS group required a slower rate of digit presentation to achieve the same level of accuracy as controls. It was also noted that three of the participants with MS were excluded from the analyses because they were unable to perform the task accurately, even after five practice trials. In sum, across tasks, IPS has consistently been found to be reduced in patients with MS.

Working Memory

Along with IPS, working memory is one of the two most frequently documented cognitive difficulties in individuals with MS (Lengenfelder et al., 2006). A contemporary neuropsychological definition of working memory is "the capacity to keep information on line as necessary for an ongoing task" (Sfagos et al., 2003, p. 1231). A popular and highly referenced theory of working memory was developed by Baddeley (1992). According to Baddeley working memory is composed of three major components, a central executive system, phonological loop, and visuospatial sketchpad. Briefly, the central executive system coordinates, controls, and manipulates information processing and is subserved by the phonological loop and visuospatial sketchpad, which are conceptualized as "slave systems" that maintain and temporarily store verbal and visual information. Impairments in working memory have been reported at the level of different components of this system for individuals with MS. For example, several researchers have observed deficits in the phonological loop (Hillary et al., 2003; Litvan et al., 1988a; Litvan et al., 1988b; Rao et al., 1993; Ruchkin et al., 1994). The phonological loop consists of a limited duration passive store for phonological codes (phonological/verbal buffer) and an articulatory rehearsal process that refreshes the buffer (Baddeley, 1986; Ruchkin et al., 1994). Immediate serial recall tasks represent one method used with MS patients to assess the integrity of the phonological loop. These tasks require participants to serially recall auditorily presented lists of short or long words under suppression and non-suppression conditions. A well-established finding with cognitively intact individuals is that long words are less likely to be recalled than short words (Rao et al., 1993). This effect is known as the word length effect and is thought to reflect the

articulatory rehearsal process because longer words are less readily rehearsed than shorter words. Articulatory suppression (e.g., counting out loud during stimulus presentation and written recall) prevents the articulatory rehearsal process and eliminates the word length effect (Baddeley, Lewis, & Vallar, 1984). Research with MS patients has found that, compared to controls, patients demonstrate a limited capacity of the articulatory rehearsal mechanism to rehearse longer words as compared to shorter words. Litvan et al. (1988a), Litvan et al. (1988b), and Rao et al. (1993) all found a more pronounced word length effect for MS patients than controls. This finding was thought to reflect an impaired articulatory rehearsal process in the phonological loop of verbal working memory, suggesting a defect in rehearsing phonological information.

Other investigators have identified deficits in the central executive system, particularly in the allocation of attentional resources and the manipulation of information (Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Grigsby, Busenbark, Kravcisin, Kennedy, & Taylor, 1994). The central executive system is also integral to the coordination of performance on two simultaneous tasks, thus dual-task paradigms have been employed to examine central executive functioning (Baddeley, 1986). For example, D'Esposito (1996) found that when compared with cognitively intact participants, patients with MS demonstrated difficulty performing two dual-tasks differing in their level of difficulty. Other evidence for impairment of the central executive comes from reports that, in comparison to controls, MS patients have greater difficulty with tasks requiring the manipulation of stored information, such as Digit Span Backwards, the Brown-Peterson task, Symbol Digit Modalities Test, and the PASAT (Grigsby, Ayarbe et al., 1994; Grigsby, Busenbark et al., 1994). From the results presented in this section it is

clear that individuals diagnosed with MS experience difficulty on tasks of working memory.

Relationship between Working Memory Accuracy and IPS

The functions of working memory and IPS are inherently entangled and each influences the performance of the other (Grigsby et al., 1994). The study of these functions has led some researchers to conclude that impaired processing speed underlies impaired working memory performance, resulting in the decreased ability of patients to acquire new information (DeLuca et al., 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). In general, this decreased efficiency affects learning and the ability to perform higher-level cognitive functions in individuals with MS (DeLuca et al., 1994; Gaudino, Donofrio, DeLuca, & Diamond, 2001; Kail, 1998; Litvan et al. 1988a; Litvan et al., 1988b; Thornton & Raz, 1997). However, some researchers have criticized these findings, pointing out that they are based on methods involving a "speed versus accuracy" confound. This confound exists because the accuracy of performance generally decreases as the speed needed to process information increases (Lengenfelder et al., 2006).

The presence of this confound makes it impossible to distinguish whether difficulties observed with MS patients are reflective of problems with working memory, IPS, or both. The acknowledgment of the difficulty in interpretation produced by this confound has led investigators to attempt to identify methods which can facilitate separately assessing these two cognitive processes. An example of such an attempt is represented by Demaree et al. (1999), who examined the effects of controlling for both the accuracy of performance and processing speed across MS and control groups. As in

the DeLuca et al. (1998) study described above, Demaree and colleagues (1999) used modified versions of the PASAT that controlled for accuracy by varying the ISI to ensure a 50% accuracy rate for all participants. They divided the patient and control groups so that that half of each group received a visual version (VT-SAT) of the test while the other half received the auditory version (AT-SAT). For both versions, the MS group required significantly longer ISIs to obtain the same level of accuracy as controls. Also, slower threshold speeds were obtained for both patients and controls on the auditory version suggesting the visual variant can be performed with greater ease. When all participants were allowed to perform the test at their own optimal threshold speed it became apparent that MS patients perform as accurately as controls when they are allotted more time to process information. Results from this study, as well as DeLuca et al. (1998), indicate that deficits in processing are due to impaired speed and not reduced accuracy.

Lengenfelder et al. (2006) also employed the VT-SAT to distinguish between IPS and working memory deficits in patients with MS, but they extended this research further by examining whether compensating for slowed speed could still improve accuracy when there are greater demands on working memory. In order to do this they administered separate trials of the VT-SAT varying in difficulty level. MS patients and control participants completed the standard "1-back" task, as was used in the Demaree et al. (1999) and DeLuca et al. (1998) studies, as well as two trials of a more difficult version referred to as the "2-back" VT-SAT. In the 2-back condition, participants are instructed to add each number presented to the number presented 2-back and report the sum out loud. For the 1-back condition and the first trial of the 2-back condition the same method of limits procedure was employed as in Demaree et al. (1999) and DeLuca et al. (1998) to

adjust the rate of stimulation presentation so that all participants obtained a 50% accuracy rate, allowing IPS to be assessed. In the second 2-back condition participants were allowed to complete the task at their optimum threshold speed from the 1-back condition, thus equating participants on processing speed so that working memory accuracy could be evaluated. If IPS is the primary cognitive difficulty in MS, equating for processing speed should result in an absence of differences in accuracy on this 2-back condition between groups. However, if working memory is impaired in MS patients or if working memory deficits interact with speed, group differences in accuracy on this second 2-back condition should be observed. Results of the standard 1-back VT-SAT replicated those of Demaree et al. (1999) and DeLuca et al. (1998). That is, the groups exhibited comparable accuracy levels but MS patients required significantly longer threshold speeds. This indicates that, at a lower working memory load, MS patients perform as accurately as controls but they require a significantly greater amount of time to do so. On the first trial of the 2-back condition a significant difference in processing speed was also obtained between the groups. On the second trial of the 2-back VT-SAT, when groups were equated on processing speed, 70% of MS patients performed as accurately as controls. However, 30% of patients were not able to reach the necessary level of accuracy regardless of the amount of information processing time allotted. According to the authors, these patients demonstrated an interaction of impairments in both IPS and working memory. For this group, impairments in working memory emerged with the additional central executive requirement of the 2-back condition.

In order to understand what differentiated those patients demonstrating working memory impairments on the 2-back condition from those who did not, performance on

additional neuropsychological measures were examined. Patients showing impairments in both functions had poorer performance on tasks that involved both working memory and processing speed but not on tasks involving either primarily speed or primarily working memory. This interaction of speed and working memory suggests that, although IPS appears to be the primary deficit, either increasing the requirement of speed or working memory load demands could disrupt performance in this impaired subgroup. The MS patients exhibiting impairments in both accuracy and processing speed on the 2-back condition differed from the other MS patients on tasks of verbal and visual learning as well as visual memory. Other researchers have described a relationship between speed and/or working memory and learning in MS suggesting that working memory may contribute to deficits in learning and long term episodic memory (DeLuca et al., 1994; Gaudino et al., 2001; Thornton & Raz, 1997). The authors concluded that IPS, not accuracy, is the primary information processing difficulty experienced by individuals with MS. The results also indicate that when the central executive is adequately taxed at a higher working memory load, there is an interaction between processing speed and working memory such that a subgroup of patients who demonstrate working memory difficulties in addition to deficits in speed emerges.

DeLuca et al. (2004) also investigated whether IPS or working memory deficits represent the primary dysfunction of information processing in MS. They compared prevalence rates of impairment on these two functions in 215 MS patients using indices of processing speed and working memory from the WAIS-III (Wechsler, 1997a) and WMS-III (Wechsler, 1997b). These indices were derived by factor analysis and have demographically corrected normative values based on a large, representative

standardization sample available. MS patients obtained significantly lower processing speed index scores than working memory index scores. All individual processing speed subtest scores were also lower than individual working memory sub-test scores. These significant effects remained after manual motor performance was controlled for by employing finger-tapping speed as a covariate. Impaired performance on the two indices was defined as performance at or below the 5th percentile of the normative standardization sample. Significantly more MS patients were found to be impaired on the processing speed index (35.3%) compared to the working memory index (12.6%). The same trend was observed for individual subtest scores. Furthermore, using odds ratios to estimate the relative risk of impairment of the two functions for an individual with MS relative to the general standardization sample, the authors found that the risk of IPS deficits was almost four times greater than that observed for working memory. The authors also compared performances of RR and SP patients and found that their results supported the hypothesis that IPS is affected early in the course of the disease while deficits in working memory ability materialize only with progression of the disease. This was based on the finding that if working memory deficits were observed in MS patients, it was only among SP patients. A possible explanation for the findings presented in this section will now be discussed.

Relative Consequence Model

DeLuca et al. (2004) first proposed a theory explaining the pattern of results obtained in the studies described in the previous section. They termed this the Relative Consequence Model and, in general, it suggests that persons with MS have a fundamental

difficulty in processing speed that consequently results in the compromise of other cognitive processes as well. DeLuca et al. (2004) explain:

> Specifically, this *Relative Consequence Model* hypothesizes that difficulties in working memory (and likely other cognitive functions) are primarily a function of deficient processing speed. As the magnitude of the processing speed deficit increases, a critical point is reached, which then influences performance on tests of working memory. Thus, this model predicts that inefficiencies in other cognitive processes are a by-product of slower cognitive processing (p. 558).

Considerable support for the Relative Consequence Model is found in the research on cognition and aging. Salthouse (1996) stated that an age-related deficit in speed is one of the major causes of variability on working memory tasks. This same relationship between deficits in processing speed and higher cognitive processes has also been suggested to be a significant characteristic of cognitive functioning in MS (DeLuca et al., 1994; DeLuca et al., 1998; Demaree, Gaudino, DeLuca, & Ricker, 2000; Kail, 1998). The aging literature also provides an explanation as to how processing speed may actually affect other cognitive functions. According to Salthouse (1996), the speed at which a cognitive activity is performed is not simply a function of the processes required to execute that activity but is also influenced by the ability to rapidly perform many different types of processing operations. Salthouse goes on to describe two distinct mechanisms that he proposes to be responsible for this speed-cognition relationship.

The basis for the limited time mechanism is "simply that the time to perform later operations is greatly restricted when a large proportion of the available time is occupied by the execution of early operations" (Salthouse, 1996, p. 404). The importance of this

mechanism is obvious when the time available for processing is limited, such as when there are external time limits or the presence of simultaneous processing demands. Performing at a slower processing speed would result in less processing being completed in a given amount of time. Thus, the operations necessary to complete a cognitive task may not be executed if processing is slow. More processing frequently results in higher levels of performance and the ability to accomplish a larger amount of processing increases with higher rates of processing. The limited time mechanism presents important implications for the performance of complex cognitive tasks. Performance on such tasks is "affected by the number of operations (e.g., associations, elaborations, and rehearsals) that can be carried out in the available time" (Salthouse, 1996, p. 404). Therefore, if complex operations are dependent on the products of simpler operations, and fewer of those products are available because of a slower processing speed, the effects of slow processing can be expected to be most pronounced on the performance of complex tasks. In other words, a complexity effect -- the positive relation between task complexity and the magnitude of deficits exhibited in speed and accuracy -- will emerge.

The second mechanism hypothesized to be responsible for the processing speed-cognition relationship is the simultaneity mechanism. This mechanism is based on the idea that products from early processing may no longer be available by the time later processing is completed. "If the rate of processing is slow, relevant information is less likely to be useful because it is more impoverished or degraded by the time that preceding operations are finally completed" (Salthouse, 1996, p. 405). In this case, the critical limitations are internal as opposed to the relationship between internal and external factors described for the limited time mechanism. It is important to note that this

degradation has been shown to be a function of slower speed of processing and not the rate of information loss or decay in working memory. A critical hypothesis of the processing speed theory is that an age-related decrease in speed is one of the major causes of the variations in working memory associated with increased age (Salthouse, 1996). There is considerable evidence supporting this hypothesis; the statistical control of measures of processing speed has been found to greatly reduce the amount of age-related variance in measures of working memory (see Salthouse, 1996). An important implication of the simultaneity mechanism is that not all of the relevant information will be available in a usable form when it is needed, leading to impairments of critical operations that could result in either a high rate of errors or time-consuming repetitions of the critical operations.

In the aging literature, it has been suggested that these two mechanisms are responsible for the relationship between processing speed and quality and/or accuracy of higher-level cognitive processes (Salthouse, 1996). DeLuca et al. (2004) found the major information processing deficit in MS to be IPS as opposed to working memory; this led the authors to suspect that these same two mechanisms may also be responsible for a majority of the variance in other cognitive difficulties in MS patients. Similar to aging, in MS it has been hypothesized that slowed IPS diminishes the strength of encoding (due to the two mechanisms described above), resulting in deficient learning leading to poor recall and recognition (Kail, 1997; Kail, 1998; Kail & Salthouse, 1994). This process ultimately affects the functional activities of everyday life. Support for this relationship is accumulating in the MS literature (DeLuca et al., 1994, 1998; Demaree et al., 2000; Gaudino et al., 2001; Kessler, Cohen, Lauer, & Kausch, 1992; Thornton & Raz, 1997).

DeLuca et al. (1994) noted that further evidence for the model is provided by the study of the neuropathology of the disease itself. The RR disease course of MS is known to be characterized by lesions or areas of demyelination, primarily in periventricular white matter regions. It is likely that this neuropathology may be responsible for the impact on processing speed in MS (Herndon, 2003). However, as the RR course evolves into a secondary progressive phase involvement of axonal properties, such as axonal degeneration, are observed in addition to increased abnormalities in normal appearing white matter (Herndon, 2003). The Relative Consequence Model predicts that the increased cerebral burden results in more pronounced deficits in processing speed and thus, the weakening of other cognitive processes as well.

The Relative Consequence Model as Applied to the CTIP

The present study included an assessment of RTs using the Computerized Tests of Information Processing (CTIP: Tombaugh & Rees, 1999). The above rationale can be directly applied to performance on this measure. The CTIP is composed of three different RT tests, a simple RT test (SRT), a choice RT test (CRT), and a semantic search RT test (SemRT). For the SRT test participants are instructed to press a key as quickly as they can whenever a stimulus appears on the computer screen. For the CRT test participants are instructed to press one key when a specific stimulus appears on the screen and to press a different key when the other possible stimulus appears on the screen. For this task a decisional component is introduced where it is speculated that participants base their choice of response on concrete or literal processing of the form of the stimulus. For the SemRT test participants are presented with a word followed by a semantic category and are instructed to press one key if the word represents a member of the

category and to press a different key if the word does not represent a member of the category. Therefore, this task also includes a decisional component; however, response choice is now speculated to be based on conceptual processing. Specifically, it is hypothesized that participants perform a search of semantic memory to determine whether the word matches the category or not.

According to the Relative Consequence Model, persons with MS have a fundamental deficiency in processing speed that will consequently result in the compromise of higher-level cognitive processes. This compromise occurs in two ways. First, MS patients whose processing speed has been reduced as a result of the neuropathology of the disease are slower in performing cognitive operations, therefore, fewer operations are completed given the same amount of processing time as an individual whose IPS has not been reduced. Second, as these patients require a greater amount of time to complete cognitive operations, by the time they have reached more complex operations the products of earlier operations are more degraded than for individuals whose processing is intact. Consequently, these patients may not have all the information available to them necessary to perform the later steps of a given task. It is assumed that a greater number of complex operations must be carried out as cognitive demands increase across the three CTIP tasks. This assumption is supported by fMRI evidence showing a progressively greater number of neural areas are activated across the three tests,

> Results showed activation during the Simple Reaction Time (RT) task in the supplementary motor, premotor, and primary motor areas. The Choice RT activated these areas plus the language areas of the dorsolateral prefrontal cortex,

superior temporal gyrus, the anterior cingulate, temporal-parietal junction and the fusiform gyrus. The Semantic Search RT task showed these areas but also more significant orbital and dorsolateral prefrontal activity (A. Smith, personal communication, May 25, 2005).

Therefore, as the number of complex operations necessary to the completion of the task increase across the tests, there is more opportunity for patients' information processing abilities to break down in the manner just described. Thus, it can be assumed that the RTs of MS patients will become increasingly longer than controls over the course of administration of the test. Because of this, the more complex tests will be more sensitive to deficits in speed of information processing.

Critique of the Neuropsychological Measures of Information Processing

Even though impaired processing speed is a common dysfunction observed in MS, and neuropsychological testing is said to offer the most sensitive means by which to detect cognitive difficulties (Feinstein, 2004), there are relatively few neuropsychological measures that effectively assess this type of impairment. A review of the advantages and disadvantages of those methods most commonly used to assess IPS follows.

Sternberg Memory Scanning Task. Although the Sternberg Memory Scanning task has been used to evaluate information processing in MS, it was not considered as a potential measure to be included in the Multiple Sclerosis Functional Composite (MSFC). The MSFC is the most commonly used outcome measure employed in clinical drug trials. Different versions of the Sternberg task exist and, depending on which is administered, very different results may be obtained. This suggests that the validity of the measure may be questionable. Moreover, there are no normative data available for the test and a

review of the literature yielded no information regarding its psychometric properties. Because there is no information by which its utility with MS patients can be determined, the Sternberg task was not considered to be a viable alternative to measures of processing speed currently in use and was not included in the present investigation of cognitive deficits in MS.

PASAT. The PASAT has been used to investigate a variety of neurological disorders other than MS that affect cognitive processing including TBI, whiplash, chronic fatigue syndrome, lupus, hypoglycaemia, renal transplant, and depression (Tombaugh, 2006). Several studies have reported that the PASAT has a high degree of internal consistency. Correlations between scores on individual trials typically range between .76 and .95 (MacLeod & Prior, 1996; Ponsford & Kinsella, 1992; Sherman et al., 1997) and a Chronbach alpha of .90 was obtained from scores on the traditional four trials for the PASAT (Crawford et al., 1998). Test-retest coefficients for short and long test-retest intervals generally fall within the range of .90 to .97 (Tombaugh, 2006).

Support for the use of the PASAT with the MS population is provided by the task force appointed by the National Multiple Sclerosis Society's Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis (Cutter et al., 1999). This task force was appointed to develop improved clinical outcome measures. The process of developing the MSFC involved an investigation of several measures purported to tap into processing speed. Cutter et al. (1999) compiled data from existing longitudinal studies from MS clinical trials and natural history studies that contained both clinical and functional measures. They analyzed tests that were included in at least two different data sets and that were measured at baseline and one-year follow-up. In order for measures to

be considered as potential candidates, they were required to meet the following criteria: (a) exhibit good correlation with biologically relevant clinical dimensions, (b) exhibit good reliability, and (c) exhibit the ability to show change over time. The task force examined the means, ranges, and standard deviations of candidate measures as well as correlations among measures. From this data they assessed construct validity as well as convergent and divergent validity. From the results of these analyses they were able to narrow the possible cognitive candidates down to a 3.0-second ISI version of the PASAT, a 2.0-second ISI version of the PASAT, and the Symbol Digit Modalities Test (SDMT). They went on to compare reliability estimates, examine means and standard deviations of change, determine the relationship between change in the candidate measures and changes in EDSS scores, and to determine concurrent and predictive validity. From these evaluations they decided to include the 3.0-second ISI version of the PASAT as the sole measure of cognitive functioning in the MSFC.

As a neuropsychological measure, the PASAT possesses several critical flaws, these will now be described.

1. Ceiling Effects

One problem with the PASAT is that it is prone to ceiling effects. That is, at slower rates of presentation near perfect or perfect scores may be obtained but the task may not be challenging enough to reflect an individual's maximal capabilities. When this occurs it is likely that the test will not be sensitive enough to detect mild cognitive changes. For example, a study by Rao et al. (1991) reported that an ISI of 2.0 seconds was actually more sensitive to impairments in MS than a 3.0 second ISI.

2. Practice Effects

There is a substantial and consistent body of literature showing that repeated administration of the PASAT improves performance. Practice effects have not only been found with cognitively intact adults (e.g., Baird, 2004; Feinstein, Brown, & Ron, 1994; McCaffrey, Westervelt, & Haase, 2001) but with those suffering from a variety of neurological pathologies including MS, TBI, whiplash, chronic fatigue syndrome, and depression (e.g., Barker-Collo, 2005; Di Stefano & Radanov, 1995; Johnson et al., 1997; Stuss, Stethem, Hugenholtz & Richard, 1989). These practice effects occur both within and between sessions and are present over a wide range of fixed ISIs, as well as when threshold values are used. The greatest practice effects occur between the first and second administrations with relatively stable performance occurring after the second session (Baird, 2004). Practice effects appear to be independent of the duration of the test-retest interval. Baird (2004) reported comparable increases in performance after groups had experienced a 20-minute, 1-week, or 3-month test-retest interval. Also, performance at the three month testing session was the same regardless if one or two intervening sessions had occurred. Moreover, the initial increase in performance was maintained with test-retest intervals as long as six months. Thus, it appears that the experience gained during the initial administration of the test produces relatively permanent internal changes resulting in increased performance when the person is tested a second time, even when this occurs six months later (Baird, 2004; McCaffrey et al., 2001).

A likely explanation for these practice effects resides in the fact that the PASAT is a difficult and complex test. Due to this complexity, participants require time and practice to develop an effective strategy to perform to the best of their abilities. Effective

strategies are probably not fully developed until after the initial administration has been completed, and it is likely the general procedural knowledge about the test and strategies for effective performance that are retained and promote higher scores on subsequent administrations (Tombaugh, 2006). The presence of practice effects raises important clinical issues concerning how to interpret PASAT scores. Increased performance on a retest may indicate that the score on the first administration does not adequately reflect an individual's abilities. These well-documented practice effects severely restrict the use of this measure in situations requiring serial assessments and in longitudinal research.

3. Chunking Strategy

It has been observed that participants sometimes abandon any attempt to add the digits consecutively and adopt a chunking strategy characterized by adding two numbers, skipping one and so on (Snyder, Cappelleri, Archibald, & Fisk, 2001; Tombaugh, 2006). The use of this strategy reduces cognitive demands and consequently decreases the sensitivity of the measure to impairments in processing.

4. Performance is confounded with age, intelligence, and math ability

Tombaugh's (2006) review of the PASAT revealed that test scores declined with increasing age in adults. Furthermore, recent research using a variety of methods to estimate IQ has shown that intelligence is a critical factor in interpreting scores on the PASAT. For example, Crawford et al. (1998) reported that a principle components factor analysis revealed the total PASAT score loaded .71 with WAIS-R Full Scale IQ (Wechsler, 1981). There was also strong evidence showing that performance on the PASAT is affected by math ability. Most of the supporting evidence has been derived from experiments that have correlated different measures of mathematical ability with

PASAT performance. For example, PASAT performance has been found to be moderately correlated with scores on the Arithmetic subtest of the WAIS (Tombaugh, 2006). Other studies involving regression analyses have reported a significant portion of the variance in PASAT performance is attributable to scores on the Arithmetic subtest of the Wide Range Achievement Test (Jastak & Wilkinson, 1974), the addition test from the French Kit (French, Ekstrom & Price, 1963), and the Computerized Addition Test (Tombaugh, 2002).

5. Aversiveness of the test

Perhaps the most significant drawback limiting use of the PASAT remains to be the difficulty of the task and the substantial anxiety and frustration it evokes in participants. It is often reported to be a very frustrating and aversive task for most participants regardless of their cognitive status (Lezak, 2004; McCaffrey et al., 1995). The aversiveness of the test is so significant that the anticipation of taking it a second time often decreases the likelihood that participants or patients will return for subsequent testing sessions (Tombaugh, 2006). This has important implications for both clinicians and researchers hoping to collect longitudinal data.

6. Ambiguity of the construct measured

Any review of the PASAT must ask the unavoidable question of just what does the test measure. In general, the PASAT is assumed to measure some type of attentional process. Support for this assumption can be found in factor analytic studies showing the PASAT loads on attention/concentration factors (Tombaugh, 2006). Additional construct validity for this assumption is provided by studies where PASAT scores have been found to correlate with other tests generally assumed to measure attention, such as Digit Span

Backwards and Total, Trails B, Digit Symbol, and Arithmetic (Baird, 2004; Crawford et al., 1998; Fisk & Archibald, 2001; McCaffrey et al., 1995). The PASAT was originally assumed to measure processing speed (Gronwall & Sampson, 1974). A survey of the literature shows that most articles contained statements supporting the PASAT as a sensitive measure of processing speed, with some articles providing support evidence. Other articles state that the test measures sustained attention and divided attention/working memory. A recent trend has emerged in which the PASAT is conceptualized as being multifactorial, as it requires successful execution of numerous cognitive functions.

In conclusion, the PASAT is useful for detecting cognitive impairments associated with a wide variety of neuropsychological disorders and is a reliable measure. Originally, it was assumed that the PASAT measured speed of information processing but it is now recognized that the PASAT is multifactorial, requiring the successful execution of a variety of cognitive functions, primarily those related to attention. At the very least, it should be considered as a measure of processing speed and working memory. Therefore, although the PASAT is non-specific, it is highly sensitive. The PASAT is negatively affected by increasing age and decreasing IQ and math ability. Administration of the PASAT evokes an undue amount of anxiety and frustration in participants, affecting performance on the test as well as on other measures administered in the same session. Also, use of the test may increase subjects' reluctance to return for follow-up assessments. When interpreting the results of the PASAT, it must be kept in mind that a low score does not necessarily indicate or confirm the presence of neurological pathology.

Symbol Digit Modality Test (SDMT). Like the PASAT, it remains unclear as to just what the SDMT measures. This is also likely due to the fact that this test is factorially complex and different underlying abilities are important to performance (Laux & Lane, 1985). A review of the literature yielded descriptions of the SDMT as a measure of perceptual speed, verbal ability, memory ability, motor speed, visual attention, and information processing speed. The SDMT is highly sensitive to neurologic pathology and it appears to possess adequate reliability (Spreen & Strauss, 1998). Smith (1991) reported test-retest correlations of .80 for the written version and .76 for the oral version, these findings are largely supported by Uchiyama et al. (1994). However, the SDMT is sensitive to the effects of practice as Smith noted gains of about four points on retest for both versions. Feinstein et al. (1994) administered a computerized version of the test to control participants who were tested at two to four week intervals over eight sessions. Participants showed a trend towards significant improvement over time ($p=.07$) with a linear progression. Results of that study also suggested that performance is affected by age as younger participants performed more quickly. However, these results are based on a small sample size ($N=10$).

Uchiyama et al. (1994) noted no significant practice effects with the written version; however, the test was given at yearly intervals over a two-year period and thus the results only suggest relative stability over longer intervals and do not provide evidence for shorter terms. Uchiyama et al. also reported that performance was associated with age and IQ; these findings are in line with those of other studies (age: Emmerson et al., 1990; Laux & Lane, 1985; Stones & Kozma, 1989; IQ: Waldmann et al., 1992). Specifically, scores decline with increasing age, decreasing IQ and less

education on both written and oral forms (Spreen & Strauss, 1998). Performance on the SDMT is also greatly affected by motor speed and agility (Crowe et al., 1999; Lezak, 2004; Polubinski & Melamed, 1986). Although some studies have not found gender differences (Gilmore et al., 1983; Waldmann et al., 1992), others have reported that females outperform males (Knuckle & Asbury, 1986; Laux & Lane, 1985; Polubinski & Melamed, 1986; Yeudall et al., 1986).

Relatively limited information is available for the SDMT normative sample. The SDMT norms described in the manual are combined from two separate groups. The first sample of 420 male and female adult volunteers is the sample from which the Lezak (1983) norms were derived and they are presented along with a larger sample of 887 male and female adult volunteers. No information was provided on the racial, urban-rural, or occupational breakdown of these samples (Morgan & Wheelock, 1995). In summary, the SDMT is a highly sensitive, non-specific measure that appears to be susceptible to practice affects. Scores are also influenced by age, gender, IQ, and education. The normative data for the test are inadequate and warrant caution when used to interpret results. The task force responsible for the development of the MSFC concluded that the SDMT was not as sensitive to the cognitive deficits associated with MS as the PASAT (Cutter et al., 1999). Performance on the test is severely confounded by motor impairments, such as those commonly present in MS.

Rationale for the Design of the Current Study

Reaction Time (RT) and the CTIP. Given the limitations of the measures currently available to assess processing speed, the present study aimed to evaluate the sensitivity of two newly developed tests to the cognitive deficits associated with MS. RT

has been suggested to be equivalent to more sophisticated and complex psychological tests with regards to its ability to discriminate between neurological patients and cognitively intact individuals (Elsass, 1986). The ability of RT measures to distinguish between MS patients and controls was demonstrated in the discussion of the neuropsychological findings of information processing speed. RT measures are also extremely sensitive to cognitive deficits associated with TBI. Van Zomeran and Brouwer (1994) reviewed the TBI RT literature and concluded that a major consequence of such injuries is a generalized decrease in the speed at which information can be processed. This general slowing is likely attributable to diffuse axonal injury (DAI), which disturbs the interconnections between various neuronal networks (Lezak, 2004). Thus, TBI appears to be similar to MS in the primary cognitive dysfunction observed as well as the neuropathology underlying that dysfunction (Bennett, Dittmar, & Raubach, 1991). Past research has shown that the CTIP is sensitive to the effects of TBI (Rees & Tombaugh, 2001; Tombaugh, Rees & Royan, 2001, Tombaugh, Rees, Stormer, Harrison & Smith, in press). TBI patients require significantly longer to respond on each of the CTIP tests compared with controls and as the complexity of the tasks increase, a more pronounced separation between performances of the groups is observed (Tombaugh et al., in press). Based on the Relative Consequence Model, as well as the findings with TBI patients, the CTIP was judged to show considerable potential as a measure of cognitive dysfunction in patients with MS.

Preliminary research conducted with MS patients has in fact supported this judgement. Cox (2003) assessed a sample of eight highly educated MS patients and reported an effect similar to that observed with TBI patients -- as the demand for

cognitive processing increased, a progressive separation occurred between controls and patients. A recently completed fMRI study comparing the performance of MS patients on desktop and scanner versions of the CTIP showed that the RTs obtained by the MS patients increased as processing demands increased both inside and outside the scanner (Walker et al., 2004). This finding is in agreement with Barker-Collo (2006), who observed the same pattern of responding for a group of 52 MS patients on the desktop version of the CTIP. Walker et al. (2004) also reported that the seven MS patients tested obtained significantly longer RT scores in comparison to the normative sample. Unlike the PASAT, practice effects have not been observed with the CTIP, it is not anxiety provoking, nor is performance affected by mathematical ability (Baird, 2004; Royan, Tombaugh, Rees, & Francis, 2004, Tombaugh et al., in press). Taken together, these findings suggest that the CTIP may offer a viable alternative with which to study cognitive functioning in patients with MS.

Adjusting-PASAT. Development of the Adjusting-PASAT was spurred by the fact that the original version recorded the number of correct responses and did not provide any data on a temporal threshold measure that showed when an individual was no longer able to consistently process information. In an attempt to better isolate the speed component of information processing, specialized versions of the PASAT appeared (e.g., DeLuca et al., 1998; Demaree et al., 1999). These versions aimed to determine precisely at what speed information processing actually breaks down by employing current computer technology to allow for the incorporation of a psychophysical stair-step/titration procedure with basic PASAT methodology. Such a procedure is also represented by the Adjusting-PASAT, for which the ISI is dependent upon the

"correctness" of a response. The interval between the presentation of digits increases by 20 ms whenever an incorrect response occurs and decreases by 20 ms whenever a correct response is given. The continuous adjustment of the ISI allows a temporal threshold to be determined where the speed of digit presentation overwhelms the subject's ability to process information. The shortest interval for which a correct response is made represents this threshold. Several studies have shown that the Adjusting-PASAT is sensitive to the same variables as the original version, such as math ability, age, and practice effects (Baird, 2004; Royan et al., 2004). Although the Adjusting-PASAT is susceptible to these drawbacks, it offers several advantages over the original version. The Adjusting-PASAT incorporates methodology that allows it to better tap into processing speed, it is not susceptible to ceiling effects, and it has the potential to be a more sensitive measure of cognitive decline than the traditional PASAT. Additionally, studies described earlier in which similar methodology was employed (DeLuca et al., 1998; Demaree et al., 1999) provide support for the utility of this measure within the MS population.

Design

The primary goal of the present study was to determine the sensitivity of the CTIP to cognitive deficits associated with MS. Therefore, performances of MS patients on this measure were compared with control participants. In addition, CTIP scores were compared to those of various measures commonly used in clinical and experimental neuropsychological settings as measures of general attentional processes. These comparisons permitted the CTIP to be cross validated against established measures of attention. Of secondary interest was the Adjusting-PASAT and its sensitivity to MS

related cognitive decline. This measure was also evaluated by comparing performances of the patients with controls. Two hypotheses were proposed in this study. First, it was expected that the MS group would perform significantly lower on the CTIP tests and the Adjusting-PASAT compared with controls. Secondly, it was hypothesized that a complexity effect would emerge. That is, the more complex CTIP tests would be more sensitive to reductions in processing speed than the simpler tests. This complexity effect was expected to be greater for MS patients than for cognitively intact participants.

Method

Participants

Sixty adults with a diagnosis of clinically definite MS were recruited from a local chapter of the National MS Society and the MS Clinic of the Ottawa Hospital. All but two of the individuals with MS were patients of the clinic. Patients were asked to sign a consent to disclose personal health information form in order to obtain EDSS scores and disease durations from their hospital records. Data previously collected for 60 cognitively intact individuals who received the same measures[2] in the same order as the patients represent that of the control group. These data were randomly selected from an ongoing research data collection pool of cognitively intact individuals who participated on a voluntary basis and were recruited from social groups, places of employment, shopping centres, university classes, and by word of mouth. English was the first language for all participants. Parking expenses were paid.

Materials

Computerized Tests of Information Processing.

For each test ten practice trials preceded the testing series.

1. Simple RT

This test measures the amount of time required to process and react to a simple stimulus and served as a baseline measure for the other RT tests. On each of 30 trials, participants were instructed to press the space bar as soon as a single stimulus ("X") appeared in the centre of the computer screen.

2. Choice RT

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[2] See Digit Symbol Substitution Test/Symbol Digit Modalities Test in the Materials section that follows.

This test measures the amount of time required to process one of two stimuli and respond differentially by presenting participants with either the word "DUCK" or "KITE" on each of 30 trials and requiring them to press one of two keys ["DUCK" = right key (?); "KITE" = left key (Z)] in response.

3. Semantic Search RT

This test measures the amount of time required to decide whether a word belongs to a specific semantic category or not. On each of 30 trials the name of one of four categories (Weapon, Furniture, Bird, or Fruit) was randomly presented on a computer screen and remained on the screen for either 2.5, 3.0, 3.5, or 4.0 seconds. Following this a word appeared below the category name and participants were instructed to press the right key (?) if the word represented a member of the category and to press the left key (Z) if the word did not represent a member of the category.

Adjusting-PASAT

A series of digits from one to nine was presented aurally using headphones. On each trial, participants were instructed to add the two preceding digits. Participants respond by saying the sum aloud and the experimenter entered their responses using the numeric keypad. The Adjusting-PASAT is a computerized modification of the PASAT that adjusts the interval between digits presented contingent on the correctness of the preceding response. Therefore, if the participant produced a correct response the following ISI decreased by 20 ms, and if the participant gave an incorrect response the next ISI increased by 20 ms. This titration procedure permits a threshold interval to be derived that represents the shortest presentation in which a participant can process the digits and produce a correct response. Each assessment began with the presentation of a

single digit followed by a 2.4-second interval and consisted of 100 trials. The testing series was preceded by a practice session consisting of 12 trials beginning with a 3.0-second interval.

Digit Symbol Substitution Test (DSST)/Symbol Digit Modalities Test (SDMT)

Patients received the DSST (Wechsler, 1981) from the WAIS-III. This measure contains nine digit symbol mappings and patients were instructed to fill in the symbol that corresponded to each digit. The total number of correct symbols produced at the end of two-minutes was recorded. Control participants had received the SDMT (Smith, 1982); this test preserves the substitution format of the DSST but reverses the presentation of the material so that the symbols are printed for numbers to be written in. These two tests are highly correlated with one another [.78 for workers exposed to neurotoxins, .73 for their controls (Bowler, Sudia et al., 1992); .91 for neurology clinic outpatients (Morgan, 1992)]. The decision was made to administer the DSST to patients, although the control participants had received the SDMT, because of the limitations of the normative data of the SDMT. It was judged that the DSST would offer a more sensitive means with which to assess the cognitive functioning of patients in comparison to the SDMT.

Digit Span

The Digit Span sub-test of the Learning and Memory Battery (LAMB: Tombaugh & Schmidt, 1992) was used and is similar to that included in the Wechsler scales. Series of numbers ranging from three to nine digits were presented sequentially and participants were instructed to repeat the series aloud after each presentation. In the first condition, responses were given in the same order as the series of digits were presented and in the

second condition responses were given in the reverse order of the digits presented. Each condition was discontinued after two consecutive incorrect responses on a trial.

Trails Making A and B (Reitan & Wolfson, 1985)

For Trails A participants were instructed to connect 25 numbered circles in numeric order. The circles were distributed in random fashion across a page. Trails B is similar to Trails A, but the circles contain either numbers or letters. Participants were instructed to connect the circles by alternating between numbers and letters; that is, 1-A-2-B, etc. Time to complete each task was recorded.

Procedure

Before testing began, participants were asked to read and sign an informed consent form and were given a structured interview designed to provide basic demographic and background information. MS participants were also asked to complete the Beck Depression Inventory (BDI-II: Beck, 1987) to assess their level of depression. This measure was included to provide descriptive information on the patient sample and to ascertain whether this would represent an important variable to include in future research. The BDI had not been administered to the cognitively intact individuals composing the research data collection pool; therefore, this information was not available for the control participants. The CTIP and Adjusting-PASAT were administered within the context of a neuropsychological battery of tests which were completed in the following order: CTIP, Adjusting-PASAT, Trails Making A and B, Digit Span, and DSST/SDMT. Testing required one and one half hours on average to complete and was conducted at the General campus of the Ottawa Hospital.

Results

Demographics

Of the 60 control participants, 31 individuals were male and 29 were female. These participants ranged in age from 18 to 81 years with a mean age of 39.83 years (SD=23.13). Of the 60 MS patients, 19 were male and 41 were female. The difference in frequencies of males and females between the groups was significant, $\chi^2(1, N=120)=4.94$, p=.026. The patients ranged in age from 28 to 75 years with a mean age of 48.88 years (SD=11.67). The difference in age between the groups was also significant, F(1, 118)=7.32, p=.008. Thirty-five of the patients were diagnosed as having MS of the relapsing-remitting type, 19 as secondary-progressive, 5 as primary-progressive, and 1 as benign.

Recent EDSS scores were available for 57 of the patients and ranged from 0 to 6.5 with a mean of 3.2 (SD=2.0). Disease durations were available for 58 of the patients and ranged from 1.6 to 457.4 months with a mean of 117.7 months (SD=104.2). Patients were asked to complete the Beck Depression Inventory II and scores ranged from 0 to 46 with a mean of 10.27 (SD=10.09). Based on the classification criteria included in the BDI-II manual (Beck, Steer, & Brown, 1996), 43 of the patients would be classified as having minimal depression (0-13), 8 as having mild depression (14-19), 5 as having moderate depression (20-28), and 4 would be classified as severely depressed (>28).

CTIP

The median RT score was judged to offer the best representation of central tendency since it is not unduly influenced by outlying scores as is the mean score. Therefore, the mean of the median scores for each individual computed over all 30

testing trials was employed in the CTIP analyses. Figure 1 compares the performances of the MS and control groups. A repeated measures ANOVA with CTIP tests as the within-subjects variable and group membership as the between-subjects variable revealed significantly longer RTs for the MS group [Group: $F(1,118)=37.34$, $p<.001$, $\eta_p^2=.24$] with RTs progressively increasing for all participants as the tasks became more complex, Test: $F(2, 236)=533.98$, $p<.001$, $\eta_p^2=.82$. Furthermore, as task difficulty increased across the three tests, the RTs of MS patients progressively diverged from that of the controls, TestxGroup: $F(2, 236)=22.25$, $p<.001$, $\eta_p^2=.16$. A series of one-way ANOVAs were performed to compare the performance on each of the CTIP tests. MS patients obtained significantly longer RTs than controls on each test, SRT: $F(1,118)=28.39$, $p<.001$; CRT: $F(1,118)=29.99$, $p<.001$; SemRT: $F(1, 118)=31.98$, $p<.001$.

Insert Figure 1 about here

Since significant differences in sex and age were found between the groups, the repeated measures analysis was run again with these variables entered as covariates. With sex and age controlled, results obtained were similar to those reported above, Group: $F(1, 116)=22.20$, $p<.001$, $\eta_p^2=.16$; Test: $F(2, 232)=5.23$, $p=.006$, $\eta_p^2=.043$; TestxGroup: $F(2, 232)=12.34$, $p<.001$, $\eta_p^2=.096$. The results were also analyzed to determine the degree to which depression may have affected the performance of MS patients. A separate repeated measures ANOVA compared the Control group's CTIP scores to those obtained by the 43 MS patients who were classified on the basis of the BD-II as having minimal depression. The results from this analysis are very similar to

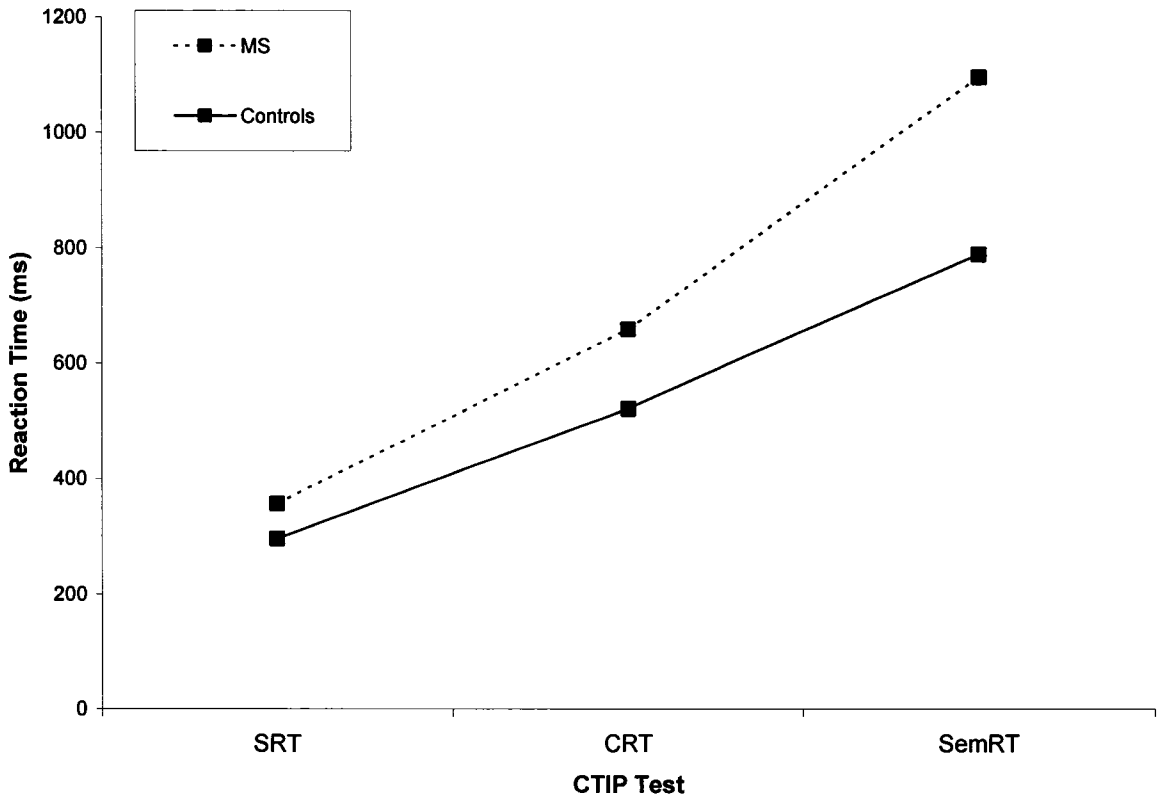

Figure 1. Reaction Times (ms) on the CTIP Tests for MS and Control Groups.

that previously reported for the entire MS sample, Group: $F(1, 101)=21.62$, $p<.001$, $\eta_p^2=.176$; Test: $F(2, 202)=481.25$, $p=.006$, $\eta_p^2=.827$; TestxGroup: $F(2, 202)=11.89$, $p<.001$, $\eta_p^2=.105$.

A repeated measures ANOVA on number of correct responses for the choice and semantic tasks as the within-subjects variable and group membership as the between-subjects variable showed no significant difference existed between the groups [Group: $F(1, 118)=2.57$, $p=.11$] with a significantly greater number correct occurring for CRT than SemRT, Test: $F(1, 118)=15.22$, $p<.001$, $\eta_p^2=.11$. However, both groups obtained a high number of correct responses on the tests [CRT: C=29.35, MS=29.10; SemRT: C=28.85, MS=28.65,]. No interactions were significant ($p>.05$).

Simple RT was employed as a baseline measure to control for any generalized effects of motor dysfunction[3] and percent-change (%-change) scores from baseline for the choice and semantic search tasks were calculated (Figure 2). A repeated measures ANOVA on these %-change scores yielded results similar to those obtained for the RT scores. Significant main effects of group membership [Group: $F(1, 118)=6.95$, $p=.010$, $\eta_p^2=.056$] and CTIP test [Test: $F(1, 118)=413.84$, $p<.001$, $\eta_p^2=.78$] were obtained. Again, a significant test by group interaction emerged, TestxGroup: $F(1, 118)=9.04$, $p=.003$, $\eta_p^2=.071$. A one-way ANOVA revealed that the groups did not significantly differ on CRT %-change from baseline, $F(1, 118)=1.84$, $p=.18$. For the semantic task, %-change from CRT was also calculated. These scores were analyzed using a one-way ANOVA and a significant result was obtained, $F(1, 118)=7.43$, $p=.007$.

[3] A repeated measures ANOVA on choice and semantic RT scores with simple RT scores employed as a covariate was considered. However, it was found that SRT scores were not an appropriate concomitant variable to use with this data as the treatments, or grouping variables, interacted with SRT scores resulting

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Insert Figure 2 about here

To determine if practice effects occurred over the 30 testing trials, the RT scores were divided into three, 10-trial blocks (Figure 3). Repeated measures ANOVAs were carried out for each CTIP test. RTs were consistent across the three SRT blocks [Block: $F(2, 236)=1.22$, $p=.30$] indicating the lack of practice effects. In contrast, RTs significantly differed between blocks of CRT trials, Block: $F(2, 236)=4.95$, $p=.008$, $\eta_p^2=.040$. Inspection of Figure 3 (middle panel) reveals that RTs of controls stayed relatively consistent across the three CRT blocks while the mean RTs of MS patients became slightly longer on each successive block of trials, GroupxBlock: $F(2, 236)=3.12$, $p=.046$, $\eta_p^2=.026$. It was considered that the slowing of patients' RTs could be a result of fatigue. However, a one-way ANOVA on RTs for the first block of CRT trials revealed MS patients took significantly longer to respond compared with controls, $F(1, 118)=21.47$, $p<.001$. Thus, the effects of fatigue cannot account for all of the difference in RTs between groups on this task as individuals with MS still responded significantly slower than controls on the first block of trials when it is unlikely that fatigue had begun to set in. For the semantic task, MS and control groups did not significantly differ between trial blocks, Block: $F(2, 236)=.17$, $p=.85$. No interactions were found to be significant in these analyses for any of the CTIP tests ($p>.05$).

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in nonparallel slopes of the treatment regression lines. When this situation arises covariance analysis is not appropriate (Neter, Kutner, Nachtsheim, & Wasserman, 1996).

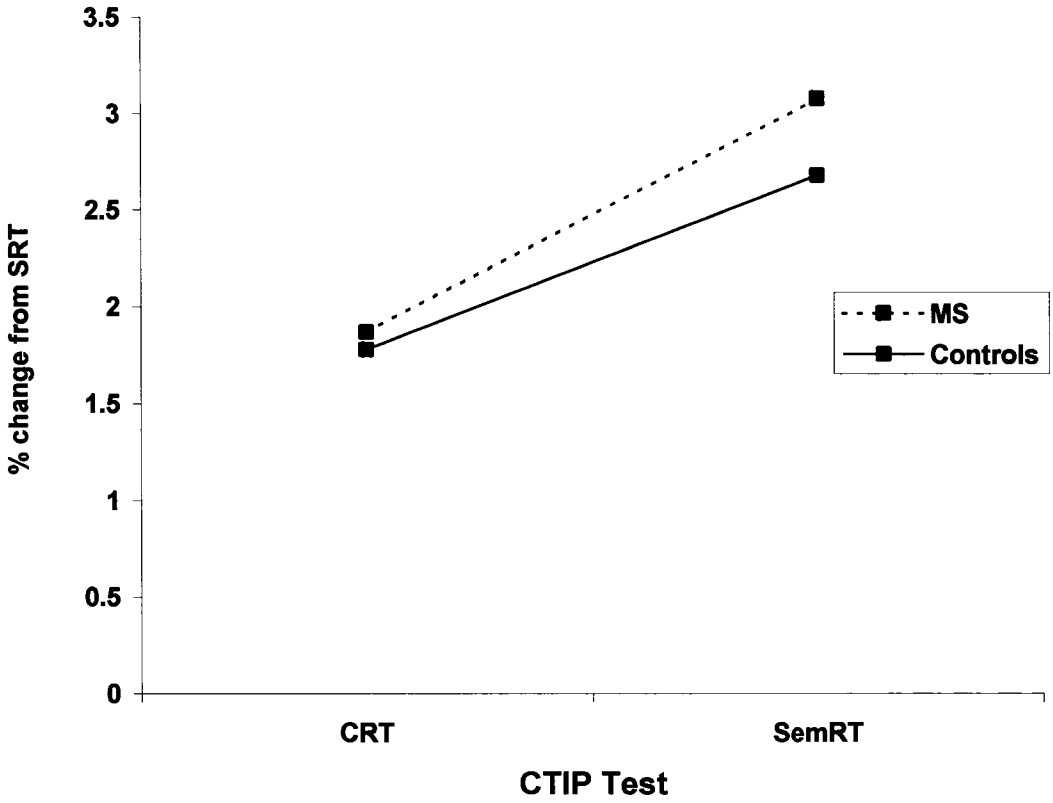

Figure 2. Percent Change from Baseline SRT for MS and Control Groups.

Insert Figure 3 about here

Past research on RT and discrimination judgements has found a robust phenomenon of longer response latencies being associated with 'different' judgements as compared with 'same' judgements (e.g., Entus & Bindra, 1970; Proctor, 1981; Tombaugh et al., in press). Figure 4 illustrates the performances of the groups on the SemRT test separately for each response class. In order to examine the RT scores for the different and same categories a repeated measures ANOVA with category as the within-subjects variable and group membership as the between-subjects variable was carried out. As expected, participants exhibited significantly longer response latencies for the different category, Category: $F(1,118)=39.82$, $p<.001$, $\eta_p^2=.25$. Also, patients with MS showed a greater increase in RT from 'same' to 'different' trials than controls, CategoryxGroup: $F(1, 118)=10.64$, $p=.001$, $\eta_p^2=.083$. To determine whether or not scores on the 'different' trials alone could account for all of the difference in RTs between groups on the semantic task, one-way ANOVAs were run for the same and different categories individually. These analyses revealed that MS patients responded significantly slower than controls for both categories, Same: $F(1, 118)= 23.21$, $p<.001$; Different: $F(1, 118)=33.50$, $p<.001$.

Insert Figure 4 about here

TBI patients have been found to exhibit greater variability in RT scores compared with controls (Tombaugh, et al., in press; Willison & Tombaugh, 2006). To explore

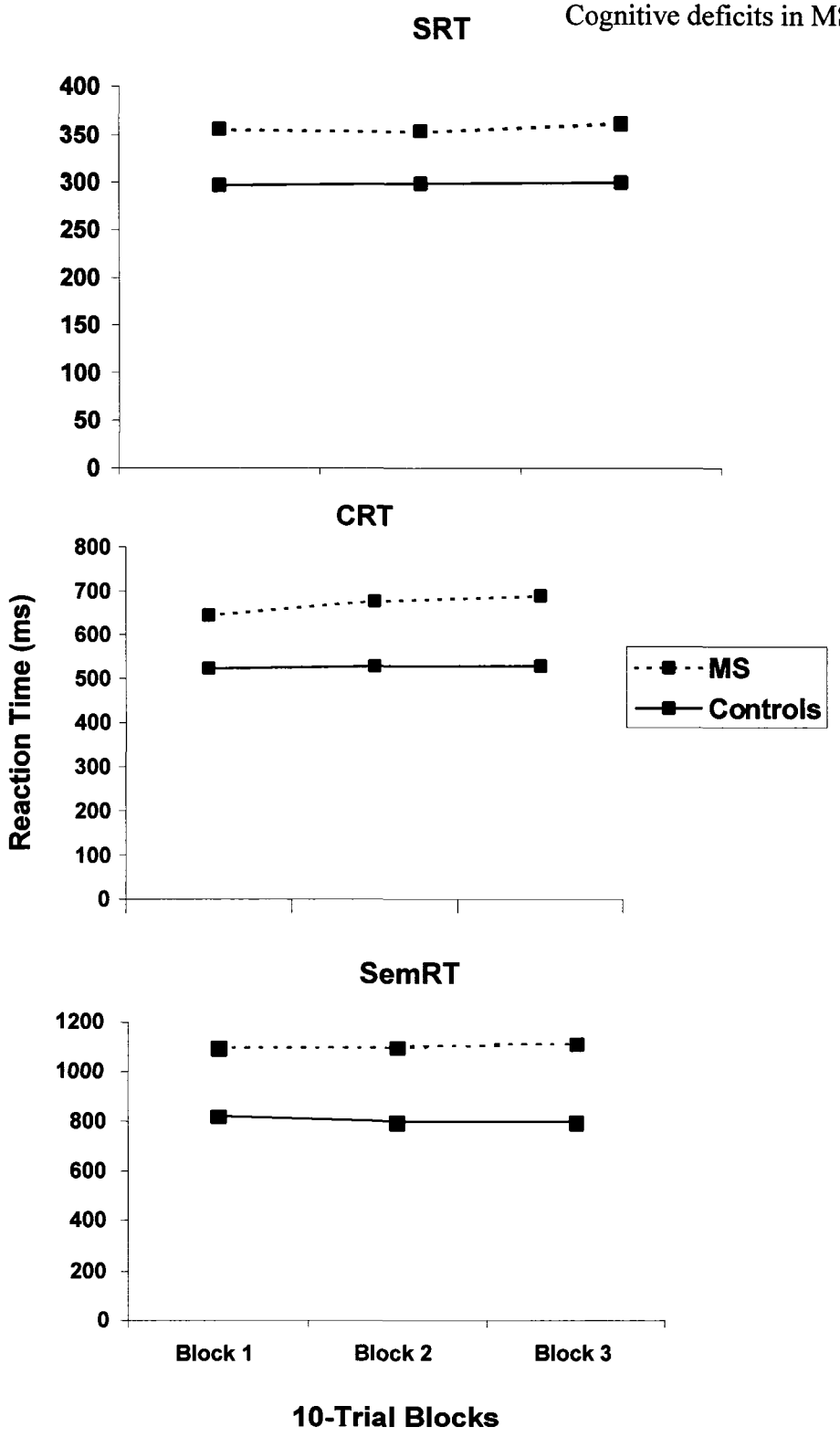

Figure 3. CTIP Reaction Times (ms) for MS and Control Groups in 10-trial Blocks.

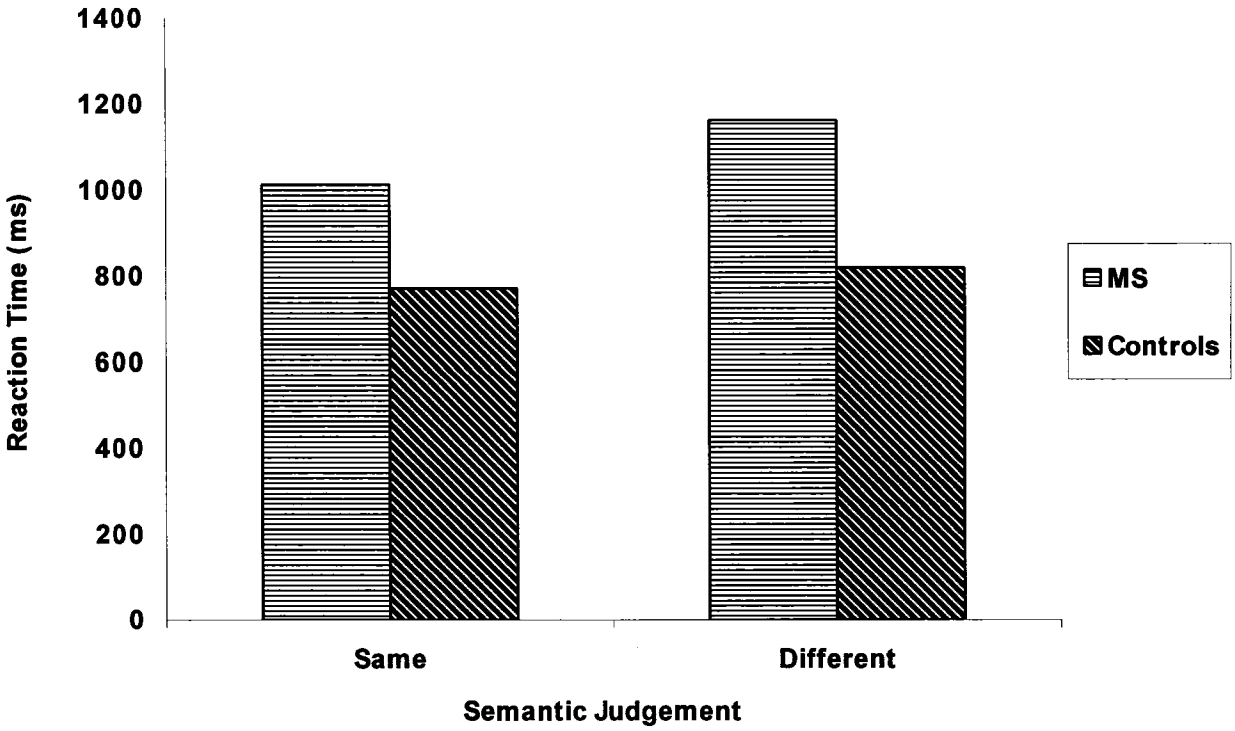

Figure 4. Reaction Times (ms) on Same/Different Judgements for MS and Control Groups on the SemRT test.

whether a similar phenomenon may exist for individuals affected by MS, coefficients of variation (CV: SD/M x 100) were calculated for the RT scores of each CTIP test. The CV provides a measure of variability that takes into account both standard deviation and the mean score and thus controls for the fact that larger mean scores are typically associated with greater variability (van Zomeron & Brouwer, 1989). A repeated measures ANOVA on CVs revealed that no significant difference in RT variability existed between controls and patients, Group: $F(1, 118)=.26$, $p=.61$. However, response variability between tests did occur [Test: $F(2, 236)=29.25$, $p<.001$, $\eta_p^2=.20$] with greater variability exhibited for the more difficult tasks as compared with the simple task. No interactions were significant ($p>.05$). Multiple pairwise comparisons using the Bonferroni adjustment procedure yielded significant results between the SRT test and both the CRT and SemRT tests ($p<.001$) but not between the CRT and SemRT tests ($p=1.00$).

Adjusting-PASAT

Seven of the participants with MS were either unable to comprehend the PASAT procedure or were unable to complete all 100 trials. These individuals were excluded from all Adjusting-PASAT analyses. All control participants were able to complete the Adjusting-PASAT. The Adjusting-PASAT variable of primary interest is the threshold score -- the shortest duration of time between the presentation of the two digits when a participant responded correctly. A one-way ANOVA failed to yield any significant difference between groups on this variable, $F(1, 111)=.10$, $p=.75$. Seventeen control participants (28.3%) and 28 MS patients (52.9%) reached their threshold at trial 95 or later. This suggests that had participants been administered additional trials they may

have obtained a shorter threshold and consequently, the threshold score may have provided a better estimate of true ability.

Neuropsychological Tests

The raw scores obtained on the neuropsychological tests were converted to percentiles using age appropriate normative tables. One individual with MS was not able to perform the written tests due to motor dysfunction and was not included in the analyses for the Trails or Digit Symbol tests. A multivariate ANOVA with the percentile scores entered as the dependent variables and group membership as the independent variable yielded a significant group difference, Group: $F(6, 112)=2.68$, $p=.018$, $\eta_p^2=.13$. However, the groups could not be distinguished based on performance on any one test alone, Trails A: $F(1, 117)=2.75$, $p=.10$; Trails B: $F(1, 117)=2.79$, $p=.097$; Digit Span Forward: $F(1, 117)=.012$, $p=.91$; Digit Span Backward: $F(1, 117)=2.19$, $p=.14$; Digit Span Total: $F(1, 117)=1.04$, $p=.31$; Digit Symbol: $F(1, 117)=.11$, $p=.74$.

Sensitivity of the Measures

The following analyses were performed to judge the clinical utility of the measures studied. Percentile scores for RTs on the CTIP were calculated from the scores of a normative sample (N=301) collected by Tombaugh and Rees (2006). The normative sample was divided into three 20-year age groups (20-39, 40-59, and 60-79). The number of MS patients falling at the 10^{th}, 5^{th}, and 1^{st} percentiles of the normative sample was determined. These percentiles represent the cut-offs commonly utilized in clinical settings to determine whether an individual has performed at an impaired level on a given test. The number of individuals and percentages of each group scoring at or below each of these cut-offs are presented in Table 1 for each CTIP test. Chi-square tests were used

to determine if any relationships existed between group membership and whether performance fell above the designated cut-offs or not. A significantly greater number of MS patients fell at each cut-off for all CTIP tests (see Table 1). It is noteworthy that greater than 50% of the MS patients fell below the 10^{th} percentile.

Insert Table 1 about here

A similar procedure was carried out for Adjusting-PASAT threshold scores. Percentile scores for the thresholds were obtained from a much smaller existing data set (N=87) collected by Tombaugh (2006) and were used as a normative comparison group. This group ranged in age from 18 to 81 years with a mean age of 34.49 years (SD=120.89). The number of individuals and percentages of each group scoring at or below the 10^{th}, 5^{th}, and 1^{st} percentiles of the normative comparison group are presented in Table 1. Chi-square tests failed to yield any significant relationships between the groups and performance level at any of the designated cut-offs ($p>.05$).

The sensitivity of the percentile scores for the neuropsychological tests included was also examined in this manner. Table 2 contains the number of individuals and percentages of each group whose score fell at or below the three designated cut-offs for each test. Chi-square tests were used to determine if any relationships existed between group membership and whether performance fell above the designated cut-offs or not. As shown in Table 2, the number of individuals falling at each cut-off for the various neuropsychological tests was similar for the two groups. Thus, in general, these tests failed to discriminate between the groups.

Table 1.

Percentage (number) of Individuals Falling at or below 10th, 5th, and 1st Percentile Cut-Off Scores for the CTIP and Adjusting-PASAT

Cut-off %iles	Control	MS
CTIP		
SRT		
10th	15% (9)	52% (31)**
5th	8% (5)	33% (20)**
1st	2% (1)	13% (8)*
CRT		
10th	27% (16)	50% (30)**
5th	10% (6)	40% (24)**
1st	3% (2)	27% (16)**
SemRT		
10th	17% (10)	53% (32)**
5th	8% (5)	47% (28)**
1st	3% (2)	40% (24)**
Adj-PASAT		
10th	12% (7)	21% (11)
5th	7% (4)	6% (3)
1st	5% (3)	0% (0)

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

Insert Table 2 about here

Correlations of Measures

Correlations (Pearson r) were used to explore certain relationships between variables of interest. First, the relationship of the disease variables and BDI scores with the CTIP and Adjusting-PASAT scores were examined for the patients. The correlational matrix generated from this analysis is presented in Table 3. The three CTIP RT scores were all significantly positively correlated with BDI scores at the .01 level. In contrast, RT scores did not significantly correlate with any of the disease variables ($p>.05$). With regards to the neuropsychological tests, both Trails A and Digit Symbol/SDMT were found to have a significant negative correlation with disease duration at the .05 level and with EDSS scores at the .01 level. Digit Span Forward was found to have a significant negative correlation with BDI scores at the .01 level. EDSS scores were found to negatively correlate with both Digit Span forward and Digit Span backward at the .05 level.

Insert Table 3 about here

It was also of interest to determine how performances on the newly developed neuropsychological tests related to one another as well as to the traditional neuropsychological measures. The correlation matrix for these variables is presented in Table 4. RT scores on the three CTIP tests were found to be highly correlated with one another for both groups with the strongest relationship existing between CRT and SemRT

Table 2

Percentage (number) of Individuals Falling at or Below the Cut-offs for the Neuropsychological Tests

	Cut-off					
	10th percentile		5th percentile		1st percentile	
Test	Controls	MS	Controls	MS	Controls	MS
Trails A	13% (8)	10% (6)	12% (7)	3% (2)	10% (6)	0*
Trails B	22% (13)	36% (21)	20% (12)	27% (16)	17% (10)	27% (16)
Digit Span Forward	7% (4)	2% (1)	3% (2)	2% (1)	3% (2)	0
Digit Span Backward	12% (7)	12% (7)	12% (7)	8% (5)	5% (3)	0
Digit Symbol	13% (8)	17% (10)	2% (1)	10% (6)*	2% (1)	0

*$p < .05$

Table 3

Correlations of Disease Variables and Test Scores for MS Patients

	Correlations			
Variables	Disease Type	Disease Duration	EDSS	BDI
SRT	-0.13	0.18	0.057	.43**
CRT	-0.06	-0.056	0.13	.33**
SemRT	-0.032	0.05	0.11	.42**
Adj-PASAT threshold	0.15	0.26	0.27	0.14
Trails A	0.09	-0.26*	-.49**	-0.23
Trails B	-0.24	-0.085	-0.19	-0.11
Digit Span Forward	-0.045	-0.204	-0.31*	-0.35**
Digit Span Backward	-0.12	-0.25	-.33*	-0.082
Digit Symbol/SDMT	-0.25	-.28*	-.59**	-0.24

* $p < .05$

** $p < .01$

scores. For the patient group, threshold scores for the Adjusting-PASAT correlated positively with SRT scores at the .05 level. CRT and SemRT scores were more strongly related with Adjusting-PASAT performance as these correlations were significant at the .01 level. The only CTIP score found to significantly correlate with this variable for controls was the SemRT score and this was a positive relation significant at the .01 level.

Insert Table 4 about here

Of the neuropsychological tests, performance on Trails A was found to negatively correlate with SRT and SemRT scores at the .05 level and with CRT scores at the .01 level for patients with MS. Trails B was only found to correlate with SemRT scores at the .05 level and with Adjusting-PASAT thresholds at the .01 level, both represent negative relationships. Digit Span forward correlated with CRT scores and Adjusting-PASAT thresholds at the .05 level and with SemRT scores at the .01 level. The only significant relationship with Digit Span backward was found for the Adjusting-PASAT threshold measure, which was correlated negatively at the .05 level. Performance on Digit Symbol/SDMT negatively correlated with all CTIP and Adjusting-PASAT variables. Significance reached the .05 level for SRT scores and the .01 level for all others. For the control participants, the only significant correlation found between any of the neuropsychological tests and CTIP or Adjusting-PASAT scores was the negative relationship of Digit Symbol/SDMT with the Adjusting-PASAT threshold measure at the .01 level.

Table 4

Correlations of New IPS Tests and Traditional Neuropsychological Measures by Group

	Correlations							
	SRT		CRT		SemRT		Adjusting-PASAT	
Variables	Controls	MS	Controls	MS	Controls	MS	Controls	MS
SRT			.47**	.55**	.41**	.59**	0.17	.35*
CRT					.69**	.83**	0.21	.35**
SemRT							.32**	.43**
Adjusting-PASAT								
Trails A	0.036	-.29**	0.036	-0.36**	0.099	-.27*	-0.23	-0.22
Trails B	-0.13	-0.018	0.008	-0.20	-0.018	-.30*	-0.21	-.37**
Digit Span Forward	-0.095	-0.22	-0.012	-.30*	0.098	-.35**	-0.059	-.35*
Digit Span Backward	0.13	0.008	0.083	-0.044	0.22	-0.17	-0.14	-0.30*
Digit Symbol/SDMT	-0.11	-.28*	-0.23	-.35**	-0.13	-.40**	-.35**	-.55**

*=significant at the .05 level (2-tailed)

**=significant at the .01 level (2-tailed)

Discriminant Function Analysis

A Discriminant Function Analysis (DA) was computed to assess the relative importance of the different tests in classifying the participants as either belonging to the MS or control group. Predictors included were the RT scores of the three CTIP tests and the Adjusting-PASAT threshold, as well as percentile scores for Trails A, Digit Span Forward, and Digit Symbol. These particular neuropsychological tests were included because the numbers of participants falling at or below the 1st percentile between groups was significant for Trails A and Digit Symbol. Also, all three were related to the newly developed neuropsychological measures of information processing. The overall DA model was significant ($p<.001$). The model had a sensitivity of 65.4% and a specificity of 76.7% and correctly classified 71.4% of participants as either MS patients or controls. The standardized coefficients for each predictor are presented in Table 5.

Insert Table 5 about here

Table 5

Standardized Discriminant Function Coefficients

Predictor	Coefficient
SRT	0.45
CRT	0.29
SemRT	0.51
Adjusting-PASAT	-0.24
Trails A	-0.34
Digit Span Forward	0.12
Digit Symbol	0.44

Discussion

CTIP and Reaction Time

For this investigation it was hypothesized that the MS group would exhibit significantly longer RTs than controls and that the differences in RTs would progressively increase as task complexity increased across the three CTIP tests. These hypotheses were supported by the results. MS patients obtained longer RTs than controls on each CTIP test with the shortest RTs occurring for the simple task and the longest RTs for the semantic search task. Although the groups studied were found to significantly differ in both the frequency of females and males and age, the differences in performance cannot be solely accounted for by these variables. When sex and age were statistically controlled, similar results were obtained. Also, when the scores of the 43 MS patients classified as minimally depressed (i.e., not depressed) were compared to the control participants the results were very similar to those obtained for the analysis including the entire MS sample. Thus, even when the cognitive effects of depression are absent, MS patients perform more poorly on the CTIP than controls.

The finding that MS patients exhibit greater response latencies on the RT tests is consistent with previous MS studies (Barker-Collo, 2006; Elsass & Zeeberg, 1983; Janculjak et al., 2002; Jennekens-Schinkel et al., 1988; Kail, 1997, 1998; Walker et al., 2004) and contributes to the mounting evidence demonstrating cognitive deficits in patients with MS. The results obtained in the present study also replicate those of preliminary research with the CTIP and MS patients. Cox (2003) found a progressive separation in the performances of MS patients and controls across the tests. Walker et al. (2004) found that MS patients responded significantly slower than the CTIP normative

sample, and both Barker-Collo (2006) and Walker et al. (2004) reported that reaction times increased parallel with task complexity across the three tests.

Impaired motor ability, one of the primary symptoms of MS, often makes it challenging to assess cognitive deficits in MS patients. This is because many neuropsychological measures, such as the Digit Symbol Substitution Test and Trails, involve graphomotor responses. Because this ability is commonly impaired in MS patients, results from such measures are often confounded by the effects of generalized motor dysfunction. In this respect, the standard PASAT which is frequently used to assess information processing in MS patients appears to have a distinct advantage as subjects respond verbally, not manually. However, the lesions characteristic of MS are distributed in such a random manner that problems of motor control affecting the formulation of verbal responses could occur. For example, dysarthria has been cited as a symptom of the disease, albeit an uncommon one (Lezak, 2004). Although the CTIP does require a motor response, the response requirement is minimal. Depending on the task, participants rest either one or both index fingers on the specified key(s), and respond as quickly as they can by depressing a key.

It is possible, however, that difficulties in neuronal signal transmission and motor control could affect even this minimal motor response. In order to control for potential motor effects, the RT scores from the simple RT task were used as a baseline measure and percent change scores were calculated for the other two tasks. Although the motor response in the SRT task is not exactly identical to that in the CRT and SemRT tasks (SRT: press the space bar; CRT/SemRT: press either the "?" or "Z" key) it is similar enough that it was judged to serve as a useful baseline measure. A repeated measures

analysis of these percent change scores revealed that significant differences between the groups remained across the CRT and SemRT tests. Even though motor dysfunction may account for some of the variance in responding, it appears that differences in cognitive processing are also present and influence the performance of MS patients.

It was speculated that the demands of the choice task would be greater than that of the simple task due to the introduction of a decisional component requiring participants to base their response choice on concrete or literal processing of the form of the stimulus. This additional processing demand was expected to produce a significant increase in RTs over and above those observed for the simple task and it was expected that this increase would be greater for MS patients, who commonly exhibit processing deficiencies, than for controls. Results of the one-way ANOVA on CRT percent change scores do not support this expectation but they are in agreement with the findings of Janculjak et al. (2002). Janculjak et al. (2002) measured both simple RT and choice RT for a group of MS patients and controls. Decision reaction time (DRT) was calculated by subtracting simple RT scores from choice RT scores. Although the RTs of patients were significantly longer than controls for both tasks, the groups did not differ on DRT. The simple RT task used in the Janculjak et al. (2002) study required participants to respond to a randomly appearing visual stimulus on the computer screen by pressing a key for each hand separately. The choice RT task required participants to use both hands in order to choose a different key for one of the two possible stimuli choices. The authors did not indicate the nature of the visual stimuli presented but this task does appear to be very similar to the CRT test included in the present study. The absence of differences between groups for this DRT variable prompted an examination of the percent change score for

the CRT test alone. A one-way ANOVA revealed that the groups did not significantly differ on this variable. Therefore, the significant result obtained for the repeated measures ANOVA on percent change scores was largely due to differences in SemRT scores between the groups.

Thus, it appears that any additional cognitive demands introduced in the CRT task are not sufficient enough to tax the information processing abilities of MS patients to the point where cognitive deficits produce an observable decline in performance, resulting in longer RTs over and above those where only the recognition of a stimulus and a motor response are involved (i.e. in the SRT task). This conclusion is in agreement with past research using the CTIP; Tombaugh et al. (in press) did not find a significant difference between mild TBI and control groups for the CRT test. The authors of that study concluded that requiring individuals to process the form of the stimulus generally involved a minimal amount of internal search and processing and, as such, was regarded as representing a relatively light cognitive load.

The CTIP employs a second choice procedure in which the cognitive load is assumed to be greater in comparison with the CRT test but the same two-item response requirement is maintained. It was speculated that the cognitive processes involved in this task include a search through the semantic lexicon to determine if the exemplar represents a match or non-match to a specific category. These cognitive demands are more extensive and require more internal processing than does the CRT test. This hypothesis is supported by the greater separation in performances of the groups observed for the SemRT test in comparison to the CRT test. To expand the support for this hypothesis, percent change from CRT was calculated for the semantic task. These scores

were entered into a one-way ANOVA and a significant group effect was obtained. Even within the semantic task different levels of cognitive demands exist, evidence of this is provided by the finding that responses for the "different" category were longer than those for the "same" category.

Tombaugh et al. (in press) found the SemRT test also yielded a significant difference between mild TBI and control groups. The present findings are further supported by the results of an fMRI study investigating the performance of MS patients on the CTIP. Walker et al. (2004) reported that no significant difference in the amount of neural activity between the simple and choice tasks existed, but between the choice and semantic tasks a significant difference was obtained. Thus, it appears that not all of the CTIP tests are equally capable of detecting cognitive deficits in MS patients. These current results suggest that the cognitive demands of the RT task must be sufficiently challenging for the tests to be sensitive to the cognitive deficits produced by MS. Moreover, the sensitivity of the RT tests appears to be roughly proportional to the cognitive demands of the test. One implication of the current results is that in future research applications, administration of only the SRT and SemRT tests is justified, at least within the MS and TBI populations. However, since the normative data collected for the CTIP included the administration of the CRT test, it is recommended that clinicians wishing to use the normative percentiles to aid in the interpretation of their client's results should continue to administer all three tests.

To determine if repeated experience with the CTIP tests had any effect on performance, the testing series was divided into three, 10-block trials. Analyses of the trial blocks showed RTs were consistent across blocks for both the SRT and SemRT

tests. Alternatively, performances between the blocks of CRT trials did significantly differ. The RTs of controls stayed relatively consistent across the three CRT blocks while those of the MS patients became slightly longer on each successive block (Block 1: 644ms; Block 2: 677ms; Block 3: 689ms). In order to determine whether the deceleration of patients' responses could be a result of fatigue, an analysis of RTs obtained on the first block of trials was completed. Results confirmed that the MS patients responded significantly slower than controls on these trials. It was assumed that the effects of fatigue would not be present during the first 10 trials of the testing series, thus the presence of a significant difference suggests that the variability in RTs between groups on this test cannot be completely accounted for by fatigue. The results of the block-by-block analyses for the CTIP tests clearly indicate that this measure is not susceptible to within session practice effects. This is consistent with previous findings indicating that repeated administrations occurring either within or between sessions do not produce gains in performances (Baird, 2004; Reicker, 2006; Willison & Tombaugh, 2006).

The lack of practice effects associated with the CTIP has important implications for use in both research and clinical practice, and makes it a viable substitute for the PASAT which is considered to be the "gold standard" measure for assessing IPS and is frequently used with MS patients, as well as various other neurologic populations. A substantial and consistent body of literature exists showing that PASAT performance is prone to the effects of practice within and between sessions. For clinical applications, this means that a client's performance on the first administration of the PASAT likely will not reflect his or her true abilities. Also, any gains in performance on subsequent

administrations may mislead one to assume that the individuals underlying neurologic condition has improved when, in fact, the gain in performance is due to the effects of having prior experience with the test. For research applications, these practice effects restrict the use of the PASAT when serial administrations are required and in longitudinal studies. For example, clinical drug trials typically involve the administration of outcome measures at a baseline stage and at various intervals following the introduction of the experimental treatment.

The MS Functional Composite includes a 3.0-second ISI version of the PASAT as the sole measure of cognitive functioning. The variable of primary interest in these clinical trial studies is change over time. Improvements in PASAT performance across the assessment intervals of these studies could be mistaken for the existence of positive effects of the experimental treatment on cognitive functioning when they may simply be a result of practice effects. Although the MSFC does encourage researchers to administer the PASAT prior to the clinical assessments in order to control for these practice effects, the frequency of this practice among clinical drug trials is variable. The CTIP represents a viable alternative for judging the cognitive status of patients with MS that is not affected by repeated administrations. Therefore, it is ideal for use in studies employing serial administrations, such as clinical drug trials.

The RT results obtained in the present study are compatible with the Relative Consequence Model (DeLuca et al., 2004). According to this model, the primary difficulty with information processing for patients with MS is reduced IPS. These IPS deficits result in the dysfunction of other higher-level cognitive processes. This is hypothesized to occur because fewer cognitive operations are able to be completed in a

given amount of time and because products of earlier operations may not be available by the time later, more complex operations are completed. Therefore, as the number of complex operations increases from the simple to the semantic task, it would be expected that the RTs of the MS patients would become increasingly longer. This trend was observed for the MS patients included in this study. However, other possible explanations for these results could apply as well. For instance, the differences in RT between the tests could be due to deficits specific to the cognitive processes involved. For example, the SemRT test is assumed to require a search of semantic memory in order to determine whether a word represents a member of a specific category or not. Subsequently, the longer RTs observed for this test could be a result of deficient memory or language abilities, which are not necessary for completion of the other two tasks, instead of an underlying, generalized cognitive slowing. One limitation of the CTIP is that it does not permit differentiation of the specific cognitive processes that contribute to performance. Therefore, it cannot be directly determined whether longer SemRT scores are due to difficulties with IPS, memory, language, etc. or an interaction of various dysfunctions. However, a large body of research confirming that reductions in processing speed are a consistent and significant effect of MS is emerging, and it is likely that such IPS deficits would influence the performance of MS patients on the CTIP.

Although the groups differed on RTs for the CTIP tests, the number of correct responses was comparable. Very few mistakes were made by participants in either group. However, a significant main effect of test was obtained indicating that across the groups more errors were made on the semantic test than on the choice test. Although this difference was significant, it was very small in magnitude (CRT: 29.23 mean correct;

SemRT: 28.75 mean correct) and probably does not have any clinical significance. The lack of a significant group effect for number correct has also been reported for TBI patients and controls. Tombaugh et al. (in press) reported 97% accuracy (i.e., 1 error) for each group. The tests composing the CTIP were designed to be as simple as possible so that any differences obtained between individuals would be because of a disparity in processing rates and not individual differences in various abilities (e.g., language or mathematical abilities). The highly accurate performances across individuals completing the CTIP suggest the accomplishment of this goal.

The effects of MS on the variability of responding were also investigated in the present study. Because standard deviation scores are often proportional to increases in reaction times (van Zomeren & Brouwer, 1989), coefficients of variation (CV) were employed to examine the relative amount of variability that occurred among the groups. Previous research has found that TBI patients exhibited increased variability in responding on the CTIP tests as compared with controls (Tombaugh et al., in press). TBI and MS appear to be somewhat similar in their neuropathologies and effects on processing speed; thus, it was of interest to investigate whether MS patients would also exhibit increased variability in comparison to controls. The results showed that the performance of MS patients was not more variable than that of the cognitively intact participants. This contrast with the findings for TBI patients may be explained by the dissimilarities of the two conditions. TBI often results in the generalized slowing of cognitive processes, but specific functions may also be altered depending on the location and severity of the neurological insult. The greater RT variability observed with TBI patients could be due to damage affecting specific cognitive domains, such as attention.

In fact, when Tombaugh et al. (in press) explored their variability data further by examining those scores representing the extreme end of the distribution of response scores (i.e., the 10^{th} percentile) they found that variability was associated with the severity of the injury. The authors suggested that much of the variability attributed to TBI is the result of extreme scores produced by patients with severe injuries and that likely reflect momentary lapses of attention.

Although there were no significant differences in RT variability between the groups, differences in response variability did exist between the different CTIP tests. Greater variability was observed for performances on the choice and semantic tasks in comparison with the simple task. This difference can likely be explained by the addition of a decisional component in the choice and semantic tests. This hypothesis is supported by the results of multiple pairwise comparisons of the CVs for the different tests. Significant results were obtained for the comparisons of the simple task with both the choice and semantic tasks, but not for the comparison of the choice with the semantic task. For the simple task, participants respond to the presentation of the stimuli with one possible response. For the other CTIP tests, participants must differentiate between the presentation of two possible stimuli and execute the appropriate response. Thus, there is much more opportunity for the introduction of variation in responding for the choice and semantic tasks in comparison with the simple task.

Adjusting-PASAT

The standard PASAT has been considered to be the "gold standard" tool with which to assess information processing for MS patients as well as many other neurologic populations. However, the PASAT possesses several limitations, one of which being that

it records only the number of correct responses and does not provide information directly pertaining to processing speed. The Adjusting-PASAT was developed in order to provide a test that was based on the standard PASAT procedure but which would offer a measure of processing speed. This was accomplished by incorporating a psychophysical stair-step/titration procedure with the basic PASAT methodology so that the ISI becomes dependent on the "correctness" of a response. This allows for the calculation of a temporal threshold representing the fastest speed of stimulus presentation at which an individual is able to process the information and respond accurately. In the present study, the groups of MS patients and controls did not significantly differ on the threshold scores obtained. This suggests that MS patients are able to process information accurately at the same speeds as cognitively intact individuals.

This finding is inconsistent with the CTIP results as well as with those of previous studies employing a similar methodology. DeLuca et al. (1998), Demaree et al. (1999), and Lengenfelder et al. (2006) included a version of the PASAT where the rate of stimulus presentation (ISI) was manipulated so that all participants would achieve an accuracy rate of 50%, allowing the IPS component of the task to be evaluated. Those studies reported that MS patients required significantly longer threshold speeds in order to achieve the same levels of accuracy as controls. These results suggest that when individuals are equated on accuracy, MS patients process information significantly more slowly than control participants. One important difference between the patient samples included in this study and those of the studies described above is that the proportions of the different disease subtypes represented are dissimilar. Of the patients included in the DeLuca et al. (1998) and Demaree et al. (1999) studies 58- and 60%, respectively, were

identified as having a progressive course. In the present study, of the patients included in the PASAT analyses, 40% had a progressive course.

This is an important difference because disease course has been found to significantly influence the nature of the information processing dysfunction observed in MS patients. DeLuca et al. (2004) reported that when an information processing deficit was observed among RR-MS patients, it was only observed in processing speed and working memory was generally intact. Conversely, among SP-MS patients the magnitude of the IPS deficit was striking compared to the RR group and the SP patients also demonstrated a significant impairment in working memory. Archibald and Fisk (2000) also examined processing speed deficits among the RR and SP subtypes. They found that RR-MS patients demonstrated impairments in IPS with intact working memory, whereas SP-MS patients showed impairments in both processing speed and working memory. The results of these studies led DeLuca et al. (2004) to suggest "speed of information processing may be slowed early in the course of the disease (e.g., RR-MS), while deficits in working memory ability become apparent only with disease progression (e.g., SP-MS)" (p. 558). Lengenfelder et al. (2006) did not report the frequency of the disease subtypes for their MS sample. However, they did find that 30% of the patients demonstrated working memory impairment in addition to processing speed deficits on a more difficult version of the VT-SAT and that these patients also performed more poorly on other tasks involving both working memory and processing speed than MS patients who did not exhibit working memory impairments on the VT-SAT. The authors concluded that for patients experiencing such an interaction of speed and working

memory, either increasing the requirement of processing speed or working memory load demands could disrupt performance.

Because a large proportion of the MS samples in the DeLuca et al. (1998) and Demaree et al. (1999) studies were composed of progressive patients, the findings that MS patients exhibited deficits in IPS when equated on accuracy could be a result of IPS deficits of a substantial magnitude and/or the interaction of IPS deficits with those of other cognitive processes. The present study included a smaller percentage of progressive patients and, therefore, the presence of such extreme deficits in IPS and the interaction of such deficits with other cognitive processes (e.g., working memory) are less likely. This offers a possible explanation as to why the MS patients assessed in the present study did not obtain significantly longer threshold scores on the Adjusting-PASAT in comparison with controls.

The Adjusting-PASAT included in the present study was composed of 100 trials, and 28% of controls and 53% of patients obtained their threshold score at trial 95 or later. This suggests that had these participants been administered additional trials their performances may have improved and consequently, the threshold scores may have provided a better estimate of true ability. Therefore, in any future researching wishing to include the Adjusting-PASAT it is recommended that a version composed of additional trials be used. An alternative solution may be to keep the same number of trials but to increase the change in the ISI dependent on the correctness of a response from 20ms to 30- or 40ms. This could allow participants to reach a lower threshold in a fewer number of trials and may eliminate the ceiling effects observed in the present investigation. The DeLuca et al. (1998), Demaree et al. (1999), and Lengenfelder et al. (2006) studies

reported that a series of 50 numbers between 1 and 9 were presented in the AT-SATs and VT-SATS, but they did not report the increment/decrement changes employed. If those adjusting versions of the PASAT involved a greater increment/decrement than the Adjusting-PASAT included in the present study this could explain why significant differences between groups were found on those measures, while a group effect was not found for the Adjusting-PASAT.

Of the 60 MS patients tested in the current study, seven were either unable to understand the PASAT procedure or were unable to complete all 100 trials. The majority of those patients who were able to complete the Adjusting-PASAT conveyed their frustration with and dislike for the test. This supports evidence showing that the Adjusting-PASAT shares one of the most significant drawbacks of the standard PASAT, the aversiveness of the task. The aversiveness of the standard PASAT is so significant that the anticipation of repeated administrations often decreases the likelihood of participants or patients returning for subsequent testing sessions (Tombaugh, 2006). Because people appear to find the Adjusting-PASAT equally as objectionable as the original, clinicians and researchers alike should take this into consideration when use of this measure is being contemplated.

Neuropsychological Tests

The MS patients did not perform significantly worse than controls on any of the neuropsychological tests administered. This finding presents numerous implications. First, the neuropsychological tests included in this study represent established measures of attention and working memory (Trails B, Digit Span Backward, Digit Symbol). The comparability of performances for MS patients and controls on these tasks implies that

the patients were not impaired within these domains. Both Trails and Digit Symbol involve a significant amount of graphomotor skills, thus, similar performances between groups on these measures suggest that patients did not possess severe motor impairments. These inferences are all relevant to the interpretation of the CTIP results, implying that performances on the RT tests are not due to differences in attention, working memory, or motor skills. Also, because both Trails and Digit Symbol involve processing speed, the results suggest that these tests do not possess the sensitivity necessary to detect IPS deficits in MS, at least for patients having a non-progressive course. Furthermore, performances on these neuropsychological tests suggest that the MS sample assessed was not cognitively impaired; this is inconsistent with the RT results from the CTIP.

Sensitivity of the Measures

The results presented thus far have focused on the comparison of the performances of the groups but have neglected to provide direct evidence that the CTIP can serve as a useful clinical tool. One way to provide such information is to determine how many participants in the MS group would have been classified as impaired in respect to a normative sample. In order to make such a determination, the number of individuals that fell below different percentile values (i.e. 10^{th}, 5^{th}, 1^{st} percentiles) were calculated. The CTIP normative sample was divided into three 20-year age groups so that participants could be evaluated against age appropriate normative data. Significant differences in the percentages of the groups that fell at or below these levels were observed at each cut-off for each CTIP test. This further supports the sensitivity of the CTIP to cognitive deficits associated with MS and provides evidence that the CTIP can function as a clinical tool. The percentages of controls scoring at or below the 5^{th} and 1^{st}

percentiles remained relatively consistent across the three tests; however, the percentages of MS patients performing at these levels tended to increase as the cognitive demands became greater across the tests.

A similar procedure was also carried out for the Adjusting-PASAT threshold scores. However, the percentiles for these scores were obtained from a much smaller data set that could not be stratified by age. Therefore, these percentiles may not be as valid as those obtained for the CTIP RTs. Nevertheless, it was decided to examine the performances in the present study against these percentiles to attain some indication of how the participants perform judged against a normative comparison group. No significant differences in the percentages of groups falling at or below the three cut-offs were obtained. Keeping in mind the limitations that have been identified, this would imply that the Adjusting-PASAT is relatively insensitive to cognitive deficits associated with MS in comparison with the CTIP.

The percentage of individuals performing at these designated cut-offs was also investigated for the percentile scores of the neuropsychological tests in order to judge their relative sensitivity. No significant differences in the percentages of groups falling at or below the 10^{th} percentile were obtained for any of the tests. At the 5^{th} percentile, a significant relationship between group membership and performance level was observed for Digit Symbol and at the 1^{st} percentile the only significant result obtained was for Trails A. The results of these analyses support the hypothesis that the MS sample tested would not have been classified as cognitively deteriorated on the basis of the traditional neuropsychological tests. They also indicate that the CTIP is more sensitive to the

cognitive deficits associated with MS than the traditional neuropsychological measures examined.

Correlations

Correlations for particular relationships of interest were examined. The relationships of the disease variables and BDI scores with the CTIP and Adjusting-PASAT scores for the patients represent one area of interest. The three CTIP RT scores were all significantly positively correlated with BDI scores. Depression is known to produce negative effects on attention (Lezak, 2004) and since depression is associated with MS these significant correlations are not unexpected. However, when only those patients classified as minimally depressed based on the BDI-II criteria were compared to the controls on the CTIP, significant differences between the group's performances remained. These results suggest that depression alone cannot account for the variance in CTIP scores. However, it is recommended that for future investigations involving RT and MS, depression scores be obtained and utilized in the analysis of the data in order to assess the contribution of the effects of depression to the variance in performances. CTIP RT scores did not significantly correlate with any of the disease variables. This supports the observation that cognitive dysfunction may occur independently of physical disability and is not directly related to disease duration (Audoin et al., 2003; Feinstein, 2004; Staffen et al., 2002).

With regards to the neuropsychological tests, both Trails A and Digit Symbol/SDMT negatively correlated with disease duration and EDSS scores. These correlations are due, at least in part, to the fact that performances on these tests were impacted by deficits in manual motor abilities. Determination of EDSS scores takes into

account motor function and it is likely that motor function may become increasingly affected the longer an individual has been diagnosed with the disease. Digit Span forward was found to negatively correlate with BDI scores. Again, this could be a result of the effects on attention and thus individuals with higher BDI scores would likely have greater difficulty attending to and immediately recalling sequences of numbers, as is required in Digit Span Forward. EDSS scores were found to negatively correlate with both Digit Span forward and Digit Span backward. These correlations are puzzling as cognitive functioning is not taken into consideration when assigning EDSS scores. No explanation for the cause of these significant relationships is apparent.

It was also of interest to determine how performances on the newly developed tests of information processing speed relate to one another as well as to the traditional neuropsychological tests. RT scores on the three CTIP tests were found to be highly intercorrelated with one another for both groups. The strongest relationship was observed for the CRT and SemRT scores. This is likely explained by greater similarities between the CRT and SemRT tests. Both the CRT and SemRT tests require some type of decision to be made and the appropriate response to follow whereas the SRT test requires only the recognition of the presentation of a stimulus followed by the execution of one possible response. For the MS patients, the Adjusting-PASAT threshold scores positively correlated with all CTIP RT scores. The CRT and SemRT scores were more strongly related with Adjusting-PASAT performance than SRT scores. The only CTIP score found to significantly correlate with the temporal threshold measure for controls was the SemRT score, this was a positive relation. Taken together, these results suggest that the more difficult CTIP tests are more strongly related with Adjusting-PASAT

performance. As task difficulty increases across the CTIP tests it is likely that the execution of more cognitive processes is involved. This is supported by fMRI evidence showing activation of a greater number of neural areas across the tests. Since PASAT procedures have been reported to require the recruitment of several cognitive domains (Tombaugh, 2006) it may be the greater cognitive demands of the more difficult CTIP tests that produce this stronger relationship.

For the neuropsychological tests, performance on Trails A negatively correlated with all CTIP RT scores for patients with MS. Trails B was only found to correlate with SemRT and the Adjusting-PASAT threshold measure, both represent negative relationships. Trails A involves scanning and visuomotor tracking and taxes attentional capabilities while Trails B additionally requires divided attention and cognitive flexibility. Thus, for these two neuropsychological measures, we see most IPS tasks are related to TRAILS A while only the more cognitively demanding IPS tasks are related to Trails B. Digit Span Forward correlated with CRT and SemRT scores as well as Adjusting-PASAT thresholds. Digit Span Forward is primarily a measure of efficiency of attention and thus it is not surprising that individuals receiving higher scores on such a measure also score higher on the RT tests requiring a decision to be made and the PASAT task which places high demands on the function of attention. The only significant relationship with Digit Span Backward was found for the Adjusting-PASAT threshold measure, which was correlated negatively. In Digit Span backward a mental manipulation component is added. The mental manipulation of numerical data is also a major component of the Adjusting-PASAT task. The lack of significant relationships found for Trails B and the CTIP tests suggests that these RT tests involve somewhat more

different cognitive processes from those involved in Trails B as compared to the Adjusting-PASAT. Performance on Digit Symbol/SDMT negatively correlated with all CTIP and Adjusting-PASAT variables. Of the neuropsychological tests included, Digit Symbol/SDMT has been most commonly associated with IPS. The significant relationships of this measure with the IPS tests support that claim. For the control participants, the only significant correlation found between any of the neuropsychological tests and CTIP or Adjusting-PASAT scores was the negative relationship of Digit Symbol/SDMT with the Adjusting-PASAT threshold measure.

Discriminant Function Analysis

A Discriminant Function Analysis (DA) was computed to assess the relative importance of different tests in classifying the participants as either belonging to the MS or control group. Predictors included were the three CTIP tests and the Adjusting-PASAT threshold, as well as Trails A, Digit Span Forward, and Digit Symbol. The decision to include those particular neuropsychological tests was based on the results that the percentages of the groups performing at or below the 1st percentile were significant for Trails A and Digit Symbol and Digit Span Forward was significantly related to the newly developed measures of processing speed. The overall DA model was significant, indicating that the function calculated using this set of scores was able to adequately classify participants as belonging to either the MS or control groups. The model had a sensitivity of 65.4% and a specificity of 76.7% and correctly classified 71.4% of participants as either MS patients or controls. The two standardized coefficients of greatest magnitude were obtained by the SemRT and SRT tests, respectively. These were followed by Digit Symbol, Trails A, CRT, Adjusting-PASAT, and Digit Span Forward,

in that order. The finding that the SRT and SemRT scores were most important in predicting group membership, while CRT scores were of far less importance, is consistent with the conclusion presented in the discussion of the percent-change analyses. This evidence further justifies the omission of the CRT test in future research. These results also support the relative insensitivity of the Adjusting-PASAT to cognitive dysfunction in patients with MS. Of the neuropsychological measures, the Digit Symbol test was of most importance in classifying individuals as MS or cognitively intact. In combination with the correlational results, this supports proposals that Digit Symbol is sensitive to reductions in IPS, the primary cognitive deficit found in MS.

Limitations of the Present Study and Implications for Future Research

The cognitive status of patients assessed in this study was unknown. Thus it was assumed that the deficits detected using the CTIP were legitimate. In an ideal evaluation of the sensitivity and specificity of the CTIP to deficits in IPS associated with MS, known-impaired and known-unimpaired patient groups would be included as well as control participants. However, the identification of known-impaired and known-unimpaired patients is extremely difficult because there is no actual "gold standard" test representing a pure measure of processing speed. Although the PASAT represented the gold standard for measuring cognition for clinical trials, this test possesses several shortcomings (Tombaugh, 2006).

The best possible way to attain these known-impaired and known-unimpaired groups would be by basing classification on the results of extensive neuropsychological and neurological examinations. If professionals in these fields could indicate patients representing exemplars of these two groups, then it could be assumed, with some degree

of probability, those patients either did or did not possess deficits in IPS. In a study including these two patient groups and a cognitively intact control group, members of the known-impaired group would be expected to perform significantly worse than both the known-unimpaired and control groups. Whereas, the known-unimpaired group would be expected to perform comparably to the control participants, given that they are cognitively intact. The observance of such findings would provide strong evidence for the sensitivity and specificity of the CTIP. A study including these groups would also offer a better means to evaluate the sensitivity and specificity of the Adjusting-PASAT. The Adjusting-PASAT may be sensitive to deficits in processing speed, but just not at the levels represented in the current sample.

The sample sizes included in the present study were relatively small and therefore may not offer the best possible representations of the populations studied. Also, small sample sizes are associated with lower levels of power for statistical results. This is not so much a concern for the CTIP, which was found to significantly differentiate between the groups. However, the increased power associated with larger sample sizes may improve the probability of finding significant results for the Adjusting-PASAT. Although the likelihood of observing a significant difference between the performances of an MS and control group composed of larger samples does not seem highly likely given the analysis of threshold scores was far from significant. An investigation of performances on the CTIP with a substantially larger MS sample would provide invaluable support for the use of this test as a neuropsychological measure to detect cognitive dysfunction associated with the disease.

Future research should also aim to include repeated administrations over time in order to determine the ability of the CTIP to detect change over time. Evidence of this ability would be of great importance to clinicians and researchers alike. For clinicians, the ability to detect change over time would mean that the CTIP could function as an indicator of disease convalescence or progression and for researchers it would mean that the test could offer a reliable means by which to assess the effects of experimental treatments on cognitive functioning.

Disease course has been reported to significantly influence the nature of the information processing dysfunction observed in MS patients (Archibald & Fisk, 2000; DeLuca et al., 2004). RR-MS patients have been observed to possess only impairments in processing speed, while SP-MS patients exhibit IPS deficits of greater magnitude as well as impairments in working memory. The present study included relatively few progressive patients and, therefore, comparisons of performances between patients diagnosed with different subtypes were prevented. Because evidence for different information processing deficits between subtypes is emerging, it is important for future research to include adequate samples of each disease course so that the potential differences in IPS deficits can be explored further.

The MS and control groups were found to significantly differ on both the variables of sex and age. Although significant results were obtained for the CTIP test even when these variables were controlled for, it would be beneficial for future studies to attempt to match the groups on sex and age. This would eliminate the need to evaluate the contributions of these variables to differences in performances between the groups. Also, control participants were administered the Symbol Digit Modalities Test (SDMT)

while MS patients received the Digit Symbol Substitution test (DSST). Although these tests are very similar and are reported to be highly correlated, the use of the different tasks biases towards finding significant differences between groups on this measure. The SDMT/DSST was the only neuropsychological measure found to differentiate between patients and controls at the 5th percentile cut-off and obtained a standardized discriminant function coefficient of the third greatest magnitude. These results could be due to differences inherent in the individual tasks as opposed to a true difference in abilities between the groups.

Conclusions

In conclusion, the results of the present study provide additional support for the CTIP's ability to function as a neuropsychological measure of information processing. The CTIP includes three RT tests that exist on a continuum ranging in the cognitive demands involved for each. The CTIP is sensitive to the cognitive effects of MS and, of most clinical relevance, it has the ability to classify subjects in the expected manner using percentile scores derived from a normative sample. The SemRT test appears to be more useful for differentiating between patients affected by neurological insult and cognitively intact individuals in comparison with the CRT test. Therefore, some researchers may opt not to use the CRT test but those wishing to apply the percentiles derived from the normative sample should administer all three tests. The CTIP is not susceptible to practice effects suggesting its potential for use in tracking recovery, indicating the presence of positive effects of treatments on cognitive abilities, and for research where serial assessments are desired. RTs appear to be related to depression, thus whenever depression represents a possible significant factor for the population of interest some

measure of depression should be obtained in order to assess its contribution to performance.

Although the Adjusting-PASAT offers several clinical and experimental advantages over the standard procedure, it does not appear to possess the sensitivity necessary to detect deficits in IPS associated with MS, at least for non-progressive patients. For those patients who are identified as impaired using this measure, poor performance may be a result of dysfunction in cognitive processes besides processing speed and/or an interaction of such dysfunction with IPS. One-hundred trials of the Adjusting-PASAT did not appear to be sufficient to obtain a precise estimate of abilities. Therefore, additional trials should be administered or the ISI titration interval that increases/decreases with the correctness of the response should be changed. As with the standard PASAT, people find the Adjusting-PASAT to be very aversive and if experience with the standard test is any indication, participants and clients may be discouraged from returning for subsequent assessments because of the anticipation of repeated administrations of the Adjusting-PASAT.

References

Archibald, C.J. & Fisk, J.D. (2000). Information processing efficiency in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 22, 686-701.

Arena, R., Mazzoni, M., Moretti, P., Lepori, P., Giraldi, C. & Muratorio, A. (1986). Reaction times to lateralized visual stimuli in multiple sclerosis. *Acta Neurologica*, 8, 545-553.

Audoin, B., Ibarrola, D., Ranjeva, J., Confort-Gouny, S., Malikova, I., Ali-Cherif, A., Pelletier, J. & Cozzone, P. (2003). Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. *Human Brain Mapping*, 20, 51-58.

Baddeley, A. D. (1992). Working memory. *Science*, 255, 556-559.

Baddeley, A.D., Lewis, V.J., & Vallar, G. (1984). Exploring the articulatory loop. *Quarterly Journal of Experimental Psychology*, 36, 233-252.

Baddelay, A. (1986). *Working memory*. New York: Oxford University Press.

Baird, B.J. (2004). *The effects of practice on speed of information processing using the Adjusting-PSAT (A-PSAT) and the Computerized Tests of Information Processing (CTIP)*. Unpublished Ph.D. dissertation. Carleton University, Ottawa, Ontario.

Banich, M. (2004). *Cognitive Neuroscience and Neuropsychology*. Boston: Houghton Mifflin Company.

Barker-Collo, S.L. (2005). Within session practice effects on the PASAT in clients with multiple sclerosis. *Archives of Clinical Neuropsychology*, 20, 145-152.

Bayles, K.A., Kaszniak, A.W., & Tomoeda, C.K. (1987). *Communication and cognition*

in normal aging and dementia. Boston: College-Hill Press.

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

Beatty, W.W. & Monson, N. (1996). Problem solving by patients with multiple sclerosis: Comparison of performance on the Wisconsin and California Card Sorting Tests. *Journal of the International Neuropsychological Society*, 2, 134-140.

Beatty, W.W., Goodkin, D.E., Monson, N. & Beatty, P.A. (1989). Cognitive disturbances in patients with relapsing remitting multiple sclerosis. *Archives of Neurology*, 46, 1113-1119.

Beck, A.T. (1987). *Beck Depression Inventory.* San Antonio: Psychological Corporation.

Bennett, T., Dittmar, C., & Raubach, S. (1991). Multiple Sclerosis: cognitive deficits and rehabilitation. *Cognitive Rehabilitation*, 9, 18-23.

Benton, A.L. & Hamsher, K.deS. (1976). Multilingual Aphasia Examination. Iowa City, IA: University of Iowa.

Bobholz, J. & Rao, S. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Current Opinion in Neurology*, 16, 283-288.

Brassington, J.C. & Marsh, N.V. (1998). Neuropsychological aspects of multiple sclerosis. *Neuropsychology Review*, 8, 43-77.

Chiaravalloti, N., Hillary, F., Ricker, J., Christodoulou, C., Kalnin, A., Liu, W., Steffener, J. & Deluca, J. (2005). Cerebral activation patterns during working memory performance in multiple sclerosis using fMRI. *Journal of Clinical and*

Experimental Neuropsychology, 27, 33-54.

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences* (2nd ed.). New Jersey: Lawrence Erlbaum.

Cohen, R.A. & Fisher, M. (1989). Amantadine treatment of fatigue associated with multiple sclerosis. *Archives of Neurology*, 46, 676-680.

Coolidge, F.L., Middleton, P.A., Griego, J.A. & Schmidt, M.M. (1996). The effects of interference on verbal learning in multiple sclerosis. *Archives of Clinical Neuropsychology*, 11, 605-611.

Crawford, J.R., Obonsawin, M.C. & Allan, K.M. (1998). PASAT and components of WAIS-R performance: Convergent and discriminant validity. *Neuropsychological Rehabilitation*, 8, 255-272.

Crowe, S.F., Benedict, T., Enrico, J., Mancuso, N., Matthews, C. & Wallace, J. (1999). Cognitive determinants of performance on the Digit Symbol coding test, the Symbol Search Test of the WAIS-III, and the Symbol Digit Modalities Test: An analysis in a healthy sample. *Australian Psychologist*, 34, 204-210.

Cutter, G.R., Baier, M.L., Rudick, R.A., et al. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain*, 122, 871-882.

Delis, D.C., Squire, L.R., Bihrle, A. & Massman, P. (1992). Componential analysis of problem-solving ability: Performance of patients with frontal lobe damage and amnesic patients on a new sorting test. *Neuropsychologia*, 30, 683-698.

D'Esposito, M., Onishi, K., Thompson, H., Robinson, K., Armstrong, C. & Grossman, M. (1996). Working memory impairments in multiple sclerosis : Evidence from

a dual-task paradigm. *Neuropsychology*, 10, 51-56.

DeLuca, J., Gaudino, E.A., Diamond, B.J., Christodoulou, C. & Engel, R.A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 20, 376-390.

DeLuca, J., Johnson, S.K. & Natelson, B.H. (1993). Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. *Archives of Neurology*, 50, 301-304.

DeLuca, J., Barbieri-Berger, S., & Johnson, S.K. (1994). The nature of memory impairment in multiple sclerosis: acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology*, 16, 183-189.

DeLuca, J., Chelune, G.J., Tulsky, D.S., Lengenfelder, J., & Chiaravalloti, N.D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology*, 26, 550-562.

Demaree, H.A., DeLuca, J., Gaudino, E.A. & Diamond, B.J. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *Journal of Neurology, Neurosurgery and Psychiatry*, 67, 661-663.

Denney, D., Lynch, S., Parmenter, B. & Horne, N. (2004). Cognitive impairment in relapsing and primary progressive multiple sclerosis: mostly a matter of speed. *Journal of the International Neuropsychological Society*, 10, 948-956.

De Sonneville, L.M.J., Boringa, J.B., Reuling, I.E.W., Lazeron, R.H.C., Ader, H.J. & Polman, C.H. (2002). Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia*, 40, 1751-1765.

DeSousa, E.A., Albert, R.H. & Kalaman, B. (2002). Cognitive impairments in multiple sclerosis: A review. *American Journal of Alzheimer's Disease and Other Dementias*, 17, 23-29.

Di Stefano, G. & Radanov, B.P. (1995). Course of attention and memory after whiplash: A two-years prospective study with age, education and gender pair-matched patients. *Acta Neurological Scandinavia*, 91, 346-352.

Diamond, B.J., DeLuca, J., Kim, H., & Kelly, S.M. (1997). The question of disproportionate impairments in visual and auditory information processing in Multiple Sclerosis. *Journalof Clinical and Experimental Neuropsychology*, 19, 34-42.

Emmerson, R.Y., Dustman, R.E., Shearer, D.E. & Turner, C.W. (1990). P3 latency and Symbol Digit performance correlations in aging. *Experimental Aging Research*, 15, 151-159.

Elsass, P. & Zeeberg, I. (1983). Reaction time deficit in multiple sclerosis. *Acta Neurologica Scandinavica*, 68, 257-261.

Elsass, P. (1986). Continuous reaction times in cerebral dysfunction. *Acta Neurologica Scandinavica*, 73, 225-246.

Entus, A. & Bindra, D. (1970). Common features of the "repetition" and "same different" effects in reaction time experiments. *Perception and Psychophysics*, 7, 143-148.

Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. *Canadian Journal of Psychiatry*, 49(3), 157-163.

Feinstein, A., Brown, R. & Ron, M. (1994). Effects of practice of serial tests of attention

in healthy adults. *Journal of Clinical and Experimental Neuropsychology*, 16, 436-447.

Filley, C.M., Heaton, R.K., Nelson, L.M., Burks, J.S. & Franklin, G.M. (1989). A comparison of dementia in Alzheimer's disease and multiple sclerosis. *Archives of Neurology*, 46, 157-161.

Fischer, J.S., Priore, R.L., Jacobs, L.D., et al. (2000). Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple sclerosis collaborative research group. *Annals of Neurology*, 48, 885-892.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C.A., Kartsounis, L.D., Thompson, A.J., Miller, D.H. & Ron, M.A. (1997). Executive function in multiple sclerosis. *Brain*, 120, 15-26.

French, J.W., Ekstrom, R.B. & Price, I.A. (1963). *Kit for reference tests for cognitive factors*. Princeton, NJ: Educational Testing Service.

Friend, K.B., Rabin, B.M., Groninger, L., Deluty, R.H., Bever, C. & Grattan, L. (1999). *Language functions in patients with multiple sclerosis*, 13, 78-94.

Gaudino, E., Donofrio, N., DeLuca, J., & Diamond, B.J. (2001). Acomparison of memory performance in relapsing-remitting, primary-progressive and secondary progressive multiple sclerosis. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, 14, 32-44.

Gilmore, G.C., Royer, F.L. & Gruhn, J.J. (1983). Age differences in symbol-digit substitution task performance. *Journal of Clinical Psychology*, 39, 114-124.

Grafman, J., Rao, S., Bernardin, L. & Leo, G.J. (1991). Automatic memory processes in patients with multiple sclerosis. *Archives of Neurology*, 48, 1072-1075.

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

Grigsby, J., Ayarbe, S. D., Kravcisin, N., & Busenbark, D. (1994). Working memory impairment among persons with chronic progressive multiple sclerosis. *Journal of Neurology*, 241, 125-131.

Grigsby, J., Busenbark, D., Kravcisin, N., Kennedy, P.M., & Taylor, D. (1994). Impairment of the working memory system in relapsing-remitting multiple sclerosis. *Archives of Clinical Neuropsychology*, 9, 134-135.

Gronwall, D. (1977). Paced Auditory Serial-Addition Task: A measure of recovery from concussion. *Perceptual and Motor Skills*, 44, 367-373.

Heaton, R.K. (1981). Wisconsin Card Sorting Test manual. Odessa, FL: Psychological Assessment Resources.

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

Hillary, F.G., Chiaravalloit, N.D., Ricker, J.H., Steffener, J., Bly, B.M., Lange, G., Liu, W.C., Kalnin, A.J., & DeLuca, J. (2003). An investigation of working memory rehearsal in multiple sclerosis using fMRI. *Journal of Clinical and Experimental Neuropsychology*, 25, 965-978.

Hooper, H.E. (1958). The Hooper Visual Organization Test manual. Los Angeles: Western Psychological Services.

Janculjak, D., Mubrin, Z., Brinar, V. & Spilich, G. (2002). Changes of attention and

memory in a group of patients with multiple sclerosis. *Clinical Neurology and Neurosurgery*, 104, 221-227.

Jastak, S. & Wilkinson, G. (1974). *The Wide Range Achievement Test, Revised: Administration manual.* Wilmington, DE: Jastak.

Jennekens-Schinkel, A., Laboyrie, P.M., Lanser, J.B.K. & van der Velde, E.A. (1990). Cognition in patients with multiple sclerosis after four years. *Journal of Neurological Sciences*, 99, 229-247.

Jennekens-Schinkel, A., Sanders, E.A.C.M., Lanser, J.B.K. & Van der Velde, E.A. (1988). Reaction time in ambulant multiple sclerosis patients: Part I. Influence of prolonged cognitive effort. *Journal of the Neurological Sciences*, 85, 173-186.

Johnson, S.K., Lange, G., DeLuca, J., Korn, L.R. & Natelson, B. (1997). The effect of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis and depression. *Applied Neuropsychology*, 4, 145-153.

Kail, R. (1997). The neural noise hypothesis: Evidence from processing speed in adults with multiple sclerosis. *Aging, Neuropsychology, and Cognition*, 4, 157-165.

Kail, R. (1998). Speed of information processing in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 20, 98-106.

Kaplan, E.F., Goodglass, H. & Weintraub, S. (1983). *The Boston Naming Test* (2nd ed.). Philadelphia: Lea & Febiger.

Kujala, P., Portin, R., Revonsuo, A. & Ruutiainen, J. (1994). Automatic and controlled information processing in multiple sclerosis. *Brain*, 117, 1115-1126.

Kujala, P., Portin, R., Revonsuo, A., & Ruutiainen, J. (1995). Attention related

performance in two cognitively different subgroups of patients with multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 59, 77-82.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, 33, 1444-1452.

Landro, N., Sletvold, H. & Gulowsen Celius, E. (1999). Memory functioning and emotional changes in early phase multiple sclerosis. *Archives of Clinical Neuropsychology*, 15, 37-46.

Laux, L.F. & Lane, D.M. (1985). Information processing components of substitution test performance. *Intelligence*, 9, 111-136.

Lengenfelder, J., Bryant, D., Diamond, B.J., Kalmar, J.H., Moore, N.B., & DeLuca, J. (2006). Processing speed interacts with working memory efficiency in multiple sclerosis. *Archives of Clinical Neuropsychology*, 21, 229-238.

Lezak, M.D. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.

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

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

Lublin, F. & Reingold, S. (1996). Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology*, 46, 907-911.

MacLeod, D. & Prior, M. (1996). Attention deficits in adolescents with ADHD and other clinical subgroups. *Child Neuropsychology*, 2, 1-10.

Maurelli, M., Marchioni, E., Cerretano, R. Bosone, D., Bergamaschi, R., Citterio, A., Martelli, A., Sibilla, L. & Savoldi, F. (1992). Neuropsychological assessment in MS: clinical, neuropsychological and neuroradiological relationships. *Acta Neurologica Scandinavica*, 86, 124-128.

McCaffrey, R.J., Cousins, J.P., Westervelt, H.J., et al. (1995). Practice effects with the NIMH AIDS abbreviated neuropsychological battery. *Archives of Clinical Neuropsychology*, 10, 241-250.

McCaffrey, R.J., Westervelt, H.J. & Haase, R. (2001). Serial neuropsychological assessments with the National Institute of Mental Health (NIMH) Aids Abbreviated Neuropsychological Battery. *Archives of Clinical Neuropsychology*, 16, 9-18.

McCarthy, M., Beaumont, J.G., Thompson, R. & Peacock, S. (2005). Modality-specific aspects of sustained and divided attention performance in multiple sclerosis. *Archives of Clinical Neuropsychology*, 20, 705-718.

McDonald, T., Compston, A. & Edan, G. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Annals of Neurology*, 50, 121-127.

McIntosh-Michaelis, S.A. & Roberts, M.H. (1991). The prevalence of cognitive impairment in a community survey of multiple sclerosis. *British Journal of Clinical Psychology*, 30, 333-348.

Milner, A.D. (1986). Chronometric analyses in neuropsychology. *Neuropsychologia*, 24, 115-128.

Morgan, S.F. & Wheelock, J. (1995). Comparability of WAIS-R Digit Symbol and the

Symbol Digit Modalities Test. *Perceptual and Motor Skills*, 80, 631-634.

Nelson, H.E. (1978). A modified card sorting test sensitive to frontal lobe deficits. *Cortex*, 12, 313-324.

Peyser, J.M., Rao, S.M., LaRocca, N.G. & Kaplan, E. (1990). Guidelines for neuropsychological research in multiple sclerosis. *Archives of Neurology*, 47, 94-97.

Polubinski, J.P. & Melamed, L.E. (1986). Examination of the sex difference on a symbol digit substitution task. *Perceptual and Motor Skills*, 62, 975-982.

Ponsford, J. & Kinsella, G. (1992). Attentional deficits following closed-head injury. *Journal of Clinical and Experimental Neuropsychology*, 14, 822-838.

Proctor, R.W. (1981). A unified theory for matching task performance. *Psychological Review*, 82, 116-149.

Rao, S.M. (1990). *Neurobehavioral Aspects of Multiple Sclerosis*. New York: Oxford University Press.

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

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

Rao, S.M., Leo, G.J., Bernardin, L. & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, 41, 685-691.

Rao, S.M., Hammeke, T.A. & Speech, T.J. (1987). Wisconsin card sorting test

performance in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of Consulting and Clinical Psychology*, 55, 263-265.

Rao, S.M., St. Aubin-Faubert, P. & Leo, G.J. (1989b). Information processing speed in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 11, 471-477.

Rao, S.M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G.J., Luchetta, T., & Unverzagt, F. (1993). Memory dysfunction in Multiple Sclerosis: its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology*, 7, 364-374.

Raven, J.C. (1960). Guide to the Standard Progressive Matrices. London: H.K. Lewis.

Rees, L. & Tombaugh, T.N. (2001). *The Adjusting-Paced Serial Addition Test (Adjusting-PSAT)*. Paper presented at NAN Research Grants Luncheon at the 21st annual meeting of the National Academy of Neuropsychology, San Francisco, Calif.

Reitan, R.M. & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery*. Tucson, Arizona: Neuropsychology Press.

Royan, J., Tombaugh, T.N., Rees, L. & Francis, M. (2004). The Adjusting Paced Serial Addition Test (Adjusting-PSAT): Thresholds for speed of information processing as a function of stimulus modality and problem complexity. *Archives of Clinical Neuropsychology*, 19, 131-143.

Ruchkin, D.S., Grafman, J., Krauss, G.L., Johnson, R., Canoune, H., & Ritter, W. (1994). Event-related brain potential evidence for a verbal working memory deficit in Multiple Sclerosis. *Brain*, 117, 289-305.

Sailer, M., Heinze, H., Schoenfeld, M., Hauser, U. & Smid, H. (2000). Amantadine influences cognitive processing in patients with multiple sclerosis. Pharmacopsychiatry, 33, 28-37.

Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103, 403-428.

Schmidt, J.P. & Tombaugh, T.N. (1995). *The Learning and Memory Battery (LAMB).* Toronto: Multi-Health Systems.

Sfagos, C., Papageorgiou, C.C., Kosma, K.K., Kodopadelis, E., Uzunoglu, N.K., Vassilopoulos, D., & Rabavilas, A.D. (2003). Working memory deficits in Multiple Sclerosis: a controlled study with auditory P600 correlates. *Journal of Neurology, Neurosurgery and Psychiatry*, 74, 1231-1235.

Sherman, E.M.S., Strauss, E. & Spellacy, F. (1997). Validity of the Paced Auditory Serial Addition Test (PASAT) in adults referred for neuropsychological assessment after head injury. *The Clinical Neuropsychologist*, 11, 34-45.

Smith, A. (1991). *Symbol Digit Modalities Test.* Los Angeles: Western Psychological Services.

Snyder, P.J., Cappelleri, J.C., Archibald, C.J. & Fisk, J.D. (2001). Improved detection of differential information-processing speed deficits between two disease-course types of multiple sclerosis. *Neuropsychology*, 15, 617-625.

Spreen, O. & Strauss, E. (1998). *A compendium of neuropsychological tests.* New York: Oxford University Press.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., Ritter, S., Golaszewski, S., Iglseder, B. & Ladurner, G. (2002). Cognitive function and

fMRI in patients with multiple sclerosis: Evidence for compensatory cortical activation during an attention task. *Brain*, 125, 1275-1282.

Stones, M.J. & Kozma, A. (1989). Age, exercise, and coding performance. *Psychology and Aging*, 4, 190-194.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 18, 643-662.

Stuss, D.T., Stethem, L.L., Hugenholtz, H. & Richard, M.T. (1989). Traumatic brain injury: A comparison of three clinical tests and analysis of recovery. *The Clinical Neuropsychologist*, 3, 145-156.

Swirsky-Sacchetti, T., Mitchell, D., Seward, J., Gonzales, C., Lublin, F., Knobler, R. & Field, H. (1992). Neuropsycholoical and structural brain lesions in multiple sclerosis: a regional analysis. *Neurology*, 42, 1291-1295.

Thornton, A.E. & Raz, N. (1997). Memory impairment in multiple sclerosis: a quantitative review. *Neuropsychology*, 11(3), 357-366.

Thornton, A.E., Raz, N. & Tucker, K.A. (2002). Memory in multiple sclerosis: Contextual encoding deficits. *Journal of the International Neuropsychological Society*, **8**, 395-409.

Tombaugh, T. & Rees, L. (1999). Computerized Tests of Information Processing (CTIP). Unpublished test. Carleton University, Ottawa, Ontario, Canada.

Tombaugh, T. (1999). Adjusting-Paced Auditory Serial Addition Task (Adjusting-PASAT). Unpublished test. Carleton University, Ottawa, Ontario, Canada.

Tombaugh, T.N. (2006). A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). *Archives of Clinical Neuropsychology*, 21, 53-76.

Tombaugh, T.N., Rees, L., Stormer, P., Harrison, A. & Smith, A. (in press). The effects of mild and severe traumatic brain injury on speed of information processing as measured by the Computerized Tests of Information Processing (CTIP). *Archives of Clinical Neuropsychology.*

Tombaugh, T.N., Rees, L. & Royan, J. (2001). *Performance of cognitively intact and traumatic brain injured patients on the computerized tests of information processing (CTIP).* Paper presented at the 21st Annual meeting of the National Academy of Neuropsychology Conference, San Francisco, Calif.

Tombaugh, T.N. & Rees, L. (2006). [Normative data for the Computerized Tests of Information Processing (CTIP)]. Unpublished data.

Uchiyama, C.L., D'Elia, L.F., Dellinger, A.M., Selnes, O.A., Becker, J.T., Wesch, J.E., Chen, B.B., Satz, P., Van Gorp, W. & Miller, E.N. (1994). Longitudinal comparison of alternative versionsof the Symbol Digit Modalities Test: Issues of form comparability and moderating demographic variables. *The Clinical Neuropsychologist*, 8, 209-218.

Van Zomeran, A.H. & Brouwer, W.H. (1994). *Clinical neuropsychology of attention.* New York: Oxford University Press.

Waldmann, B.W., Dickson, A.L., Monahan, M.C. & Kazelskis, R. (1992). The relationship between intellectual ability and adult performance on the Trail Making Test and the Symbol Digit Modalities Test. *Journal of Clinical Psychology*, 48, 360-363.

Walker, L., Smith, A., DeMeulemeester, A.C., Freedman, M., Mendella, P.D., Tombaugh, T.N. & Theoret, G. (2004). *Performance of multiple sclerosis*

patients on desk-top and scanner versions of the Computerized Tests of Information Processing (CTIP). Paper presented at the European Charcot Foundation, Taormina, Sicily, Italy.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scales-Revised.* New York: Psychological Corporation.

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale-III.* San Antonio: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale-III.* San Antonio: The Psychological Corporation.

Western, S.L. & Long, C.J. (1996). Relationship between reaction time and neuropsychological test performance. *Archives of Clinical Neuropsychology*, 11, 557-571.

Woodcock, R.W., & Johnson, M.B. (1989). *Woodcock-Johnson Psychoeducational Battery-Revised.* Chicago: Riverside.

Yeudall, L.T., Fromm, D., Reddon, J.R. & Stefanyk, W.O. (1986). Normative data stratified by age and sex for 12 neuropsychological tests. *Journal of Clinical Psychology*, 42, 918-946.

Zakzanis, K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. *Archives of Clinical Neuropsychology*, 15, 115-136.

Zillmer, E. & Spiers, M. (2001). *Principles of Neuropsychology.* Belmont: Wadsworth.

Appendix A

Descriptions of Neuropsychological Tests

Animal Naming. Subjects are asked to name as many animals as they can think of within a given amount of time.

Boston Naming Test (BNT). Sixty line drawings ranging from simple, high frequency vocabulary to rare words are presented one at a time on cards and two prompting cues (phonemic and stimulus) are given if the person is unable to produce the word spontaneously.

Controlled Oral Word Association Test (COWAT). Consists of three word-naming trials. Either the letter sets C-F-L or P-R-W may be used. The examiner asks the subject to say as many words as they can think of that begin with the given letter of the alphabet within a certain amount of time, excluding proper nouns, numbers, and the same word with a different suffix.

Digit Span. Includes Digits Forward and Digits Backward, each of which consists of sequences of numbers progressing in length that the examiner reads aloud at the rate of one per second. In Digits Forward, the subject must repeat the sequences aloud in the same order as they were presented and in Digits Backward, the subject must repeat them aloud in the reverse order of how they were presented. The test is discontinued after two consecutive incorrect responses on the same trial.

Finger Tapping Test. Using a specially adapted tapper, the subject is instructed to tap as rapidly as possible using the index finger of the preferred hand, then with the non-preferred hand. This is a measure of motor speed.

FAS. This test is similar to the COWAT except it uses the set of letters F-A-S.

Grip Strength. The subject holds the upper part of the dynamometer in the palm of their hand and squeezes the stirrup with their fingers as hard as they can. This test measures the strength or intensity of voluntary grip movements of each hand.

Grooved Pegboard. This test incorporates complex coordination into the pegboard task. It consists of a small board containing a 5 X 5 set of slotted holes angled in different directions. Each peg has a ridge along one side, requiring it to be rotated into position for correct insertion.

Hooper Visual Organization Test (HVOT). This test consists of thirty drawings of common objects contained in a test booklet. Each object is cut into two or more parts and illogically arranged in the drawing. Subjects are asked to name the object.

Paced Auditory Serial Addition Task (PASAT). This task requires subjects to add each number presented (ranging from 1 to 9) to the number immediately preceding it, so that the second number is added to the first, the third to the second and so on, and to say the sum aloud. Traditionally four trials are used, each with different time intervals between digits (i.e., inter-stimulus intervals [ISI]) of 2.4, 2.0, 1.6, and 1.2 seconds.

Purdue Pegboard. The purpose of this test is to measure finger and hand dexterity. The board consists of two parallel rows of 25 holes each. There are four cups at the top of the board; the end cups hold the pegs and the middle cups contain collars and washers. In the first three subtests, the subject places as many pins as possible in the holes, first with the preferred hand, then with the non-preferred hand, and finally with both hands. They are allotted 30-seconds on each trial. In the fourth subtest, the subject uses both hands alternately to construct assemblies consisting of a peg, washer, collar and another washer. They are allotted one-minute.

Raven's Progressive Matrices. This test consists of a series of visual pattern matching and analogy problems pictured in non-representational designs. It requires the subject to conceptualize spatial, design, and numerical relationships ranging from the very obvious and concrete to the very complex and abstract.

Sternberg Memory Scanning Task. For each block of trials subjects are asked to memorize a set of one, two, or four digits. On each trial the subject is shown a test digit and is asked to decide if it belonged to the set of digits held in memory. Either fixed or varied administration procedures may be used. Both accuracy and response time are measured.

Stroop Test. The subject reads randomized colour names printed in black from either white cards or a computer screen with a white background. Then, the subject is asked to read the colour names printed in incongruent coloured ink, ignoring the colour of the ink. The subject is then asked to name the colour of shapes. Finally, the subject is asked to name the colour in which colour names are printed, the colour of the ink is incongruent to the name. Time required to complete each task is measured. Many variations in the Stroop task exist.

Symbol Digit Modalities Test. As with the Symbol Digit Substitution Test, nine digit symbol mappings are presented. However, subjects are required to provide the number associated with the given symbols either orally or graphically. The score is calculated as the total number of correct symbols produced within a given amount of time.

Tower of London (TOL). The subject is required to move coloured beads one at a time from their initial position on upright sticks to achieve a new, predetermined arrangement in as few moves as possible and following certain rules set out beforehand.

Verbal Fluency. This test consists of both the FAS and Animal naming tests described above.

Wisconsin Card Sorting Test (WCST). The test consists of four stimulus cards, placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses, and the fourth with four blue circles on them. The subject is then given two packs of cards, each containing sixty-four response cards, which have designs similar to those on the stimulus cards, varying in colour, geometric form and number. The subject is asked to match each of the cards in the decks to one of the four stimulus cards and is given feedback each time whether he or she is right or wrong. After ten consecutive correct responses, the matching criteria is changed without notifying the subject and then they must try to learn what the new criterion is based on the examiner's feedback.