COGNITION IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: CONSEQUENCES MAY BE RELATIVE TO WORKING MEMORY AND NOT PROCESSING SPEED

by

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ABSTRACT

Background and Objectives: Patients with multiple sclerosis (MS) have reported that the disease affects their ability to think. According to the *Relative Consequence Model* (DeLuca et al., 2004), patients with MS have a fundamental difficulty in processing speed that, in turn, compromises other cognitive functions. However, previous research examining the hypothesis suffers from several methodological flaws. For example, most studies employed processing speed measures that are confounded by working memory. The objectives of the present study were to: (1) investigate the relations between processing speed and other cognitive abilities while addressing methodological flaws in previous work, (2) examine whether working memory may contribute to cognitive deficits, and (3) determine the contributions of different cognitive functions to the confounded measures used previously.

Methods: Seventy adults with relapsing-remitting MS and disease duration of no more than ten years and 72 controls completed multiple measures assessing processing speed, working memory, learning, and executive functioning. Structural equation modeling was used to test the separate hypotheses of the mediating roles of processing speed and working memory. Regression analyses were used to examine the contributions of different cognitive functions to the confounded measures.

Results: Group membership did not predict processing speed, thus, the mediating role of processing speed could not be examined. With working memory assigned as a mediating variable, group had a significant *direct effect* on working memory but only *indirect effects* via working memory on the other cognitive functions. Processing speed and working memory contributed to performance on the Paced Auditory Serial Addition Test

and the Symbol Digit Modalities Test, with learning additionally contributing to Symbol Digit Modalities Test performance.

Conclusions: The results do not support the *Relative Consequence Model* in patients with early relapsing-remitting MS and they challenge the notion that working memory impairment only emerges at later disease stages. The results do support the mediating role of working memory in the relations between MS and other cognitive functions. The findings are consistent with the multifactorial interpretation of clinical measures of processing speed, which may facilitate their usefulness as screening measures but prevents them from identifying specific cognitive functions affected.

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CHAPTER ONE: INTRODUCTION

Multiple sclerosis (MS) is a neurological disease in which the myelin of the central nervous system is damaged resulting in inflammation, demyelination, and the formation of lesions, also known as sclerotic plaques[1]. Because myelin is vital to the normal transmission of neural impulses, the loss of myelin results in the disruption or inhibition of these impulses so neuronal information slows or never reaches its target. For the most part, damage is considered to be randomly distributed throughout the central nervous system. Accordingly, MS is associated with a broad range of symptoms including a variety of sensory and motor symptoms, neuropsychiatric disorders, and cognitive deficits.

The frequency of cognitive dysfunction in MS is high with prevalence rates estimated to range from 40% to 60% of patients (Banich, 2004; Heaton, Nelson, Thompson, Burks & Franklin, 1985; McIntosh-Michaelis & Roberts, 1991; Peyser, Rao, LaRocca & Kaplan, 1990; Rao, Leo, Bernardin & Unverzagt, 1991). Previous research shows that a large number of cognitive processes are affected in MS, including information processing speed, working memory, learning, memory, and executive functioning. Of these, slowed processing speed is one of the most commonly reported cognitive deficits (e.g., Benedict et al., 2006). Researchers in the field have proposed that slowed information processing speed is the primary deficit in MS and that inefficiencies in more complex mental abilities are a consequence of slower cognitive processing (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). However, research that

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[1] See Appendix A for a general overview of MS.

has tested whether slowed processing speed accounts for other cognitive impairments in MS is scant and several methodological flaws challenge the quality of the existing evidence. For example, the measures used to index processing speed are often confounded by other cognitive abilities, such as working memory. The objectives of the present study were to: (1) investigate the relations between information processing speed and cognitive functions often impaired in patients with MS while addressing methodological flaws in previous work, (2) examine whether working memory contributes to deficits in the cognitive functions and, thus, whether working memory may underlie the results of previous studies that employed confounded measures, and (3) determine the contributions of different cognitive functions to performance on the confounded measures that have been employed in MS research.

Information Processing Speed in MS

Slowed information processing has been frequently documented for individuals diagnosed with MS (Archibald & Fisk, 2000; Audoin et al., 2003; Brassington & Marsh, 1998; DeLuca, Johnson, & Natelson, 1993; Demaree, DeLuca, Guadino, & Diamond, 1999; Denney, Lynch, Parmenter, & Horne, 2004; D'Esposito et al., 1996; Diamond, DeLuca, Kim, & Kelly, 1997; Feinstein, 2004; Kail, 1997c, 1998; Kujala, Portin, Revonsuo, & Ruutainenl., 1995; Lengenfelder, Bryant, Diamond, Kalmar, Moore, & DeLuca, 2006; Lengenfelder, Chiaravalloti, Ricker & DeLuca, 2003; Litvan, Grafman, Vendrell, & Martinez, 1988b; Rao, St. Aubin-Faubert, & Leo, 1989b; Reicker, Tombaugh, Walker, & Freedman, 2007; Ruchkin, Grafman, Krauss, Johnson, Canoune, & Ritter, 1994; Sailer, Heinze, Schoenfield, Hauser & Smid, 2000). Information processing speed has been measured using various methods throughout the MS literature.

Kail (1997c) 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 required 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 MS patients and controls on multiple measures of processing speed and found that, across all tasks, the MS group performed approximately 46% more slowly than controls. In contrast with Kail's (1997c) 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.

Classical reaction time procedures are a sensitive measure of processing efficiency (Milner, 1986) and have been used to assess MS patients' ability to process information. Research studies have found that individuals with MS respond significantly slower than controls on simple, choice, and go-no-go reaction time tasks involving visual and auditory stimuli (Arena et al., 1986; Elsass & Zeeberg, 1983; Janculjak, Mubrin, Brinar, & Spilich, 2002; Jennekens-Schinkel, Sanders, Lanser, & van der Velde, 1988; Kujala, Portin, Revonsuo, & Ruutiainen, 1994). For example, Reicker et al. (2007) evaluated the ability of patients with MS to process information quickly in comparison to

a group of non-clinical controls using a recently developed series of reaction time tasks, the Computerized Test of Information Processing (Tombaugh & Rees, 2008). This measure is composed of three different reaction time tests, a simple reaction time test, a choice reaction time test, and a semantic search reaction time test. The complexity of cognitive processing is progressively increased across the three tasks. The MS group responded significantly slower than controls on each of the reaction time tests. Moreover, as the tests became more difficult (i.e., as processing demands increased), the difference between the performances of the two groups progressively increased (see Figure 1 for a diagram depicting these results). These results suggest that the reduction in processing speed caused by MS occurs across varying levels of cognitive complexity but that these deficits are strongest for more demanding tasks.

In addition to reaction time, investigators have also used the Sternberg Memory Scanning Test (Sternberg, 1969) to examine speed of information processing. This test assesses the rate at which information held in short-term memory 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 (i.e., memory scanning speed). 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, St. Aubin-Faubert, and Leo (1989b) found significant differences between MS patients and controls. This finding is supported by the results of

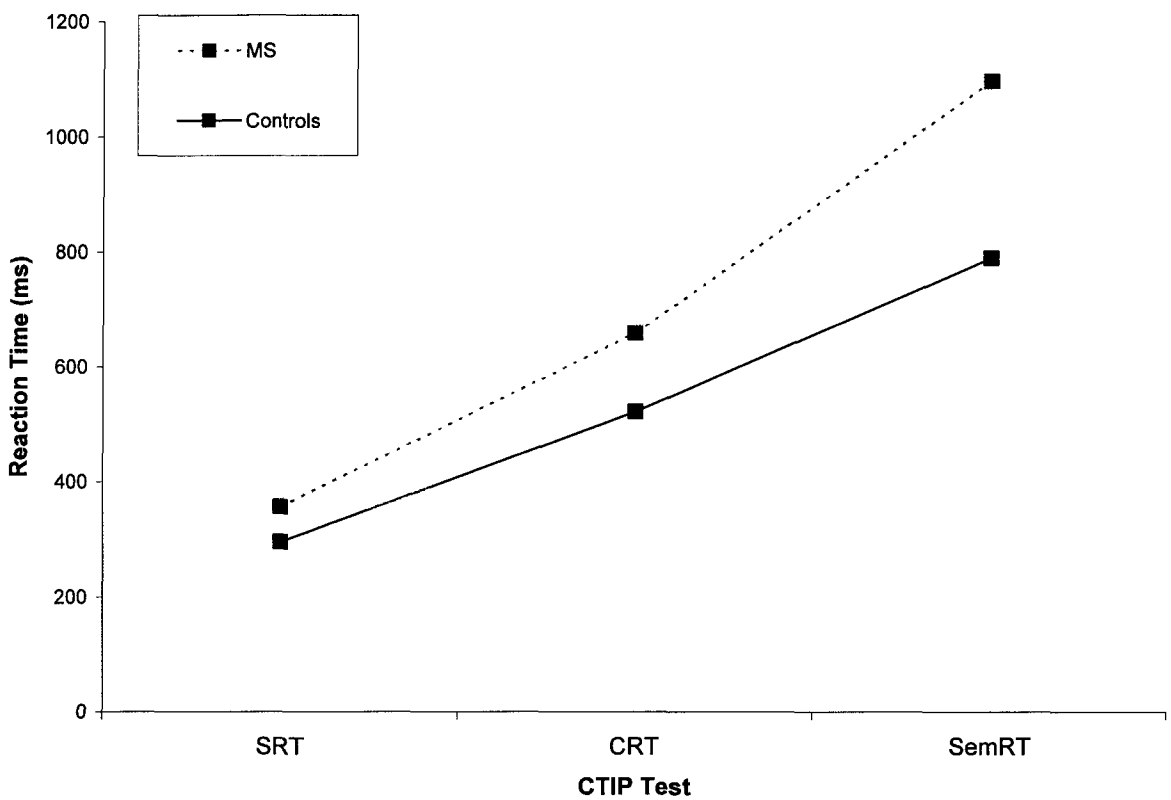

Figure 1. Reactions Times (ms) on the Computerized Test of Information Processing from Reicker, Tombaugh, Walker, & Freedman, 2007.

Note. SRT, Simple Reaction Time; CRT, Choice Reaction Time; SemRT, Semantic Search Reaction Time.

Archibald et al. (2004), Archibald and Fisk (2000), and Janculjak et al. (2002). In contrast, Drew, Starkey, and Isler (2009), Janculjak et al. (1999), and Litvan et al. (1988b) did not find patients' memory scanning speed 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 various studies.

Processing speed has also been assessed using the Stroop test. The incongruent colour naming trial of the Stroop provides a measure of interference whereas the preliminary trials of the Stroop (word reading, colour naming) are assumed to measure processing speed because they involve the rapid execution of relatively low-demanding operations so that as many items as possible can be completed in a specified amount of time (Lynch, Dickerson, & Denney, 2010). Several studies have found deficient processing speed on the preliminary trials of the Stroop in patients with MS (Bodling, Denney, & Lynch, 2009; Bodling, Lynch, & Denney, 2008; Denney et al., 2004; Denney, Sworowski, & Lynch, 2005; Jennekens-Schinkel, Laboyrie, Lanser, & van der Velde, 1990; Kujala et al., 1995; Lynch et al., 2010). In contrast, Santiago, Guardia, Casado, Carmona, and Arbizu (2007) reported relapsing-remitting MS patients with mild to moderate disability performed comparably to controls on all trials of the Stroop. Another measure that has been used extensively in the study of processing speed is the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). This task requires participants to add each number presented (ranging from 1 to 9) to the number immediately preceding it and to say the sum aloud, hence the second number is added to the first, the third to the second and so on. Traditionally four trials are used, each with different time intervals between digits (i.e., inter-stimulus intervals of 2.4, 2.0, 1.6, and

1.2 seconds) and the number of correct responses is recorded. However, it is also common in the MS literature for a single trial employing an inter-stimulus interval of 3.0 seconds to be used (Cutter et al., 1999). DeLuca, Johnson, and Natelson (1993) found MS patients differed from controls on both fast and slow inter-stimulus intervals. Modified versions of the PASAT that allow for the speed of processing to be measured while participants are equated on accuracy have also been administered to patients with MS (Auditory Threshold-Serial Addition Test, Visual Threshold-Serial Addition Test; Chiaravalloti, Demaree, Gaudino, & DeLuca, 2003; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). Accuracy is controlled for by employing a method of limits procedure in which the inter-stimulus interval increases or decreases contingent upon the correctness of the previous response. This procedure results in an optimum inter-stimulus interval, or threshold, at which each subject is 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 obtained with these modified tests have consistently shown that MS patients require a slower rate of digit presentation to achieve the same level of accuracy as control participants (Chiravalloti et al., 2003; DeLuca et al., 1998; Diamond, Johnson, Kaufman, & Graves, 2008; Lengenfelder et al., 2006).

In sum, considerable evidence supports the conclusion that the rate at which information can be processed is impaired for patients with MS. Accordingly, some researchers have proposed that slowed processing speed is the primary cognitive deficit in MS and that slowing may be responsible for the deficits observed in other cognitive

functions as well. This hypothesis is the basis of the *Relative Consequence Model* (DeLuca et al., 2004; Lengenfelder et al., 2006).

The Relative Consequence Model

The *Relative Consequence Model* proposes that persons with MS have a fundamental deficit in processing speed such that inefficiencies in higher-level cognitive domains, such as working memory or learning and memory, are due to slowed cognitive processing instead of being a direct result of the disease pathology. That is, deficiencies in the ability to acquire new information, for example, are thought to arise not because the disease has in some way damaged or altered regions of the brain or functional circuits involved with this ability. Instead, the *Relative Consequence Model* posits that deficient learning occurs because the effects of the disease have reduced the rate at which information can be taken in and processed and this has, in turn, limited a person's ability to acquire new information. DeLuca et al. (2004) explain more formally:

> 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).

Research addressing the hypothesis proposed in the *Relative Consequence Model* is limited, although the theory is consistent with the results of several studies (Arnett, 2004; Chiaravalloti et al., 2003; DeLuca, Barbieri-Berger, & Johnson, 1994; Diamond et al., 2008; Drew et al., 2009; Litvan et al., 1988b). However, there are issues with

ascribing the results of these studies to processing speed specifically. These issues and their implications will be discussed in the following section.

Criticisms of Research Addressing the Relative Consequence Model

Demaree, Frazier, and Johnson (2008) provide an account of the methodological problems that limit the conclusions that can be drawn from existing research on the relation between processing speed and other cognitive abilities. They highlight three types of problems. First, the cognitive constructs under study have been poorly operationalized. Neuropsychological measures often show relatively poor discriminant validity in that they measure other cognitive domains besides the one that they are intended to measure. Demaree et al. advised this may lead to the false conclusion that processing speed is associated with other cognitive abilities when such associations are actually a result of operational confounds. Furthermore, studies using only one measure or very similar measures to index a cognitive construct make it difficult to determine whether results may be attributable to the particular validity of the measure, the modality of stimulus presentation, and/or the behavioural response requirements.

Therefore, although several research studies have found significant relationships between processing speed and memory, particularly where measures of acquisition of unstructured verbal information were used (Demaree et al., 2008), the attribution of the relationship to processing speed specifically may be unwarranted. For example, Litvan and colleagues (1988b) reported that the number of correct responses obtained by MS patients was impaired for the two highest rates of presentation of the traditional PASAT and that performance at the higher presentation rates and retrieval of information from long-term memory were significantly correlated. These results led the authors to conclude

that slowed information processing contributes to long-term memory impairment in patients with MS. DeLuca et al. (1994) reported that an MS group required significantly more trials to reach criterion on a verbal list-learning task employing a selective reminding procedure in comparison with controls. The authors also found that PASAT performance significantly correlated with the number of trials to reach criterion for the MS patients. This led DeLuca et al. (1994) to conclude that the "correlation between PASAT performance and memory performance supports the hypothesis that deficient encoding in MS is a result of problems in information processing speed and efficiency" (p. 188). DeLuca et al. (1998) also reported that the threshold score from the Auditory Threshold – Serial Addition Test was significantly correlated with trials to criterion for a visual learning task, but not for the verbal task. Finally, Diamond et al. (2008) reported significant associations between the Visual Threshold-Serial Addition Test and both verbal and visual learning and memory. The authors took these findings to provide evidence that processing speed influences cognition.

The studies discussed above all employed a single task or slightly different variations of one task to operationalize processing speed – the PASAT. Although this measure is sensitive to a variety of neurological disorders, as a processing speed measure the test possesses several critical flaws. The issues regarding the use of the PASAT were outlined by Tombaugh (2006). The most important flaw for studies using this measure to examine the relation between processing speed and cognition is that the constructs measured by the PASAT are ambiguous. In general, it is assumed that the test measures 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 test 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, Obonsawin, & Allan, 1998; Fisk & Archibald, 2001; McCaffrey et al., 1995). The PASAT was originally assumed to measure processing speed (Gronwall & Sampson, 1974) and a survey of the literature shows that most articles contained statements supporting the task is a sensitive measure of processing speed, with some of these articles providing supportive evidence. However, other authors state that the test measures sustained and divided attention and 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.

Given these issues concerning the PASAT, the results from the majority of studies investigating relations between processing speed and other cognitive abilities must be interpreted carefully. Although this line of research suggests that slowed processing speed may be associated with poorer execution of other cognitive functions, the relations between performance on the PASAT and other cognitive measures may have arisen due to factors besides processing speed. It cannot be ruled out that the associations found between performance on the PASAT and other cognitive measures were completely or partially due to the operational confounds of intelligence, math ability, strategic planning, or working memory efficiency, for instance, which are known to affect the test. Or perhaps the associations resulted because both the PASAT and the other cognitive measures each involved presentation of stimuli in the same sensory modality or because they each may have required a verbalized response.

Indeed, the inconsistency of results between the DeLuca et al. (1994) and the DeLuca et al. (1998) studies highlights these potential confounds. Using PASAT performance to index processing speed, DeLuca et al. (1994) reported that processing speed was significantly correlated with trials to criterion on a verbal learning task. In contrast, DeLuca et al. (1998) did *not* find a significant association between processing speed and trials to criterion on the task using Auditory Threshold-Serial Addition Test performance, which better isolates the speed component of the task. The authors of the latter study hypothesized that "the association between traditional PASAT performance and measures of learning and memory may be due to other cognitive components involved in the successful execution of this task, such as flexibility in thinking or multitasking" (p. 387). Hence, even research within the same laboratory is susceptible to the effects of operational confounds inherent to the PASAT.

Furthermore, operational confounds may explain the inconsistent findings regarding executive functioning found by Drew et al. (2009). The authors reported that when the association between memory scanning speed on the Sternberg Test and performance on the tasks composing the Delis-Kaplan Executive Function System battery (D-KEFS; Delis, Kaplan, & Kramer, 2001) was evaluated, processing speed did not appear to contribute overall to executive functioning. In addition to memory scanning speed, Drew et al. also examined correlations between both initial response speed (i.e., intercept) from the Sternberg Test and the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997a)] Processing Speed Index measures and executive functioning. For these measures, stronger evidence was found for a relation between processing speed and executive functioning, particularly for executive tasks involving inhibition or switching.

However, because of the pattern of findings of a stronger relationship when based on Processing Speed Index measures and initial response speed versus a weaker relationship when based on memory scanning speed, it was unclear whether information processing speed was the underlying link as opposed to perceptual and motor processes. However, it should be noted that the MS sample did not exhibit impaired memory scanning speed relative to controls, leading the authors to note the possibility that a stronger relationship between memory scanning speed and executive functioning may exist for patients experiencing more severe impairment in this function.

Besides poor operationalization of the constructs, another methodological problem that was highlighted by Demaree et al. (2008) is inadequate statistical methods for examining the mediator hypothesis, that is, the extent that processing speed accounts for the relations between MS and other cognitive functions. All of the studies described thus far have only employed simple bivariate correlations and even more recent studies perpetuate these limitations. For example, Sweet et al.'s (2010) conclusion that, of the component processes of verbal working memory, only subvocal articulatory rehearsal and not short-term buffering is related to processing speed in MS was based on bivariate correlations. Similarly, Drew et al. (2009) reported a significant bivariate association between memory scanning speed from the Sternberg Test with the sub-tests composing the WAIS-III Working Memory Index. Mediational hypotheses involve complex interrelations among variables. Bivariate correlations only demonstrate that two variables share significant variance and, thus, do not permit the complete and simultaneous testing of all the relations of interest in mediational hypotheses.

Other studies examining the link between processing speed and higher-level cognitive functions in MS have employed simple manipulations. For example, Arnett (2004) investigated the influence of speed of presentation on the ability to recall information from a story memory test. Both college students and patients with MS were able to recall more elements from a story when it was read slowly compared with when it was read quickly, suggesting that processing speed influences the acquisition of information, or learning. In addition, Chiaravalloti et al. (2003) divided patients into high trial and low trial groups depending on the number of trials required to reach a learning criterion and reported that, after controlling for processing speed, the high trial group recalled the same amount of information at various delay intervals as the low trial group. However, this result was only in contrast to a trend toward significance between the MS high trial and MS low trial groups when processing speed was not accounted for. Furthermore, the composite score used to index processing speed was composed of tasks that all involve a substantial working memory confound. Thus, the authors' conclusion that deficits in processing speed are an important influence on learning and memory performance in MS was not well substantiated. Similar to bivariate correlations, simple manipulations also do not allow for all components of a mediational hypothesis to be addressed and are also insufficient to establish mediation (Demaree et al., 2008).

Demaree and colleagues (2008) also identified a third problem with the literature: the failure to examine other potential mediators of cognitive decline in patients with MS. The possibility exists that cognitive dysfunction in MS is a result of processing speed, executive functions, working memory, basic sensory or motor functions, co-morbid disorders, all of the above, or perhaps a common factor influencing each of these specific

functions (Demaree et al., 2008). However the research described thus far has not explored complex inter-relations amongst factors that could potentially affect cognitive performance. Diamond et al. (2008) represent an exception; the influence of fatigue and depression on the relation between processing speed and cognition was also investigated in that study. Partial correlations were computed to determine the influence of depression and fatigue on the associations found between processing speed and immediate memory, both verbal and visual learning and memory, and verbal fluency. When depression and fatigue were controlled statistically, the associations between processing speed and both immediate memory and verbal fluency were reduced. These findings suggest that depression and fatigue may influence the association between processing speed and cognition. However, as noted above, because a modification of the PASAT was employed to index processing speed, this relation may not be due to processing speed at all. Nonetheless, it is possible that depression and fatigue may affect cognitive functioning and also influence relations between any individual cognitive functions. Therefore, the potential influence of these factors should be investigated.

In addition to the concerns raised by Demaree et al. (2008), I observed that all of the studies described above have included mixed-course MS samples. A mixed-course sample is composed of patients diagnosed with various subtypes of MS as opposed to a sample consisting of MS patients who are all diagnosed with the same subtype of the disease (see page 39 for a discussion on the differences among the subtypes.) Several studies that have compared cognitive functioning across the three disease sub-types have found significant differences on various cognitive measures suggesting that the type or degree of impairment may depend on disease course (Amato et al., 2010). Therefore,

results from research on processing speed and cognition in MS that currently exist could potentially be attributable to the cognitive status of one or more disease types versus another, but the investigations that have been conducted do not allow for this discrimination to be made.

The Present Study

As indicated above, one goal of the present study was to address past methodological flaws. The ways in which the present study attempted to address these issues will now be discussed in turn beginning with the issue of operational confounds.

Operationalization of Processing Speed

The present study sought to overcome operational confounds in three ways: (1) by employing measures of information processing speed with a theoretical basis, (2) by employing multiple measures of processing speed as opposed to relying on a single measure, and (3) by implementing a statistical technique that emphasizes shared or common variance among the measures of processing speed.

Before I explain how the processing speed measures employed in the current study benefit from a relatively greater theoretical basis than others commonly used in neuropsychological research, I will begin with a discussion of the theoretical conceptualization of processing speed.

Although there has been strong interest in measuring processing speed and relating it to other mental abilities, there is no one solid theoretical framework providing a clear definition of the construct and an explanation of how processing speed is linked to higher-order cognitive functions that has been universally accepted or applied. Information processing speed has been the focus of an immense number of recent

neuropsychological investigations but still few researchers have included a definition or description of the psychological construct under study. To emphasize this point, I refer to a question posed by DeLuca in his 2008 text, "Information Processing Speed in Clinical Populations", where he asks "Even with the renewed interest in studying information processing speed during the last 30 years, why is it that today we still do not have an accepted working model of human information processing that is integrated into larger theories of cognitive operations of the brain?" (p. 265). He continues by noting that "In reality, clinical and cognitive science today lack an integrative model of perhaps one of the most elemental yet essential workings of the human mind; the speed with which mental operations is conducted." (DeLuca, 2008, p. 265). The lack of a clear theoretical definition may have occurred because of the nature of the construct alluded to in DeLuca's statement; information processing speed is both ubiquitous and superficially simple, and yet complex. It is a basic, fundamental characteristic of the human information processing system and, as such, is an active component of all cognitive processes and is thus involved to some extent in all cognitive tasks. To frame the present research, I will propose a working definition of processing speed that is based on Salthouse's theoretical discussions of the concept.

Salthouse's concept of a limited processing resource. Salthouse has used the notion of mental capacity to explain the nature of reduced processing speed in cognitive aging (e.g., Salthouse, 1985). He explains that the information-processing approach has always been concerned with identifying factors that limit an individual's performance and provides examples of results that support the idea of a general, finite processing resource. The first example he noted was that performance tends to deteriorate as tasks

increase in complexity even though no change in the identity or sequence of components may be apparent between tasks. Second, performance on one or both tasks decreases when performed simultaneously as compared to when performed alone, regardless of the similarity of the two tasks. This is known as the dual-task phenomena and a possible interpretation of such results is that the limited common resource is necessary for successful completion of both tasks and performance on one or both tasks is weakened to the degree that the resource was unavailable (Salthouse, 1985).

The most common proposals as to the nature of the limiting resource have been space, in the form of a limited working memory capacity; energy, in the form of attentional/concentration capacity; and time, in the form of basic operation time or processing rate (Salthouse, 1985). The resource of time is the most novel of the three in the information processing literature, although processing speed has received strong interest in the area of psychometric intelligence for some time (Jensen, 2006). Kail and Salthouse (1994) argued that the maximum rate that elementary cognitive operations are executed can be considered a processing resource -- the faster processing is performed, the better the cognitive performance. Furthermore, people vary in the speed with which processing operations can be executed. Finally, the advantages of fast processing are: (1) more operations can be performed in a given amount of time and (2) later operations can be carried out before the products of earlier operations have decayed (Salthouse, 1985). Thus, processing speed was conceptualized as the rate at which elementary cognitive operations are executed and was considered to represent a processing resource with the potential to influence general cognitive functioning in the present study.

Neurophysiological characterization of processing speed. The speed of information processing is not considered to be the same as nerve conduction velocity. Instead, it is defined as the speed at which elementary cognitive operations can be carried out (Salthouse, 1996). However, nerve conduction velocity undoubtedly influences the rate of information processing because the operation of the central nervous system is based on the transfer of neural signals. Indeed, processing speed has been associated with decreased nerve conduction velocities identified with the use of neuroelectrophysiological techniques [e.g., event-related potentials (ERPs)], as well as with decreased neurotransmitter activity (e.g., diminished cholinergic function, fewer receptor sites for dopamine, altered glutamate activity), lowered white matter integrity, and diminished glucose metabolism (DeLuca, 2008). Thus, various potential mechanisms of information processing rate have been suggested but none adequately accounts for the variance in processing speed (DeLuca, 2008). Processing speed does not appear to be associated with particular regional or functional brain systems but, instead, is a characteristic of many such systems (Dickinson & Gold, 2008). Given the general nature of the construct, it is not surprising that it is a sensitive marker for many developmental and clinical disorders. Also, it appears to be particularly sensitive for those conditions associated with diffuse damage to or effects on the brain such as aging, closed head injury, schizophrenia, and MS. However, reduced processing speed has also been indicated for depression, Parkinson's disease, and learning disabilities. For MS, as well as other conditions resulting in diffuse damage and slowed processing speed, it has been proposed that such damage may result in functional disconnections of regional brain systems in addition to slowed transmission of information.

Another aspect of processing speed that has been related to neuronal underpinnings is the developmental differences in the rate at which information can be processed. Overall, processing speed has been found to improve substantially over the course of development in childhood and adolescence[2] (Cerella & Hale, 1994; Kail, 1991a) and the pattern of change appears to be non-linear based on the observation that reaction time declines rapidly during childhood and continues to decline, but much more slowly, during adolescence (e.g., Kail, 1991b). Kail (2008) has used the analogy of the central processing unit (CPU) of a personal computer to explain developmental-related differences in information processing speed. He posits that the operating speed of a CPU is fixed and that differences in processing rates between different CPUs are due to lower level properties, specifically, differences in circuitry between different CPUs. Similar to how operating rates of CPUs are dictated by their circuitry, Kail (2008) links developmental differences in processing speed to neuronal functioning. Important neural changes occur concurrently with substantial changes in processing speed during childhood and adolescence, including changes in the number of transient connections in the central nervous system and increases in myelinisation (Kail, 2008). Research using diffusion tensor imaging has linked white matter change to more rapid processing, for example, a study comparing speed of visual search between six- and 17-year olds reported age-related changes in speed were associated with increases in parietal white matter (e.g., Mabbott, Laughlin, Noseworthy, Rockel, & Bouffet, 2005). However, Kail

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[2] Effects of experience and practice do not sufficiently account for age-related differences in information processing speed (Kail, 2008).

(2008) noted that literature linking processing speed to neuronal development is scarce and that the little evidence that does exist is often indirect and speculative.

In sum, biological factors appear to be determinants of the rate at which information can be processed but, because relevant research is extremely limited at this time, it would be premature to surmise what biological factors are important and how they are important.

Operational definitions of processing speed. Salthouse (2000) noted that the measure of choice for processing speed in experimental contexts typically depends on the research tradition of the investigator. One measure is decision speed, or the time to respond to moderately complex material that will produce errors for some participants even in the absence of time limits. Another is perceptual speed, which is considered to be the time to respond to simple content that is not expected to produce errors in the absence of time limits (Salthouse, 2000). Examples of perceptual speed measures are search and substitution tasks. Psychomotor speed measures, typically involving simple tasks such as finger tapping or marking lines in specific locations on a paper, have also been used. Another form of processing speed measure is the psychophysical speed task, which commonly takes the form of decision accuracy for briefly presented visual or auditory stimuli (e.g., inspection time). Additionally, the time course of internal responses has been investigated, for example, by measuring the latency of a particular component of the event-related potential (ERP). Thus, many different measures have been used to index processing speed in research.

Various clinical measures have also been developed to assess processing speed, such as the PASAT described in the discussion of research addressing the *Relative*

Consequence Model in MS. Other examples of clinical measures are the Digit Symbol-Coding subtest from the Wechsler scales and the Symbol Digit Modalities Test (Smith, 1991). Both of these have been used with a variety of clinical populations. For the Digit Symbol-Coding task, examinees are presented with nine digit-symbol mappings and test items present the digits only so examinees must fill in the symbol that corresponds to each digit. The total number of correct symbols produced at the end of two minutes is recorded. As with the Digit Symbol-Coding task, the Symbol Digit Modalities Test presents nine digit-symbol mappings. However, participants are required to provide the digit associated with the given symbols on test items either orally or graphically. The total number of correct digits produced at the end of ninety seconds is recorded. Another clinical measure of processing speed is the Trail Making Test (Reitan, 1958). This measure is composed of two conditions, for Trails A participants are instructed to connect twenty-five numbered circles in numeric order. The circles are distributed in random fashion across a page. Trails B is similar to Trails A, but the circles contain either numbers or letters. Participants are instructed to connect the circles by alternating between numbers and letters; that is, 1-A-2-B, etc. Time to complete each condition is recorded.

Of all the variables employed to index processing speed, classical reaction time procedures appear to be the most popular. Reaction time can be generally defined as the amount of time between a stimulus and a response and can involve various modalities, such as visual or auditory stimuli, and various methods of responding, such as a key press or verbalization (Martin & Bush, 2008). Reaction time tasks can also vary in complexity. Those involving a single stimulus and single response are classified as simple reaction

time, whereas those for which certain stimuli are to be responded to but other stimuli should be ignored are classified as recognition or go-no-go reaction time. Tasks requiring the subject to respond in one way for certain stimuli and in another way for different stimuli are termed choice reaction time.

It is important to keep in mind that all of these tasks are influenced by a variety of cognitive factors, not just processing speed. Because of this complexity, they will vary in their effectiveness at measuring the rate at which information can be processed. Therefore, researchers should use multiple measures of processing speed and take into account other possible determinants of performance.

How processing speed was measured in the present study. In the present study, processing speed was assessed using scores from three reaction time tests that comprise a computerized measure of information processing, the Computerized Test of Information Processing (Tombaugh & Rees, 2008). The three tests include a simple reaction time test, a choice reaction test, and a semantic search reaction time test[3]. The amount of information to be processed, or the cognitive load, progressively increases across the three tests. Salthouse (1996), an authority on processing speed and cognition in aging, states:

> The tasks used to assess processing speed should be relatively simple, such that most of the individual differences in performance are attributable to how quickly one can carry out the relevant operations rather than to variations in

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[3] See page 51 for descriptions of the Computerized Test of Information Processing reaction time tests.

> amount of knowledge or in other cognitive abilities [...] However, the speed measure should not merely represent input and output processes or sensory and motor processes, or else they may not reflect the duration of relevant cognitive operations (p. 407).

The Computerized Test of Information Processing tests meet these criteria well. The tasks were designed such that they would be easy enough that most individuals could do very well on them in terms of accuracy and such that individual differences in variables such as intelligence, education, and knowledge would not influence performance. The words used as stimuli in the choice and semantic search tasks were chosen for their simplicity and general familiarity. The presentation of stimuli and the response requirements were also designed to be as simple as possible so that interpretation or strategic planning would not influence performance. The fact that examinees, whether they are healthy participants or patients diagnosed with such neurological disorders as traumatic brain injury or MS, consistently achieve perfect or near-perfect accuracy on the tests is evidence that these intentions were successfully achieved (Reicker et al., 2007; Tombaugh, Rees, Stormer, Harrison, & Smith, 2007). However, the CTIP is not so simplistic that it only taps into peripheral processing; instead, it is assumed that cognitive processing is indexed to greater degrees across the three tests. Additionally, unlike the PASAT, practice effects have not been observed with the Computerized Test of Information Processing, it is not anxiety provoking, nor is performance affected by mathematical ability (Baird, 2004; Royan, Tombaugh, Rees, & Francis, 2004; Tombaugh et al., 2007). Taken together, the Computerized Test of

Information Processing was judged to provide a valid and reliable measure of information processing speed.

Minimizing operational confounds through statistical techniques. As noted at the beginning of the section on operational confounds, in addition to employing a more theoretically appropriate measure of processing speed, the present study also sought to minimize operational confounds through the use of a statistical approach known as structural equation modeling to test the relations of interest. This technique offers the advantage of reducing concerns about construct validity because latent processing speed and higher-order cognitive factors are identified using multiple distinct measures instead of one individual measure. This methodology helps to limit the influence of stimulus and response confounds, minimize the specific variance associated with single measures, and emphasize the common, construct-relevant variance (Demaree et al., 2008; Salthouse, 1996), therefore yielding more generalizable findings.

Inadequate statistical methods for testing mediation

Besides poor representation of the constructs under study, another methodological problem that Demaree et al. (2008) had identified as affecting research on the relation between processing speed and cognition was inadequate statistical methods for examining the mediator hypothesis. The majority of previous studies only employed simple bivariate correlations or manipulations deemed insufficient to establish mediation (Demaree et al., 2008). Thus, previous research did not establish whether processing speed deficits actually mediate dysfunction observed in other cognitive domains.

An additional benefit of using structural equation modeling is that it offers more advanced statistical methods for examining mediational hypotheses than other techniques. Other techniques can allow one to determine whether two different cognitive constructs share significant variance, and whether a diagnosis of MS accounts for incremental variance but they do not reveal whether one construct actually mediates cognitive decline. Structural equation models permit greater power of the inferences made regarding what variables mediate cognition and the strength of the mediation (Demaree et al., 2008). With mediational hypotheses, there is less interest in variables or constructs in isolation but more interest in interrelationships between variables and the effect of some variables on others. Tabachnick and Fidell (2007) note that when complex and multidimensional phenomena are of interest, structural equation modeling is the only analysis that allows complete and simultaneous tests of all the relationships. Thus, structural equation modeling allowed for empirical linkages between group membership (i.e., MS patients vs. controls) and potential mediating factors and between mediating factors and other cognitive constructs to be evaluated simultaneously.

Failure to examine other potential mediators

A third problem identified by Demaree and colleagues (2008) was that the available literature has failed to examine mediators of cognitive decline in patients with MS other than processing speed. They noted that research done thus far has not explored complex inter-relations amongst different factors that could potentially affect cognitive performance. The present study sought to examine three other factors that could possibly be contributing to cognitive decline in MS, specifically, working memory, depression, and fatigue. Each will be discussed in turn now.

Working Memory. Along with information processing speed, working memory is one of the most frequently documented areas of cognitive difficulty in individuals with MS (Lengenfelder et al., 2006). Working memory was investigated as a potential mediator in the present study because the majority of research that has been done to examine the link between processing speed and other cognitive functions has employed measures of processing speed that are confounded by working memory abilities (DeLuca et al., 2004). Thus, it is possible that the results of past work may have mistakenly been attributed to processing speed when they actually reflected working memory abilities.

Theoretical conceptualization of working memory. Working memory is the cognitive system that temporarily stores, processes, and manipulates information (Demaree et al., 2008). Working memory is responsible for handling the active maintenance of information in the face of ongoing processing and/or distraction (Conway et al., 2005). Baddeley and colleagues (Baddeley, 2002; Baddeley & Hitch, 1974) proposed a multiple component theory of working memory that identifies four major components – a central executive system, episodic buffer, phonological loop, and visuospatial sketchpad. Briefly, the central executive system is conceptualized as a domain-general, controlled attentional resource that is required to coordinate processing and maintenance (Baddeley & Hitch, 1974). The central executive is sub-served by the phonological loop and visuospatial sketchpad, which are conceptualized as domain-specific storage components or "slave systems" that maintain and temporarily store verbal and visual information (Baddeley, 2002). Finally, the episodic buffer represents a limited capacity storage system that is presumed to be domain-general and capable of combining information from the slave systems and information from long-term memory

and can bind, or integrate, this information into episodes or scenes (Baddeley, 2002). Thus, the episodic buffer allows for communication and integration between short- and long-term memory stores (Baddeley, 2000).

The relation between processing speed and working memory. Working memory is characterized as having a "capacity" that is based on the notion that the short-term stores composing the working memory system are limited. Processing speed has been hypothesized as a determinant of the capacity of working memory. Demaree et al. (2008) suggested that faster processing speeds are associated with better working memory ability because faster rehearsal will yield improved creation and maintenance of working memory stores. In this view, the functions of working memory and processing speed are inherently entangled and each influences the performance of the other (Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994a).

The developmental literature provides evidence for the relation between processing speed and working memory. A number of studies that have examined age-related differences in both constructs support the idea that age-related change in processing speed influences working memory (e.g., Chuah & Mayberry, 1999; Hitch, Halliday, & Littler, 1989; Kail, 1992, 1997a, 1997b; Kail & Hall, 2001; Kail & Park, 1994). For the most part this influence appears to be indirect, for example with faster processing speeds enabling more rapid execution of processes that refresh information in the slave systems of working memory (Kail, 2008). However, it should be noted that more rapid refreshing of information allowed by improved processing speed is not the only explanation of age-related change in working memory as other processes seem to be

important in the development of working memory as well. Still, increasing processing speed is clearly one contributor to more efficient working memory.

In an attempt to address the need to incorporate information processing speed into theoretical models of cognitive functioning, DeLuca (2008) proposed a new model of working memory, termed the *Working Memory-Processing Speed Model,* that extends Baddeley's (1986) popular model to incorporate the role of processing speed. The traditional model has been modified in two important ways. First, two mechanisms by which processing speed has been hypothesized to influence higher-order cognition have been added to the traditional model. They are (1) the limited time mechanism and (2) the simultaneity mechanism. Briefly, the limited time mechanism indicates that slower processing speed means that less processing can be completed in a given amount of time and the simultaneity mechanism indicates that slower processing can result in products from early processing being no longer available by the time later processing is completed (Salthouse, 1996). DeLuca (2008) stated "it is clear that these processing speed mechanisms can affect working memory accuracy, and may have a particular influence on the operation of the slave systems of working memory." (p. 268). The second modification of the traditional working memory model is the addition of the concept of complex processing speed (Chiaravalloti et al., 2003). Because evidence suggesting that complex processing speed influences higher order cognitive processes (Chiaravalloti et al., 2003) has been found, DeLuca hypothesizes that the central executive of Baddeley`s model would be particularly influenced by complex processing speed (see Figure 2 for a diagram representing the *Working Memory-Processing Speed Model*).

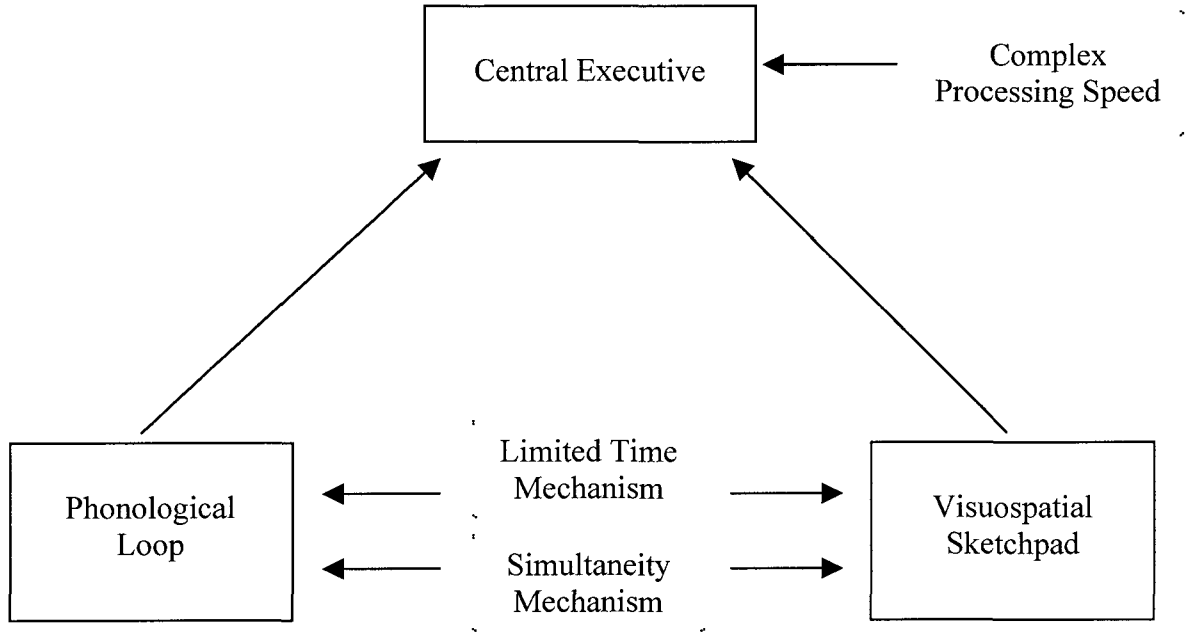

Figure 2. The *Working Memory – Processing Speed Model* Adapted from DeLuca (2008).

Although it is clear from the above accounts that processing speed and working memory are related, in these models they do not represent the same function but instead are considered to be separate processes. This separation is supported by evidence from developmental research that has found these abilities develop independently and come to maturation at different periods of time in adolescence (Martin & Bush, 2008).

One theory that has combined both conceptual ideas that processing speed is linked with working memory abilities and that processing speed can influence the execution of higher-order cognitive functions is the *Developmental Cascade Model* developed by Fry and Hale (1996). Fry and Hale (1996) noted that, as children mature, their information processing becomes faster, they are able to hold more items in working memory, and they perform better on tests of fluid intelligence. Their observation of the co-occurrence of these changes led Fry and Hale (1996) to propose the *Developmental Cascade Model*. The model attempts to delineate the relations among these changes; it proposes that increases in children's information processing speed lead to improvements in working memory which, in turn, yield increased fluid intelligence (Fry & Hale, 1996). To evaluate this model, 214 individuals aged seven to 19 years were administered multiple processing speed tasks, multiple working memory tasks, and an untimed measure of fluid intelligence (Raven's Standard Progressive Matrices; Court & Raven, 1982). Using structural equation modeling, Fry and Hale (1996) showed that almost half of the age-related increase in fluid intelligence was mediated by developmental changes in processing speed and working memory and, furthermore, nearly three quarters of the improvement in working memory was mediated by developmental changes in processing speed. Thus, their findings supported the theory of a developmental cascade. In addition,

Fry and Hale (1996) statistically controlled for age-related differences in speed, working memory, and fluid intelligence in order to investigate whether a similar cascade might affect individual differences (as opposed to age-related differences) in cognition. Results showed that individual differences in speed had a direct effect on working memory capacity which, in turn, was a direct determinant of individual differences in fluid intelligence.

Besides fluid intelligence, developmental related improvements in processing speed and working memory have been associated with improved accuracy on arithmetic word problems as well (Kail & Hall, 1999). Further support for the *Developmental Cascade Model* is provided by Kail (2006), which included longitudinal as well as cross-sectional data. Two measures of processing speed, two measures of working memory, and Raven's Standard Progressive Matrices were administered to 185 children ranging in age from eight to 13 years old and testing was repeated one year later (with 160 children completing the tests at follow-up). The cascade model was evaluated using structural equation modeling and the results replicated the findings of Fry and Hale (1996), that is, developmental change in processing speed was linked to greater working memory capacity which was associated with better performance on Raven's Standard Progressive Matrices at both baseline and follow-up. In summary, there is a precedent outside of the MS literature for the ideas that processing speed is linked with working memory abilities and that processing speed and working memory can influence the execution of higher-order cognitive functions.

Working memory in MS. Working memory impairment is common in MS (Lengenfelder et al., 2006) and dysfunction has been reported at the level of different

components of this system. 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. Researchers have found that MS patients demonstrate a larger word length effect than controls (Litvan et al., 1988a, 1988b; Rao et al., 1993). Because the word length effect is thought to reflect the articulatory rehearsal process (i.e., longer words receive fewer rehearsals than shorter words), the results were interpreted as evidence for a deficit 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 et al., 1994a; Grigsby, Busenbark, Kravcisin, Kennedy, & Taylor, 1994b). 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 et al. (1996) found that when compared with non-clinical controls, patients with MS demonstrated difficulty performing dual tasks. 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 et al., 1994a, b).

A few studies point to central executive dysfunction as the primary working memory impairment in MS. For instance, Lengenfelder et al. (2003) has attempted to determine the specific components of working memory affected in MS by examining performance on tasks that were presumed to involve different components. The authors stated that the n-back task primarily requires maintenance and storage of information within the phonological loop and that central executive involvement is minimal for the 0- and 1-back conditions but increases in later conditions. On the other hand, the PASAT was identified to not only require maintenance and rehearsal of information within the phonological loop but to also substantially tax the central executive because information must be manipulated. Overall, the MS sample performed significantly worse than controls on the PASAT but not on the n-back. Lengenfelder et al. suggested the PASAT is essentially a 1-back task because participants must maintain a number one place back in the presentation of stimuli. Because MS patients performed comparably to controls on the 1-back version of the n-back task but worse than controls on the PASAT, the authors concluded that the phonological loop remains intact but that the central executive is impaired in MS. However, PASAT performance is influenced by other factors besides central executive functioning that likely do not apply to the n-back task, such as mathematical ability and anxiety (Tombaugh, 2006). Because more differences exist between these two measures than central executive involvement alone, the results just discussed do not provide definitive evidence. However, Lengenfelder et al. bolstered their argument that central executive dysfunction is the primary working memory impairment

in MS based on the results of comparisons between MS participants classified as cognitively impaired or not. The cognitively impaired patients performed comparably to unimpaired patients on the 0- and 1-back conditions of the n-back task but they produced fewer correct responses on the 2-back condition. The authors attributed the significant difference on the 2-back condition to the increased central executive involvement required in this condition. Parmenter, Shucard, and Shucard (2007a) have also reported that MS patients performed worse than controls on the 2-back condition of an n-back task, but not on the 0- and 1-back conditions.

In addition, Arnett et al. (1999) provided support for central executive dysfunction as the primary working memory impairment in MS based on the pattern of results found on simple and complex span tasks. Simple span tasks, such as digit span, measure short-term memory capacity and are thought to only tax the storage components of working memory. In contrast, complex span tasks, like reading span, require both the storage and processing functions of working memory and, thus, will tax the central executive in addition to one of the domain-specific storage components. Arnett et al. found that depressed MS patients performed worse than non-clinical controls on a reading span task. The difference between non-depressed MS patients and controls was also substantial (controls produced an average of five more correct responses) and, although the difference only approached significance, the power was low for that comparison. In contrast, simple span scores did not differ between any of the groups. Scores from other tests measuring interference and rate of forgetting did not differ between the groups and were not correlated with reading span scores, ruling out these factors as possible explanations for the worse reading span performance of MS patients.

The results suggest that the phonological loop is not affected but that central executive functioning is deficient in MS.

In sum, working memory impairment is common in MS, with deficits observed at the level of the phonological loop and central executive. Furthermore, there is evidence to suggest that central executive dysfunction is the primary working memory impairment in MS.

Taken together, the research presented above establishes that working memory is commonly affected in MS, that a relation exists between processing speed and working memory, and that past research examining the link between processing speed and other cognitive domains in MS typically used measures confounded by working memory ability. Therefore, it was important to evaluate the potential for working memory to act as a mediator of cognitive decline in MS in the present study.

Dependent Variables: Learning and Executive Functioning. The conceptualization of processing speed and working memory and their relation to cognitive functioning in MS have already been discussed. These topics will now be addressed for the dependent variables of learning and executive functioning included in the present study. Memory, the most intensely studied cognitive function in individuals with MS, has been found to be consistently impaired (Chiravalloti & DeLuca, 2008). Over the years, disagreement existed whether difficulties with learning (i.e., the encoding or acquisition of new information) or delayed recall (i.e., retrieval of previously learned information from long-term storage) represented the primary memory impairment in MS. However when learning-to-criterion procedures have been employed, MS patients require more exposures to learn the items than controls but, subsequently, do not differ from

controls in terms of delayed recall and recognition of the items (DeLuca et al., 1994; 1998). Thus, it appears that retrieval and recall remain intact whereas a deficit in the acquisition of information is responsible for memory dysfunction in MS. Because learning is frequently impaired in patients with MS, this construct was judged to be an important dependent variable to include when evaluating the abilities of processing speed and working memory to mediate dysfunction in other cognitive constructs.

A recent review of theoretical conceptualizations and assessment instruments appropriately described "executive functions" as an umbrella term that can refer to a variety of cognitive processes such as reasoning, problem-solving, planning, sequencing, resistance to interference, utilization of feedback, multitasking, and cognitive flexibility (Chan, Shum, Toulopoulou, & Chen, 2008). Indeed the category of executive functions includes an assortment of very different cognitive processes; however, the seemingly random combination has been justified in the sense they can be encompassed within a common theme. All of these abilities are considered to be higher-order cognitive functions, likely representing the highest point of cognitive development in both the individual and evolutionary sense, and they make it possible for us to formulate goals and plans, maintain these goals over time, choose and initiate actions to achieve these goals, and monitor and adjust our behaviour accordingly (Aron, 2008). Thus, executive functioning has been conceptualized as a series of abilities that are implemented to achieve a goal (Chan et al., 2008).

In terms of executive functioning in MS, deficits in concept formation, abstract reasoning, planning, cognitive flexibility, problem solving, and verbal fluency have been reported (Arnett et al., 1999; Brassington & Marsh; 1998; Beatty & Monson, 1996;

Drew, Tippett, Starkey, & Isler, 2008; Foong, et al., 1997; 1999; McIntosh-Michaelis et al., 1991; Nagy et al., 2006; Parmenter et al., 2007b; Rao, Hammeke, & Speech, 1987; Rao, 1990; Santiago et al., 2007; Zakzanis, 2000). Because executive functioning is also frequently impaired in patients with MS, this construct was also included as a dependent variable in the models evaluating the ability of processing speed and working memory to mediate dysfunction in other cognitive constructs. The executive functioning factor in the present study was represented with scores from tasks involving concept formation and cognitive flexibility, and verbal fluency[4]. Regarding verbal fluency, performances on such tests are thought to require a systematic search through semantic memory, which is directed by some component(s) of the executive system. Therefore, poor performance on fluency tasks are considered to index executive functioning and not just language.

Depression and Fatigue. In addition to working memory, the potential contributions of depression and fatigue were also examined in the present study. Depression is common in MS with up to 60% of patients having the disorder (Minden & Schiffer, 1991) and, in the general population, depression has been associated with cognitive decline (Christensen, Griffiths, MacKinnon, & Jacomb, 1997). Although previous studies addressing depression and cognitive functioning in MS have yielded inconsistent results, a review of the literature concluded that when studies are adequately powered and include a representative MS sample, there is evidence for a relation between

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[4] A measure of planning and problem solving was also intended to be included with the executive functioning factor but because the scores from this task did not correlate with the other measures, it could not be included in the structural equation models.

depression and cognitive functioning (Arnett, Barwick, & Beeney, 2008). Fatigue is a debilitating symptom experienced by most people diagnosed with MS; however, it has rarely been addressed in previous studies of cognitive functioning. Chiaravalloti and DeLuca (2008) state that fatigue is likely a contributing factor to cognitive performance, particularly when tasks involve attentional demands. Because of the above, it was deemed important to assess the contributions of depression and fatigue to cognitive functioning in the present sample of patients with MS.

Mixed-Course Samples

In addition to the concerns raised by Demaree et al. (2008), I also observed that all of the studies described addressing the relationship between processing speed and other cognitive domains included mixed-course MS samples. This focus is problematic because there is evidence of differences in cognitive functioning across the three disease sub-types of relapsing-remitting, secondary-progressive, and primary-progressive MS. Because the type or degree of cognitive impairment may depend on disease course, it cannot be determined whether the results from past research on processing speed and cognition in MS could potentially be attributable to the cognitive status of one or more disease types versus another. Before describing the findings related to cognitive functioning between these groups, I will present a general overview of the sub-types of MS.

Sub-types of MS. Although most patients experience various combinations of symptoms, three distinct patterns of disease course have been categorized: relapsing-remitting, secondary-progressive, and primary-progressive. The relapsing-remitting 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 partial or full recovery may occur 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 relapsing-remitting MS fails to exhibit a period of stability the diagnosis is changed to secondary-progressive MS. Patients with this form of the disease may have relapses but symptoms progressively increase between relapses. Fifty percent of relapsing-remitting patients will be re-diagnosed as secondary-progressive (Lublin & Reingold, 1996). Primary-progressive 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 primary progressive subtype occurs in 15% of patients (Lublin & Reingold, 1996).

Differences in cognitive functioning between disease sub-types. Cognitive impairment has been reported in all disease sub-types, although it appears to be more severe in secondary-progressive MS (Amato et al., 2010). In terms of patterns of impairment across the sub-types, relapsing-remitting and secondary-progressive patients have been found to have worse spatial working memory and semantic fluency compared with primary-progressive patients (Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006). In addition, relapsing-remitting patients have been reported to be less impaired compared with secondary-progressive patients on the Symbol Digit Modalities Test (Huijbregts et al., 2006; Potagas et al., 2008) and the PASAT (Huijbregts et al., 2006), suggesting a worsening of processing speed and/or working memory ability with

disease progression. De Sonneville et al. (2002) found that the degree of general cognitive slowing was worse for secondary- and primary-progressive patients relative to relapsing-remitting patients. In addition, patients diagnosed with progressive forms of the disease have shown more difficulties with verbal learning relative to relapsing-remitting patients and relapsing-remitting and secondary-progressive patients have shown more difficulties with visuo-spatial learning relative to primary-progressive patients (Gaudino, Donofrio, DeLuca, & Diamond, 2001). Two studies have reported impaired visuo-spatial working memory for secondary-progressive relative to primary-progressive patients (Foong et al., 2000; Comi et al., 1995).

Thus, because cognitive dysfunction appears to differ in the degree and the nature of deficits across the different disease sub-types, only patients with relapsing-remitting MS, the most common form of the disease, were included in the present study in an attempt to provide a better understanding of cognition in this sub-type specifically.

Summary

In the present study I intended to investigate the relations between information processing speed and other cognitive abilities in patients with MS while avoiding the methodological flaws affecting previous work, specifically, operational confounds of the processing speed measure, inadequate statistical techniques to test meditation, the failure to examine other potential mediators, and the use of mixed-course samples. Working memory was identified as an especially important potential mediator to investigate because working memory deficits are common in MS and previous work has typically employed processing speed measures specifically confounded by working memory ability. In addition, because depression and fatigue are both common symptoms of MS

with the potential to contribute to cognitive dysfunction, it was deemed important to examine these factors as well. Finally, because the degree and nature of cognitive deficits appear to differ between disease sub-types, relapsing-remitting MS was chosen as the focus of the present study in order to allow for a more clear interpretation of results.

Hypothesis 1 – The *Relative Consequence Model*

Two hypotheses regarding the relations among MS, processing speed, working memory, and other functions commonly impaired in MS were tested. First, to determine if processing speed functions as a mediator between the effects of MS and measures of cognitive functioning, a structural equation model including linkages between (1) the presence of MS (i.e., group) and processing speed, (2) between processing speed and cognitive functions frequently impaired in patients with MS (working memory, learning, and executive functioning), and (3) between the presence of MS and the cognitive functions was evaluated. See Figure 3 for the structural model that was proposed to test hypothesis 1 (Relative Consequence structural model). Absence of a line connecting variables indicates that no relation was tested between those variables.

If cognitive deficits are not a direct result of disease pathology, but instead are a by-product of reduced processing speed, it was expected that the tests of the indirect effects of group membership on the cognitive domains would be significant. Furthermore, the direct effects of group membership on variables representing the cognitive domains were expected to be either non-significant or substantially smaller than the total effects on those variables because the total effects include both direct effects and the effects mediated through processing speed. Such results would be consistent with the hypothesis that processing speed may be mediating some of the MS-related effects on

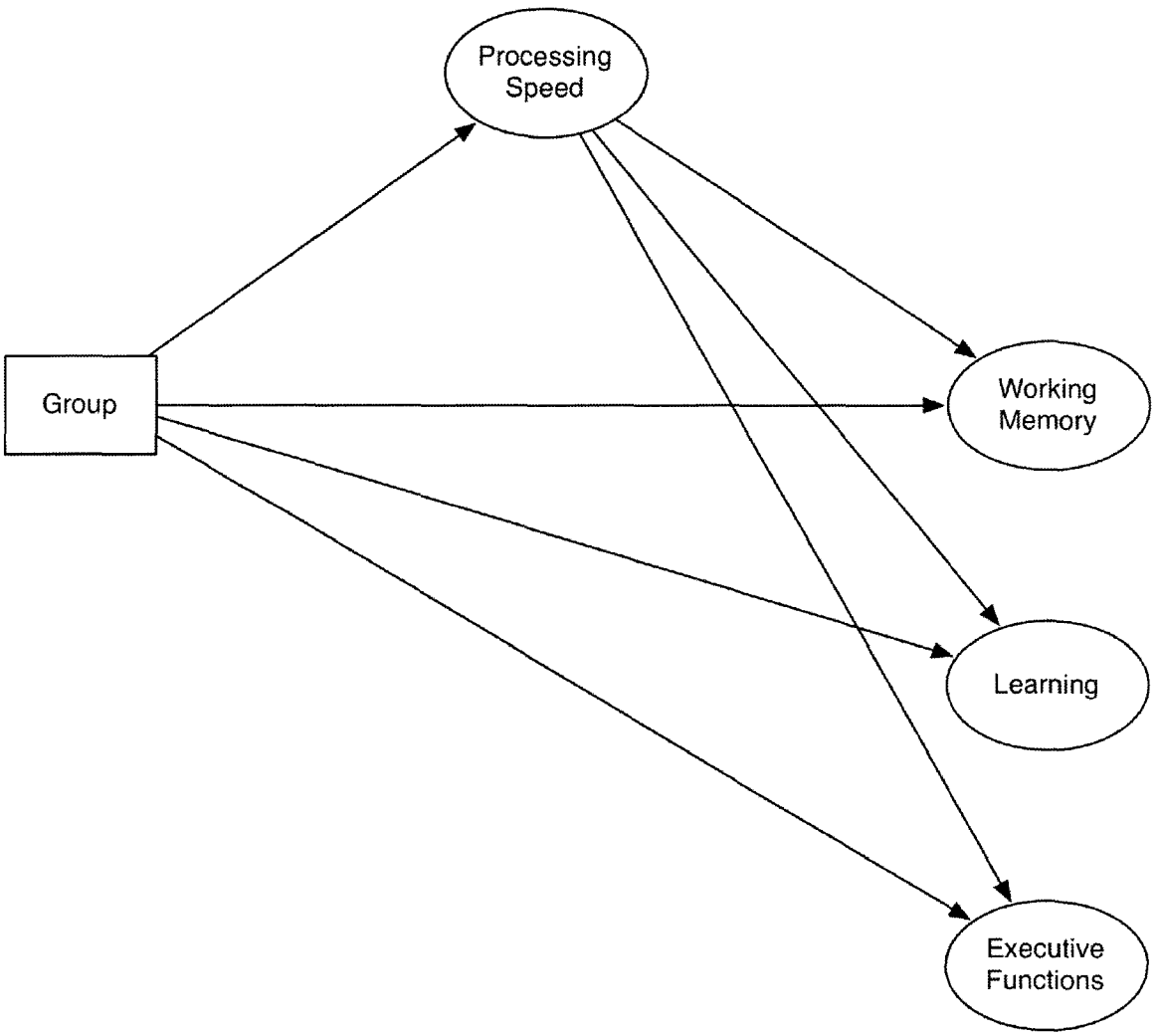

Figure 3. Hypothesis One – The *Relative Consequence Model.*

other aspects of cognitive functioning. However, a finding that the indirect effects are not significant and the direct MS-related effects are not substantially smaller than the total MS-related effects would be inconsistent with the hypothesis that processing speed is an important contributor to differences in cognitive functioning between patients with MS and controls.

Hypothesis 2 – The Mediating Role of Working Memory

To determine if working memory mediates cognitive dysfunction in MS, a second structural equation model including linkages between (1) the effects of MS and working memory, (2) between working memory and cognitive functions frequently impaired in patients with MS (processing speed, learning, and executive functioning), and (3) between the effects of MS and the cognitive functions was evaluated. As shown in Figure 4, if working memory contributes to cognitive dysfunction in MS, than similar results as those originally hypothesized for the previous model were also expected for this model.

Hypothesis 3 – Controlling for Depression and Fatigue

In order to account for possible effects of depression and fatigue on the cognitive functions for patients with MS, the structural equation models from Hypotheses 1 and 2 were modified to include observed depression and fatigue covariates. Paths linking the depression and fatigue variables to all cognitive factors were included. With these paths included in the models, the relations investigated in the previous two structural models were once again assessed but this time the possible effects of depression and fatigue on the relations were controlled for. If depression and fatigue do contribute to cognitive dysfunction in MS then the pathways between these variables and the cognitive factors were expected to be significant and the path coefficients representing the relations

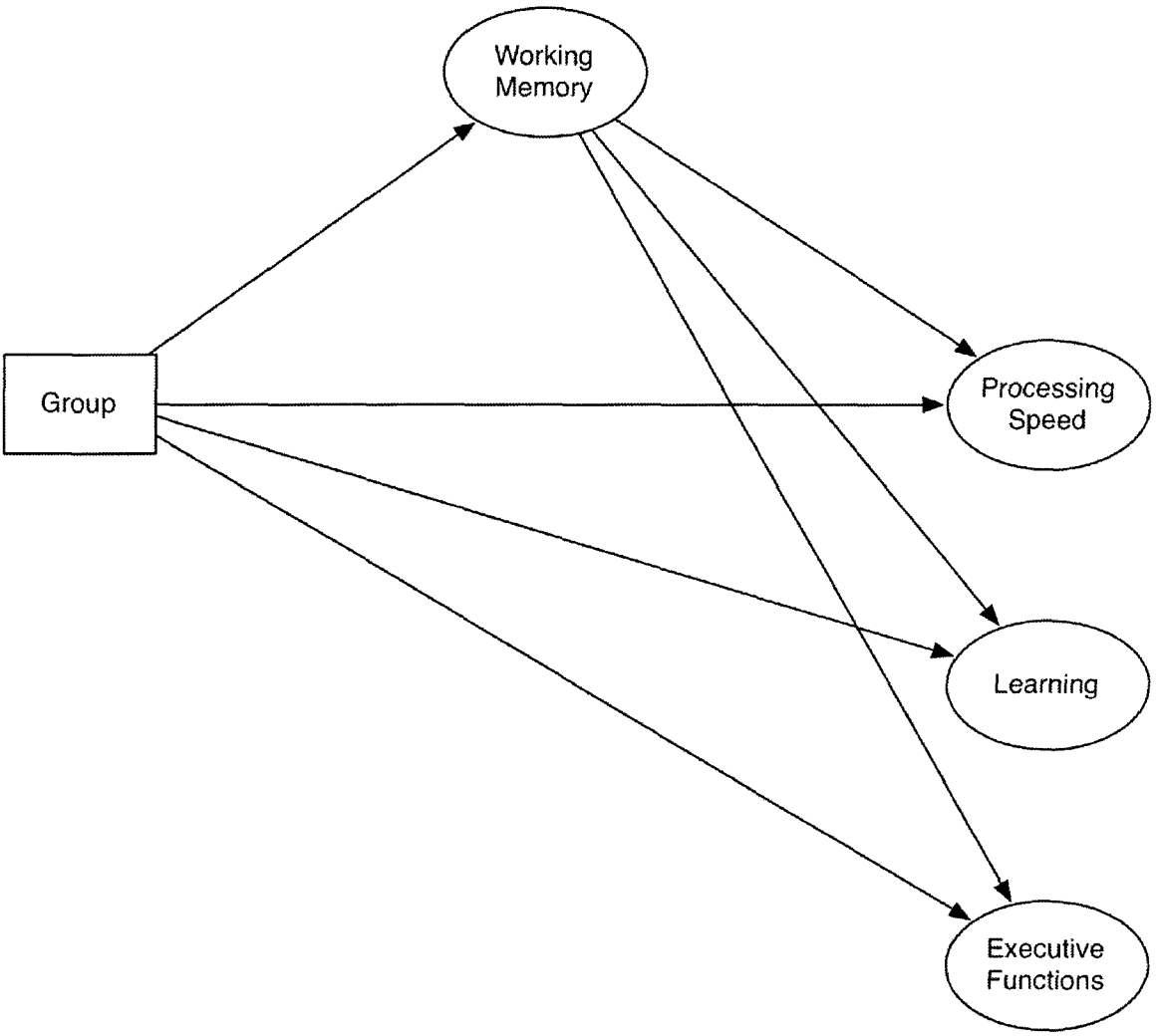

Figure 4. Hypothesis Two – Mediating Role of Working Memory.

between MS and the cognitive constructs were expected to be altered.

Hypothesis 4 – The Contributions of Different Cognitive Functions to Multifactorial Measures

The 3s PASAT and the Symbol Digit Modalities Test are frequently used to assess cognitive functioning in MS. Both tests were administered in the present study. However, they were not included in the structural models because there is no strong theoretical basis upon which they could be ascribed to a specific cognitive factor. For instance, in the neuropsychological literature, the PASAT is sometimes referred to as a measure of processing speed, sometimes as a measure of working memory, and sometimes as both. Originally, Gronwall and Sampson (1974) assumed that the PASAT measured speed of information processing. More recently, however, the PASAT has been conceptualized as multifactorial, requiring sustained attention, working memory, and the simultaneous performance of several other cognitive functions under specific time constraints (Cicerone, 1997; Madigan et al., 2000; Tombaugh, 2006). Thus, any attempt to attribute performance on the PASAT to a single cognitive process, such as speed of information processing, is unwarranted. Similarly, the Symbol Digit Modalities Test has also been suggested to involve processing speed and working memory resources but incidental learning is acknowledged to occur during performance as well (Benedict et al., 2006; Drake et al., 2010; Forn et al., 2011; Lezak, 2004). Thus, although the PASAT and the Symbol Digit Modalities Test were not included in the structural equation models, I used the wealth of measures collected in the present study as an opportunity to evaluate the contributions of different factors to performance on these ubiquitous measures. Specifically, it was hypothesized that processing speed and working memory would

contribute to performance on both the PASAT and Symbol Digit Modalities Test, with learning additionally contributing to Symbol Digit Modalities Test performance.

CHAPTER 2: METHODS

The present study is associated with a larger, longitudinal investigation of cognitive decline in MS that has two goals: (a) examination of the relative ability of several tests of processing speed to detect cognitive impairment in relapsing-remitting MS and (b) evaluation of the effectiveness of the tests to monitor change in cognitive status over three years. The data for the present study is a portion of the baseline data from the larger, longitudinal study. Because a large number of measures were administered as part of the battery for the longitudinal study and because MS patients experience difficulties with fatigue, data were collected in two sessions spaced approximately one week apart.

Participants

Seventy adults with a diagnosis of clinically definite MS of the relapsing-remitting type were recruited from the MS Clinic of the Ottawa Hospital. Patients were informed by clinic staff (i.e., physician or nurse) that a research study was underway and asked if they would be interested in participating. Those patients who responded that they were interested were asked to sign a recruitment form (see Appendix B) indicating that they gave permission to be contacted directly so that the study could be described more fully and an investigator could request their participation. Individuals with a history of any neurological disease or injury other than MS, drug or alcohol abuse, or psychiatric disorders other than depression were excluded from participating in the study. Documentation of diagnosis, disease subtype, Expanded Disability Status Scale (EDSS) score, and disease duration were obtained.

Seventy-two non-clinical control volunteers were recruited through family members and friends of participants with MS, social groups, places of employment, university classes, advertisements, and word of mouth. Individuals with a history of any neurological disease, drug or alcohol abuse, or psychiatric disorders other than depression were excluded from study participation. Every attempt was made to match the MS and control groups on age, education, and sex. All MS and Control participants were required to read and sign an informed consent form (Appendix C) before participation commenced and complete a structured interview (Appendix D) designed to provide basic demographic and health information. Expenses related to parking were paid for all participants and those control volunteers recruited through university classes received course credit for participating in the study.

Materials

Demographic and Health Status Information

Visual acuity: *Rosenbaum Pocket Vision Screener.* This is a brief, standardized, hand-held eye chart that was used to determine if a participant's visual acuity is adequate to perform the tests. Small print characters presented during neuropsychological testing are similar to the characters presented at the 20/50-70 threshold when the Rosenbaum card is positioned 14 inches from the corrected eye. All participants were able to read the characters at the smallest indicated threshold.

Pre-morbid intellectual functioning: *The North American Adult Reading Test (Spreen & Strauss, 1991).* This measure is a reading test of 61 irregularly spelled words (printed in four columns on two sheets of paper) that participants are asked to read aloud. The examiner records errors on a separate scoring sheet, which contains correct

pronunciations for each word. Based on the high correlation between reading ability and intelligence of a normal population, the number of correct responses is entered into a formula to calculate an estimate of the Wechsler Adult Intelligence Scale (WAIS) – Full Scale Intelligence Quotient (Crawford, Parker, Stewart, Besson, & De Lacey, 1989).

Depression: ***Beck Depression Inventory – Fast Screen (*****BDI-FS; *Beck, Steer, & Brown, 2000).*** The BDI-FS is a self-report measure designed to screen medical patients for depression and has been validated with an MS sample (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003). The BDI-FS consists of seven items assessing symptoms of sadness, anhedonia, pessimism, past failure, self-dislike, self-criticism, and suicidal ideation. Participants are asked to rate their experience of these symptoms from 0 to 3. Possible scores range from 0 to 21 with higher scores suggesting more depressive symptomatology. This questionnaire was administered in order to determine the extent to which performance on neuropsychological measures was influenced by depressive symptomatology.

Fatigue: ***Fatigue Impact Scale (FIS; Fisk et al., 1994).*** The FIS is a 40-item, self-report questionnaire assessing fatigue characteristics of MS. Participants rate the degree to which the items pertain to themselves, ranging from 0 (no problem) to 4 (extreme problem). The items of the scale are based on interviews with MS patients about how fatigue impacts their lives. Examples of items include "Because of my fatigue I feel less alert" and "Because of my fatigue I feel unable to meet the demands that people place on me." This measure was included so that the level of fatigue experienced by participants could be determined allowing for the relationship between fatigue and performance on the cognitive measures to be examined.

Information processing speed

Computerized Test of Information Processing (Tombaugh & Rees, 2008). For each test ten practice trials precede the testing series. Three reaction time tests are included: (1) simple, (2) choice, and (3) semantic search. Simple Reaction Time measures the amount of time required to process and react to a simple stimulus and serves as a baseline measure for the other reaction time tests. On each of 30 trials, participants are instructed to press the space bar as soon as a single stimulus ("X") appears in the center of the computer screen. Number correct and time to respond are recorded. Choice Reaction Time 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. Number correct and time to respond are recorded. Semantic Search Reaction Time 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 remains on the screen for either 2.5, 3.0, 3.5, or 4.0 seconds. Following this a word appears below the category name and participants are instructed to press the right key (?) if the word represents a member of the category and to press the left key (Z) if the word does not represent a member of the category. Number correct and time to respond are recorded.

Working memory

Because several researchers have posited that the primary working memory difficulty experienced by individuals with MS is at the level of the central executive (e.g.,

D'Esposito et al., 1996; Diamond et al., 1997), the proposed study included measures that primarily assess this component of the working memory system.

Reading Span. The version of this test used in the current study was based on recommendations of Conway et al. (2005). The background task requires participants to read aloud a sentence presented on a computer screen and verify whether the information is true or false while the primary task requires them to keep track of single letters appearing to the right of each sentence. At the end of each block of trials, participants are instructed to try and recall all of the letters that were presented in that block. Blocks consist of 2, 3, 4, 5, or 6 trials and block size is pseudo-randomly ordered throughout the task. Three practice blocks consisting of two trials each are administered prior to the test blocks. The sentences range from 10 to 17 words each. The total number of letters recalled in the correct serial position is summed across blocks and recorded.

Letter-Number Sequencing subtest from the Wechsler Memory Scale-III (Wechsler, 1997b). The examiner verbally presents different sets of increasingly longer sequences of intermixed letters and numbers ranging in length from two to eight stimuli. After each sequence, the participant is asked to first repeat the numbers starting with the lowest in the series and then the letters in alphabetical order. For example, if presented with the series "6-F-2-B" the correct response would be "2-6-B-F". If a subject responds incorrectly for all three trials of one length, the test is discontinued. The total number of correct trials is recorded.

Learning

Immediate Recall List Learning subtest from the Learning and Memory Battery (LAMB: Schmidt & Tombaugh, 1995). Participants are told they will be asked

to recall a list of 15 words five times and that each of the words belongs to a different category. The examiner then names each category represented in the task. On the first learning trial all 15 words are read and the examinee is asked to repeat all of the words they remember in any order. On the following four learning trials, only the words that were missed the time before are read but the examinee is still instructed to repeat as many of the 15 words as they remember (selective reminding procedure). If the examinee cannot recall all of the words on any of the learning trials then a cued recall trial is administered for the missed words. Cued recall consists of reminding the examinee of the category into which a missed word falls (e.g., "Which word was a type of colour?"). One point is earned for each correct free recall answer and these points are summed to form the Sum Free Recall score. One point is earned for each correct cued recall answer and these points are summed and added to the Free Recall score to form the Free Recall + Cued Recall score. This is done for each learning trial individually. Total Free Recall and Total Free Recall + Cued Recall scores are also obtained by summing across all five learning trials.

Immediate Recall from the Brief Visuospatial Memory Test-Revised (BVMT-R: Benedict, 1997). This measure consists of three learning trials where participants are presented with a matrix of six simple abstract designs (simple geometric shapes and open-sided figures) for 10s. After each learning trial, participants are asked to draw the figures as accurately as possible and in the same location as they remember seeing them on a blank page. Between zero to two points is allotted for each figure reproduced based on the accuracy of the drawing and whether it is placed in the correct location. Points are

summed across each figure reproduced for each learning trial and a total learning score is also calculated by summing points across all learning trials.

Logical Memory-I subtest from the Wechsler Memory Scale-III (Wechsler, 1997b). The Logical Memory test involves free recall following auditory presentation of short prose stories. Two short stories are presented; each is composed of 25 units or ideas and the second story is presented twice. After each story is read, examinees are immediately asked to recall as many details from each story as they can. One point is awarded for each idea that is correctly recalled. The number of correctly recalled details is recorded and the total number of correct details is summed across trials.

Executive functions

Delis-Kaplin Executive Functions Systems Sorting Test (Free Sort Only; Delis, Kaplan, & Kramer, 2001). Two sets of stimulus cards each consist of six cards of different shapes, with a single word printed in the center. Participants are asked to sort the cards into two groups of three cards each and then to describe how they formed the groups. Participants are allowed four minutes for each card set and are asked not to repeat sorts. The number of correct target sorts completed for each card set was recorded and summed across the two card sets.

Phonemic Verbal Fluency from the Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976). Phonemic verbal fluency is measured by requiring the person to say as many words as possible beginning with "F", "A", and "S". A 60s interval is used for each letter and the number of correct responses is summed across the three letters.

Additional Neuropsychological Tests

Symbol Digit Modalities Test – Oral administration (Smith, 1991). At the top of test form, individuals see nine different symbols paired with the numbers 1 through 9. For the practice and test items, participants are required to say the number corresponding to each symbol on the test form. The participant is given 90s to complete as many items as possible and is instructed to work as quickly and accurately as they can. The number of correct responses produced within 90s is recorded.

Paced Auditory Serial Addition Test (Gronwall, 1977). A modified version of the test allowing computer administration was used. Four versions of the test were administered across the two testing sessions. Two versions employed an inter-stimulus interval (ISI) of 3s and two versions employed an inter-stimulus interval of 2s. For each ISI, the same numbers formed the stimuli. The order of presentation of the individual numbers was varied, however, between two versions (3s Form A, 3s Form B, 2s Form A, 2s Form B). The number of digits presented and the inter-stimulus intervals are the same as those encouraged for use with MS patients (Rao, Leo, Bernardin, & Unverzagt, 1991). These versions of the PASAT are those which have been selected as the only cognitive measure to be included in the Multiple Sclerosis Functional Composite (Cutter et al., 1999). In each version, participants are presented with a series of 61 numbers (ranging from 1 to 9) auditorally (using headphones) and participants are instructed to add each number to the one immediately preceding it and to say the sum aloud. The examiner enters participants' responses using the numeric keypad on the keyboard and the computer program tallies the number of correct responses occurring within the inter-stimulus interval. Computerized administration allows for more accurate recording of

responses occurring within the specified time interval. Because of well-known practice effects associated with the PASAT (Tombaugh, 2006), data from the four versions administered during the first testing session were not analyzed. The data that were analyzed comes from the 3s Form A version that was administered just once during the second testing session. This procedure is consistent with that recommended in the Multiple Sclerosis Functional Composite manual for dealing with practice effects on the PASAT.

Procedure

Upon arrival at the first session, participants were asked to read and sign the informed consent form and then the structured interview was administered to obtain basic demographic and health information. Following this, the battery of neuropsychological tests and questionnaires commenced. Approximately one week later, participants returned to complete the remaining tests comprising the battery. The tests were administered in a fixed-order for all participants with the exception of the Computerized Test of Information Processing and PASAT in the second testing session. The order of administration of these two measures was counter-balanced such that participants with an even subject code received the Computerized Test of Information Processing earlier in the battery and the PASAT later in the battery and participants with an odd subject code received the tests in the reverse order. The general order of administration of the tests was chosen so that measures assessing a common cognitive function would not follow one another and so that tests involving stimuli that could possibly cause interference were not administered between the immediate and delayed recall of learning and memory measures. The first session typically took one and a half hours to complete and the

second session typically took two hours to complete. For all MS participants and the majority of control participants, testing sessions were held at the General campus of the Ottawa Hospital. For those control participants recruited through university classes, testing sessions were held at Carleton University.

Data Preparation

Missing data

The amount of missing data was minimal. For the control group, 2.8% of data were missing for the Reading Span variable (i.e., two participants) and 1.4% of data were missing for the Symbol Digit Modalities Test variable (i.e., one participant). For the remaining variables, no missing data occurred. At the case level, three participants were missing data on only one variable; all other participants had complete data. For the MS group, 1.4% of data were missing for each of the Letter-Number Sequencing, Reading Span, Phonemic Verbal Fluency, Symbol Digit Modalities Test, and Beck Depression Inventory-Fast Screen variables (i.e., one participant per variable) and 4.3% of data were missing for the 3s PASAT variable (i.e., 3 participants). For the remaining variables, there was no missing data. At the case level, eight participants were missing data on only one variable; all other participants had complete data.

For both instances of missing data on the Symbol Digit Modalities Test variable, the data were missing due to examiner error that occurred during the recording of participants' responses. For the Reading Span variable, one instance of missing data was due to a control participant requesting to discontinue the test because the test was found to be challenging and caused frustration. For the other two instances of missing data on the Reading Span variable, the test was either discontinued (a control) or not

administered (an MS participant) at the examiner's discretion because the examiner either observed the participant was experiencing difficulty and becoming frustrated with the Reading Span task or a related task. These decisions were made because the examiner did not wish the participant to experience any further frustration which could affect subsequent performance. Both instances of missing data occurring for the Letter-Number Sequencing and Phonemic Verbal Fluency variables were due to a participant requesting to discontinue the test. Two instances of missing data on the 3s PASAT variable were due to computer malfunction/examiner error and one instance was due to an MS participant requesting to discontinue the testing session because they were feeling tired that day with only the 3s PASAT remaining to be completed. The instance of missing data on the Beck Depression Inventory-Fast Screen variable was due to a participant failing to return the questionnaire after requesting to complete it at home due to time constraints.

Little's MCAR test (Little, 1998) was used to assess the portion of the Missing Completely at Random (MCAR) assumption that can be empirically tested, that is, that the probability of 'missingness' on any individual variable is *not* related to the scores obtained on any other variables in the equation. Little's MCAR test was significant for both groups; Controls: χ^2 (26) = 47.30, p=.007; MS: χ^2 (77) = 114.97, p=.003. It is preferable to interpret the results of Little's MCAR test alongside the results of separate variance t-tests. However, because of the small amount of missing data, t-tests could not be computed for the variables with missing data with the exception of the Reading Span variable for the Control group and the 3s PASAT variable for the MS group. The results of the t-tests for those variable did not even approach significance at the Bonferonni-corrected alpha level controlling for Type-I error rate across the thirteen t-tests calculated

per variable ($p > .004$). The other requirement of the MCAR assumption is that the probability of 'missingness' for an individual variable is not related to the actual value of the variable. For the Symbol Digit Modalities Test variable and two instances of missing data for the 3s PASAT variable, it is safe to assume that this component of the MCAR assumption would be met given that missing data were due to examiner error. Thus, the decision was made to proceed by imputing the missing values. For the remaining variables with missing data, the assumption that the probability of 'missingness' for a given variable is not related to the actual value of the variable cannot be confirmed because it is likely that when a test is discontinued at a participant's request or the examiner's discretion, the participant may not have performed well on that measure. Thus, it cannot be ruled out that in such cases the data were not missing at random. However, because the amount of missing data was extremely minimal for such cases (no more than one variable missing for each of five participants), the decision was made to also proceed by imputing these values.

For all cognitive variables, regression imputation was used to estimate appropriate values for missing data. Missing scores for individual variables were substituted with predicted scores obtained from regression equations based on the appropriate group with independent variables found to be significant from the following set: age, education and other observed variables used to represent the same cognitive factor in the SEM analyses. For the Beck Depression Inventory-Fast Screen, mean substitution (employing the appropriate group average) was used for the single instance of missing data.

Assumptions

Univariate outliers were assessed by examining z-scores for any cases having an absolute value greater than three (i.e., more than three SD's from the mean for the group to which the outlier belonged). No extreme outliers were identified; the largest z-score observed for any variable was 4.66. Because the univariate outliers identified only had values that were slightly larger than ±3.00, instead of deleting these cases, the scores in question were replaced with a value that was within three SD's of the mean (z-score = ±3.0) but that maintained the scores rank of having the largest absolute magnitude for the given variable. This allowed for the influence of the extreme scores to be reduced while maintaining the original ordinal relationship of the scores for these variables. It should be noted that the data were checked to ensure outliers were not merely data entry errors.

One criterion used to identify multivariate outliers was Mahalanobis distance at p=.001 (Tabachnick & Fidell, 2007). Mahalanobis distances for all cases were obtained through SPSS REGRESSION. Mahalanobis distances were evaluated as χ^2 with degrees of freedom equal to the number of variables, in this case eleven. Therefore, any case with a Mahalanobis distance greater than $\chi^2(14) = 36.12$ was considered to be a multivariate outlier. The largest Mahalanobis distance obtained was 29.67, thus, no case met the criterion for a multivariate outlier. Cook's distances were also obtained and the largest value observed was .12, thus, all values were well below 1.00. Because of these findings, no case was judged to have a substantially large influence on the regression coefficients. Finally, leverage values for all cases, also obtained through SPSS REGRESSION, were examined. The largest value obtained for any of the cases was 0.42. This value is well

below (N-1) / N = (142-1) / 142 = 0.99. Therefore, no case was judged to have a substantial influence on a point on the fit of the regression.

Normality was assessed by examining histograms, stem-and-leaf plots, box-plots and normal-probability plots of the individual observed variables. Although distributions for some variables did not appear to be perfectly normal, observed deviations from normality were judged to be minor for most variables. However, deviations from normality appeared to be more substantial for the Choice RT, Semantic Search RT, 3s PASAT, BVMT-R immediate recall, Beck Depression Inventory-Fast Screen, and Fatigue Impact Scale variables. Results of Kolmogorov-Smirnov tests of normality were also examined and significant results (suggesting non-normality) were obtained in the control group for the following variables: Logical Memory I, BVMT-R immediate recall, Simple RT, Semantic Search RT, confirmed correct sorts from D-KEFS Sorting, 3s PASAT, Beck Depression Inventory-Fast Screen, and Fatigue Impact Scale. Significant results were obtained in the MS group for the following variables: Logical Memory I, Simple RT, Choice RT, Semantic Search RT, confirmed correct sorts from D-KEFS Sorting, Letter-Number Sequencing, 3s PASAT, and Beck Depression Inventory-Fast Screen. However, it should be taken into consideration that this test is very sensitive to even mild departures from normality and is likely to be significant with large sample sizes (Field, 2009). Therefore, the results of other statistical tests of normality were also considered. Specifically, skewness and kurtosis values for each variable were changed to z-scores by dividing by their respective standard errors. In small to moderate samples, conventional but conservative alpha levels (.01 or .001) are used to evaluate the significance of skewness and kurtosis z-scores (Tabachnick & Fidell, 2007). The Choice

RT, Semantic Search RT, 3s PASAT and Beck Depression Inventory-Fast Screen variables met the criterion for significance at the .001 level (±3.29) for skewness in both groups. The Fatigue Impact Scale variable was skewed at this level for the control group and the Simple RT variable was skewed at this level for the MS group. Significant kurtosis was also identified at the .001 level for the Simple RT and Choice RT variables in the MS group and for the Beck Depression Inventory-Fast Screen in the control group. The Choice RT, Semantic Search RT and Fatigue Impact Scale variables showed significant kurtosis at the .01 level (±2.58) in the control group and the Beck Depression Inventory-Fast Screen variable showed significant kurtosis at this level for the MS group. Finally, significant skewness was identified for the BVMT-R immediate recall variable in both groups and for the Simple RT variable in the control group at the .01 level.

Because the Simple RT, Choice RT, Semantic Search RT, 3s PASAT, BVMT-R immediate recall, Beck Depression Inventory-Fast Screen, and Fatigue Impact Scale variables showed consistent deviations from normality, transformations were applied to correct the deviations. The positive skewness characterizing the Simple RT, Choice RT, and Semantic Search RT variables was found to be best ameliorated with a logarithmic (LOG10) transformation and the negative skewness characterizing the 3s PASAT and BVMT-R immediate recall variables was found to be best ameliorated with a reflect and square root transformation. The positive skewness characterizing the Beck Depression Inventory-Fast Screen and Fatigue Impact Scale variables was found to be best ameliorated with a square root transformation. It should be noted that when the measurement model defined to test Hypotheses 1 and 2 was run with and without transformations applied to above mentioned variables, essentially the same results were

obtained in terms of parameter estimates. However, because indices of model fit are sensitive to departures from normality and because maximum likelihood estimation assumes normality, analyses proceeded using the transformed data.

The data were screened for the presence of multicollinearity or singularity by first examining bivariate correlations between all variables. No correlations were found to be $\geq .70$. Furthermore, tolerance values were examined. Because no values were found to be below .2 (the smallest values observed was .34), it was concluded that no problematic relationships existed among the variables. Multicollinearity was also not judged to be an issue with the present dataset given that the AMOS program (Arbuckle, 2009) converged indicating the covariance matrix was non-singular.

In sum, structural equation modeling analyses were performed using complete and imputed data from 142 participants. Maximum likelihood estimation was employed to estimate all models.

CHAPTER THREE: RESULTS

Characteristics of the Groups

The ratio of males to females was very similar for the two groups: 13/59 for the Control group and 13/57 for the MS group, χ^2 (1, N = 142) = .006, p = .937. Table 1 presents additional demographic information (age, number of years of education) and scores obtained on the measures of intelligence, depression, and fatigue, as well as the results of independent samples t-tests used to compare the groups on these variables. The groups did not significantly differ on age, education or intelligence. As expected, the groups did significantly differ on depression and fatigue with MS participants obtaining higher scores on the measures of these variables. Table 1 also presents disease duration and Expanded Disability Status Scale scores for the MS participants. The sample was characterized by a short disease duration and mild neurological disability (Kurtzke, 1983), on average.

Comparisons between the performances of the groups on the individual observed variables included in the structural equation modeling analyses are presented in Table 2. MS patients responded more slowly than controls on the processing speed measures, although group differences were not significant for the choice and semantic search reaction time tasks. The patients performed significantly worse than controls on the working memory measures and two of the learning measures, with medium effect sizes. There were no significant differences between the groups on the executive functioning measures. Thus, the patients with MS exhibited deficient working memory and learning. In contrast, processing speed and executive functioning appeared unimpaired overall. The absence of significant deficits in processing speed and executive functioning may be

Table 1. Characteristics of the Groups.

	Group					
	Control (N=72)		MS (N=70)			
	Mean	SD	Mean	SD	$t(140)$	Cohen's d
Age	40.69	11.83	40.34	8.78	.20	.03
Years of Education	15.10	1.93	14.81	1.98	.90	.15
North American Adult Reading Test	112.79	7.07	110.87	6.98	1.63	.28
Beck Depression Inventory-Fast Screen	1.53	2.18	2.83	2.70	-3.15**	-.53
Fatigue Impact Scale	25.44	21.37	48.53	31.69	-5.10***	-.86
Months of Disease Duration	-	-	52.63	36.05		
Years of Disease Duration	-	-	4.37	3.02		
Expanded Disability Status Scale	-	-	2.84	8.53		

Note. **p<.01; ***p<.001.

Table 2. Comparisons Between the Groups on the Observed Variables.

	Group					
	Control (N=72)		MS (N=70)			
	Mean	SD	Mean	SD	$t(140)$	Cohen's d
Processing Speed						
CTIP Simple RT (ms)	288	41	303	46	-2.17*	-.37
CTIP Choice RT (ms)	524	99	545	106	-1.18	-.20
CTIP Semantic Search RT (ms)	785	210	830	222	-1.26	-.21
Working Memory						
Reading Span	32.74	10.06	28.50	7.49	2.84**	.48
Letter-Number Sequencing	13.32	3.01	12.06	2.57	2.67**	.45
Learning						
L.A.M.B. Immediate Recall	53.60	7.66	49.76	7.87	2.95**	.50
BVMT-R Immediate Recall	26.64	5.56	26.88	5.40	-.26	-.04
Logical Memory I	48.36	8.38	43.84	8.90	3.12**	.53
Executive Functions						
D-KEFS Sorting	10.08	1.83	10.07	2.16	.04	.01
Phonemic Verbal Fluency	42.01	9.78	40.88	11.43	.63	.11

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

related to the short disease duration and relapsing-remitting disease course characterizing the patient sample.

Correlations among the Observed Variables

Correlations among the observed variables included in the structural equation modeling analyses are presented for the overall sample in Table 3 and separately for each group in Table 4. These tables include correlations for the transformed versions of those variables requiring transformation. Because a reflect and square root transformation was applied to the BVMT-R immediate recall variable, the correlations involving this variable will have the opposite sign than what would have resulted for the untransformed variable. The correlations for all other variables may be interpreted as usual. The correlations for the overall sample provide support for the groupings of variables according to different cognitive factors; variables were significantly correlated with all other variables assigned to the same factor, although the strength of the correlations varied considerably across groups of variables. A comparison of the correlations obtained separately for the two groups revealed consistencies with whole sample patterns for some variables but discrepancies for others.

Fisher's r-to-z transformation tests were conducted employing SPSS syntax created by Field (2009) in order to determine whether any differences between correlations for the control and MS groups were significant. The correlation between Reading Span and Logical Memory I significantly differed between the MS and control groups (.50 vs. 17, $z_{Difference} = 2.20$, $p = .03$), with a larger, positive correlation between the variables observed for the Control group in comparison to a smaller, positive correlation for the MS group. The correlation between Phonemic Verbal Fluency and

Table 3. Product Moment Correlations of Observed Variables for the Overall Sample.

Variable	1	2	3	4	5	6	7	8	9	10
1. Simple RT	-									
2. Choice RT	.56***	-								
3. Semantic Search RT	.34***	.62***	-							
4. Reading Span	-.26**	-.32***	-.41***	-						
5. Letter-Number Sequencing	-.10	-.27**	-.33***	.51***	-					
6. L.A.M.B. Immediate Recall	-.11	-.10	-.15	.41***	.31***	-				
7. BVMT-R Immediate Recall	.14	.32***	.27**	-.33***	-.27**	-.34***	-			
8. Logical Memory I	-.16	-.18*	-.27**	.39***	.33***	.51***	-.30***	-		
9. D-KEFS Sorting	-.06	-.16	-.28**	.21*	.25**	.07	-.05	.09	-	
10. Phonemic Verbal Fluency	-.01	-.09	-.16	.30***	.29***	.12	-.09	.07	.29**	-

Note. *p<.05; **p<.01; ***p<.001.

Table 4. Product Moment Correlations of Observed Variables for the Control and MS Groups.

Variable	1	2	3	4	5	6	7	8	9	10
1. Simple RT	-	.61**	.31**	-.20	-.04	-.11	.25*	-.15	-.07	-.05
2. Choice RT	.50***	-	.53**	-.20	-.28*	-.12	.32**	-.10	-.18	-.02
3. Semantic Search RT	.35**	.69***	-	-.45***	-.39**	-.11	.26*	-.20	-.34**	-.20
4. Reading Span	-.25*	-.38**	-.37**	-	.47***	.41***	-.33**	.17	.25*	.46***
5. Letter-Number Sequencing	-.07	-.23	-.25*	.49***	-	.29*	-.24*	.24	.27*	.35**
6. L.A.M.B. Immediate Recall	-.02	-.04	-.14	.36**	.26*	-	-.37**	.45***	.20	.25*
7. BVMT-R Immediate Recall	.06	.33**	.29*	-.36**	-.31**	-.35**	-	-.17	-.20	-.07
8. Logical Memory I	-.07	-.21	-.29*	.50***	.35**	.52***	-.46***	-	.06	.25*
9. D-KEFS Sorting	-.06	-.14	-.21	.18	.24*	-.08	.12	.13	-	.30*
10. Phonemic Verbal Fluency	.05	-.11	-.10	.17	.23*	-.05	-.14	-.12	.26*	-

Note. The values below the diagonal correspond to the Control group and the values above the diagonal correspond to the MS group. *p<.05; **p<.01; ***p<.001.

Logical Memory I also differed between the control and MS groups (-.12 vs. .25, $z_{Difference}$ = -2.19, p = .03), with a larger, positive correlation between the variables observed for the MS group in comparison to a smaller, negative correlation for the Control group. None of the other comparisons were significant ($p > .05$). In sum, the overall correlations support the logic used to create factors for the structural equation modeling analyses that follow and suggest that the patterns of relations within the groups are very similar to those for the whole sample.

The Hypothesized Measurement Model

Because the structural equation model of interest aims to assess the extent to which relations between cognitive constructs are valid and because these constructs are latent and not observed, it is critical that the measurement of each latent construct is psychometrically sound. Thus, an important preliminary step in the analysis of the structural equation model is to first evaluate the validity of the measurement model. Accordingly, a confirmatory factor analysis was performed through AMOS 18.0 (Arbuckle, 2009) on the measures presumed to measure each latent cognitive function. The hypothesized model is presented in Figure 5 where ovals represent latent factors, rectangles represent measured variables, and circles represent error variance. The absence of a line connecting variables implies no hypothesized direct effect. A four factor model of processing speed, working memory, learning, and executive functioning is hypothesized. The Simple RT, Choice RT, and Semantic Search RT variables serve as indicators of processing speed. The Reading Span and Letter-Number Sequencing variables serve as indicators of working memory. The Logical Memory-I, LAMB immediate free recall, and BVMT-R immediate recall variables serve as indicators for the

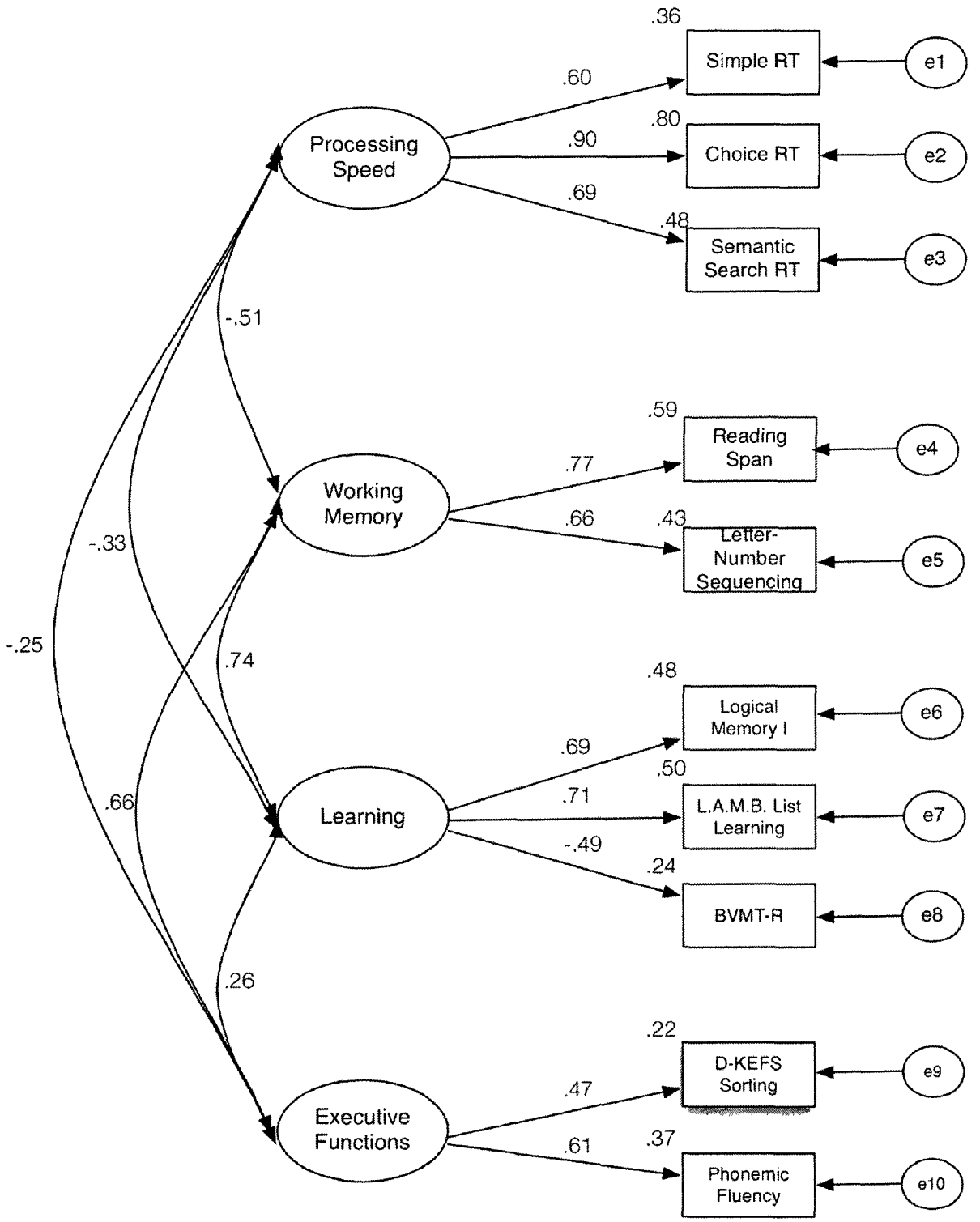

Figure 5. Measurement Model Showing Standardized Solution.

Note. See page 77 for an explanation of the values contained in the figure.

learning factor. The confirmed correct sorts variable from the D-KEFS Sorting test and the Phonemic Verbal Fluency variable serve as indicators for executive functioning.

Model Assessment. As recommended by Byrne (2001), the first step taken to assess the hypothesized model was to evaluate the fit of individual parameters in the model by examining: 1) the feasibility of the parameter estimates, (2) the appropriateness of the standard errors, and (3) the statistical significance of the parameter estimates.

With regards to feasibility, the sign and size of parameter estimates should be consistent with underlying theory. If issues such as correlations greater than 1.00, negative variances, or a covariance or correlation matrix that is not positive definite were to occur, it would be concluded that unreasonable estimates are present in the model. For the hypothesized model, all correlations were less than 1.00 and were judged to be reasonable, no variances were negative, and the covariance matrix was positive definite.

Regarding standard errors, excessively large or small values are another indicator of poor model fit. However, because standard errors are influenced by the units of measurement in observed variables, there is no specific criterion for what is too small or too large. The standard errors observed for the working memory, learning, and executive functioning factors were judged to be very similar as the values ranged from 9.75 to 18.00. In contrast, the standard error for the processing speed factor was much smaller at .001. However, all of the observed variables representing the processing speed factor had been log transformed to ameliorate skewness. Therefore, the smaller standard error associated with the processing speed factor was concluded to be valid given the units of the variable used to scale the factor.

The statistical significance of parameter estimates is evaluated using the critical ratio test statistic. Employing a p-value of .05, a test statistic greater than ±1.96 indicates that the estimate is significantly different from zero. Estimates not meeting this criterion are non-significant and the associated parameters (except for error variances) are considered to be unimportant to the model and should be deleted (Byrne, 2001). The critical ratios for all structure coefficients (i.e., factor loadings), covariances, and variances in the hypothesized model were greater than ±1.96 except for the covariances between processing speed and executive functioning and learning and executive functioning factors (C.R.s = -1.77 and 1.66, respectively). Therefore, aside from these covariances, none of the other parameters were non-significant and none of the other components of the model were candidates for removal.

After assessing individual parameters, the overall fit of the model was examined through the goodness-of-fit indices provided in the AMOS 18.0 output. The first index considered was the χ^2 test statistic which assesses the fit between the sample covariance matrix and estimated population covariance matrix under the restrictions imposed by the hypothesized model (Byrne, 2001). The independence model that tests the hypothesis that all variables are uncorrelated was easily rejected, $\chi^2(45, N = 142) = 361.79, p < .001$. Table 5 presents the fit indices for the various models that were analyzed. As can be seen in Table 5, substantially more support was found for the hypothesized measurement model than for the independence model and the outcome indicated good fit. Although the χ^2 test statistic indicated good fit, because there are known problems due to the sensitivity of this index to sample size and the assumptions associated with its basis on the central χ^2 distribution, other fit indices must always be interpreted as well (Byrne, 2001).

Table 5. Fit Indices for the Measurement and Structural Models.

Model	df	χ^2	*p*-value	CFI	RMSEA	90% C.I.		AIC	BCC	BIC
						Lower	Upper			
Measurement Model	29	37.83	.126	.97	.046	.000	.084	89.83	94.23	166.68
Relative Consequence Structural Model										
Initial Structural Model	35	48.22	.068	.96	.052	.000	.085	110.22	115.98	201.85
Final Structural Model	38	52.26	.062	.96	.052	.000	.083	108.26	113.47	191.03
Final Covariate Model	46	66.43	.026	.95	.056	.020	.084	130.43	136.93	225.01
Working Memory Structural Model										
Initial Structural Model	35	48.22	.068	.96	.052	.000	.085	110.22	115.98	201.85
Final Structural Model	40	51.15	.111	.97	.044	.000	.077	103.15	107.99	180.00
Final Covariate Model	59	94.14	.002	.92	.065	.039	.089	158.14	165.20	252.73

The comparative fit index was considered next. Values of .95 or greater indicate a model has good fit. The CFI employs a noncentral χ^2 distribution and does a good job of estimating model fit even in small samples (Tabachnick & Fidell, 2007). The CFI for the hypothesized measurement model exceeded the criterion indicating good fit.

Three alternative methods including a parsimony adjustment when assessing fit are the Akaike information criterion (AIC), Browne-Cudeck criterion and the consistent Bayesian Information criterion (BIC). Although not overly informative when considered alone, the AIC, BCC and BIC are presented because they are useful for judging different non-nested models in comparison to one another (Tabachnick & Fidell, 2007). Thus, the values will be used to compare the fit of a hypothesized model with later revised models. For these indices, smaller values for a given model relative to another indicate a better-fitting, parsimonious model.

Another useful index is the root mean square error of approximation (RMSEA), which estimates the discrepancy or lack of fit in the hypothesized model compared to a model with optimally chosen parameter values (i.e., the saturated model; Byrne, 2001; Tabachnick & Fidell, 2007). Browne and Cudeck (1993) stated that values less than .05 indicate good fit but values up to .08 can be considered reasonable errors of approximation. Furthermore, MacCallum, Browne, and Sugawara (1996) stated that RMSEA values ranging between .08 - 1.0 indicate mediocre fit, and those greater than 1.0 indicate poor fit. Based on these interpretations, the RMSEA value of .046 obtained for the hypothesized measurement model also indicates that the model has good fit.

Potential areas of misspecification (i.e., misfit) in the model were evaluated by examining: 1) the residual covariance matrix and 2) the modification indices provided in

the AMOS 18.0 output. The values contained in the residual covariance matrix represent the discrepancy between the covariances in the unrestricted sample covariance matrix and the covariance matrix under the restrictions imposed by the hypothesized model for all pairs of observed variables (Byrne, 2001). Because the fitted residuals are dependent on the unit of measurement of the observed variables, the values can be most readily interpreted by examining the standardized residuals which have been transformed so they are all on the same unit of measurement and are directly comparable. Values greater than 2.58 are considered to be large (Jöreskog & Sörbom, 1988). Examination of the standardized residual covariance matrix revealed the largest value was 2.35; therefore, no values were greater than 2.58.

The modification indices provided in the AMOS 18.0 output represent the expected reduction in overall χ^2 value (i.e., improved model fit) if a given fixed parameter were to be freely estimated in a subsequent model (Byrne, 2001). In addition to the modification indices, parameter change values representing the predicted estimated change in parameter values associated with a given modification are available in the output as well. These values offer important information as to the sensitivity of the evaluation of fit to any re-parameterization of the model (Byrne, 2001). Both items are provided for model covariances, variances, and factor loadings. However, because all variances were freely estimated in the hypothesized model, no modification indices or parameter changes values exist for these parameters. Although a few modifications were listed by the program, none would have substantially improved model fit and none were accepted because the changes would have been illogical or problematic (i.e., allowing an

observed variable to load on an additional factor resulting in a non-simple factor structure).

In sum, all parameter estimates obtained were feasible and the different fit indices suggest that the model represents a good fit to the data. The standardized residuals and modification indices did not identify any areas of misspecification in the model requiring adjustment. Thus, it was deemed that the hypothesized measurement model did not require improvement and no modifications were made. Although the covariances between the processing speed and executive functioning and the learning and executive functioning factors did not reach the criterion for significance, because they did approach significance (p = .076, .098, respectively) and removing them actually results in slightly less good fit, these parameters remained in the measurement model.

The measurement model including standardized parameter estimates is illustrated in Figure 5. The values situated above the single-headed arrows are the factor loadings, the values beside the observed variables are the squared multiple correlations (i.e., the variance in an observed variable explained by the factor), and the values beside the double-headed arrows are correlations. As noted above, all loadings were significant and, furthermore, the majority of loadings were high suggesting convergent validity. The only exceptions occurred for the BVMT-R immediate recall variable assigned to the learning factor and the confirmed correct sorts variable assigned to the executive functioning factor. The loadings for these variables were fair. Although, the lower values do suggest that the BVMT-R immediate recall and confirmed correct sorts variables contributed less to identification of their respective factors than other variables. The correlations between

factors ranged from medium to large but no correlations were so large as to indicate multicollinearity.

Now that it is known the measurement model is operating adequately, findings related to the assessment of the hypothesized structural model can be examined and interpreted with confidence.

Hypothesis 1 – The Relative Consequence Model

To determine if processing speed functions as a mediator between the effects of MS and measures of cognitive functioning, structural equation modeling was used to simultaneously evaluate linkages between (1) the effects of MS and processing speed, (2) between processing speed and other cognitive functions frequently impaired in patients with MS (working memory, learning, and executive functioning), and (3) between the effects of MS and the other cognitive functions. See Figure 3 for the structural model that was proposed to test hypothesis 1. Absence of a line connecting variables indicates that no effect was predicted. Because it seemed logical to assume the individual cognitive functions would be related, correlated disturbance terms for the factors were also included in the model. Correlations between the actual factors themselves, as opposed to their disturbances, were not included because it is not possible to estimate these parameters in addition to the direct effects on them already included in the model. Given that the hypothesized direct and indirect effects were deemed to be of greater importance to understanding the relations among the constructs of interest, priority was given to the direct effects. The possible correlations between individual cognitive factors were dealt with by modeling the correlated disturbance terms.

Amos 18.0 (Arbuckle, 2009) was used to analyze the structural equation model. A number of fit statistics were employed to evaluate how well each model fit the data. These included the chi-square test, the comparative fit index, as well as the root-mean square error of approximation. The coefficients for all of the paths specified in the model were estimated. These values represent the change in the dependent variable (arrow pointing to) expected to result from a change of one unit in the predictor variable (arrow is pointing away from) when other possible determinants specified in the model were held constant. Bias-corrected bootstrap confidence intervals are the preferred method for testing the significance of indirect effects as this method produces the most accurate confidence limits, the most accurate Type I error, and yields the largest power for detecting significant indirect effects (e.g., Cheung & Lau, 2008; MacKinnon, Lockwood, & Williams, 2004). As such, bias-corrected bootstrap confidence intervals based on 1000 bootstrap samples were used to estimate 95% confidence intervals for all model parameters. Parameter estimates with 95% confidence intervals not including 0 were considered statistically significant at the .05 level. Tests of significance were based on 95% confidence intervals estimated for the unstandardized coefficients. Unstandardized coefficients are the common metric employed in structural equation modeling because the most widely used estimation methods assume the analysis of unstandardized variables (Kline, 2005) and because standardized coefficients can be problematic (Duncan, 1975; Kim & Mueller, 1976; Kim & Ferree, 1981). Although tests of significance were based on unstandardized estimates, standardized coefficients are also presented and discussed in order to describe the results of the structural equation model fully.

If cognitive deficits are not a direct result of disease pathology, but instead are a by-product of reduced processing speed, it was expected that the tests of the indirect effects of group membership on the cognitive domains would be significant. Furthermore, MS-related effects on variables representing the cognitive functions were expected to be substantially smaller than the total MS-related effects on those variables because the total effects include both direct effects and the effects mediated through processing speed. Such results would be consistent with the hypothesis that processing speed may be mediating some of the MS-related effects on other aspects of cognitive functioning. However, a finding that the indirect effects are not significant and the direct MS-related effects are not substantially smaller than the total MS-related effects would be inconsistent with the hypothesis that processing speed is an important contributor to differences in cognitive functioning between patients with MS and controls.

Model Assessment. As shown in Table 5, support was found for the hypothesized model. For instance, the RMSEA obtained for the hypothesized structural equation model was .052 with a 90% confidence interval of .000-.085 and, as discussed earlier, the point estimate obtained indicates good fit. The lower bound of the confidence interval is below the criterion indicating good fit and the upper bound is below the criterion indicating poor fit. Therefore, the hypothesized structural model was considered to represent a good fit of the data.

All parameter estimates were judged to be feasible. There were no correlations greater than 1.00, no variances were negative, and the covariance matrix was positive definite. Regarding the statistical significance of the parameter estimates, four parameters did not meet the criterion for significance (i.e., the bias-corrected boot strap confidence

intervals included zero). This occurred for the estimate corresponding to the direct effect of group on processing speed (B[5] = .02, SE = .01, 95%C.I. = -.01, .05), the direct effect of group on executive functioning (B = -.31, SE = 1.63, 95%C.I. = -3.78, 2.66), the direct effect of processing speed on executive functioning (B = -21.70, SE = 11.56, 95%C.I. = -41.71, 3.85), and the covariance between the disturbance terms associated with learning and executive functioning (B = 6.59, SE = 6.45, 95%C.I. = -4.43, 20.59). These findings suggest that the parameters just described are unimportant to the model and represent candidates for removal.

Model Modification. As for the measurement model, the residual covariance matrix and the modification indices were examined in order to assess potential modifications that could improve model fit. Examination of the standardized residual covariance matrix failed to show any values larger than 2.58 (the largest value was -2.32). Once again, the modification indices did not suggest any amendments that were judged to be theoretically reasonable or acceptable.

However, because of the issues regarding non-significant individual parameters discussed above, it was clear that the model required modification before the resulting parameter estimates were to be interpreted. The non-significant parameters were addressed in a sequential manner (i.e., a single adjustment was performed at a time) because such modifications have the potential to significantly alter the estimates of other parameters (Byrne, 2001). Because the estimate for the direct effect of group on executive functioning represented the largest deviation from significance, this parameter

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[5] B; unstandardized regression coefficient.

was removed first. Following this adjustment, the direct effect of processing speed on executive functioning now met the criterion for significance. However, the other non-significant parameter estimates still failed to reach significance and, thus, they were removed from the model as well. The resulting solution did not possess any unfeasible parameter estimates, no correlations were greater than 1.00, negative variances did not occur, and the covariance matrix was positive definite.

Regarding model fit, the modifications made to the hypothesized structural model essentially did not result in any substantial differences compared with the original model (see Table 5). Once again, no modification indices were deemed to be worthwhile. In sum, it was judged that the structural model now represented a good fit of the data and no further modifications were necessary. The final structural model including standardized coefficients is illustrated in Figure 6.

Now that it is known that the structural model is operating adequately, findings related to the parameters estimates can be examined and interpreted with confidence. Table 6 presents the estimated coefficients, standard errors, and confidence intervals corresponding to the effects included in the final structural model.

Direct Effects. As indicated above, the path between group and processing speed included in the hypothesized structural model was not significant, indicating group membership did not significantly predict processing speed, and was removed from the final model. The same applied to the path between group and executive functioning. Because the path between group membership and the hypothesized mediating factor was not significant, it would be inappropriate to discuss indirect effects. Therefore, only direct effects will be reported and discussed for this structural model. Group membership did

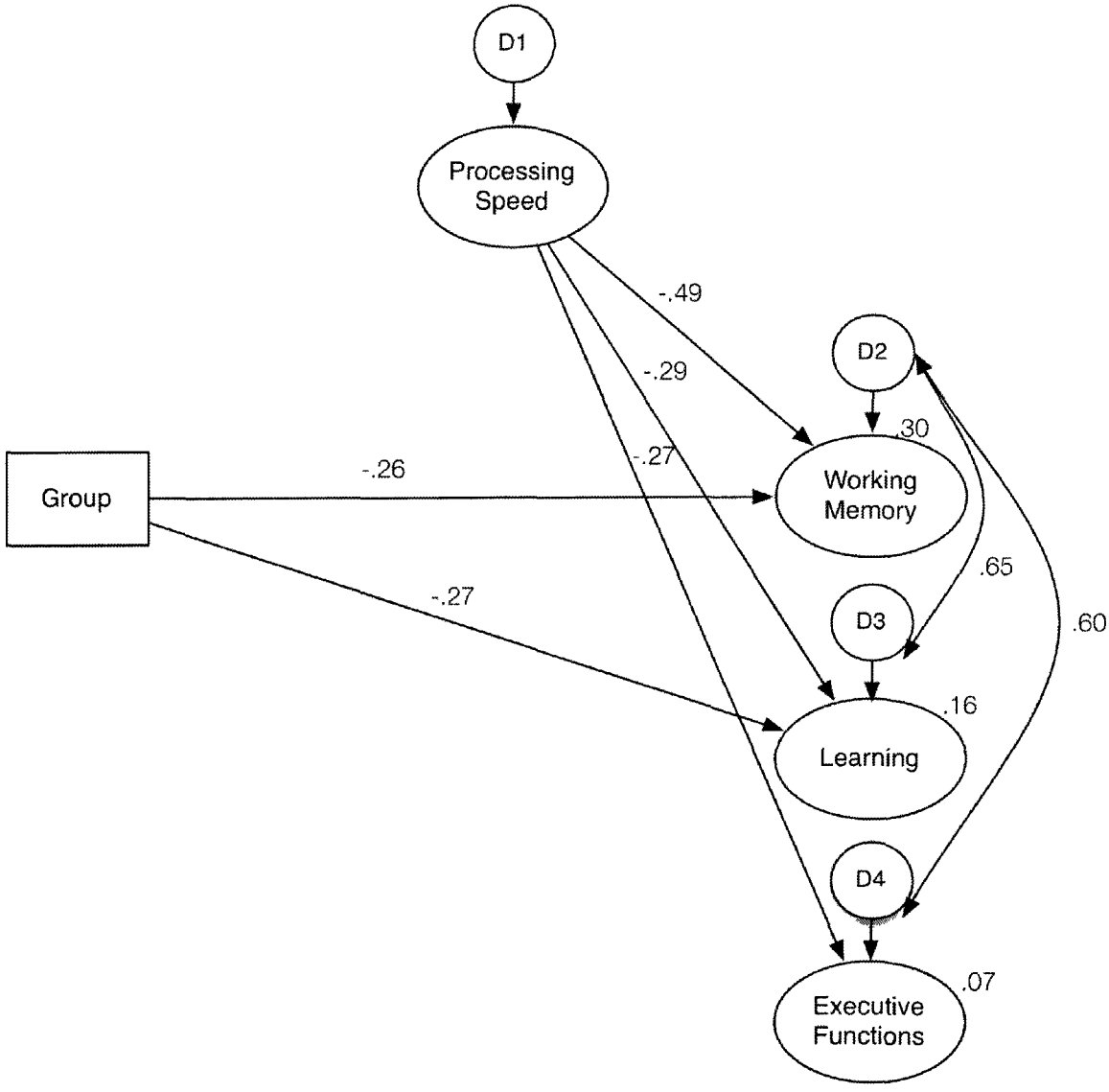

Figure 6. Final Structural Model for Hypothesis One – the Relative Consequence Structural Model.

Note. Measurement model not shown.

Table 6. Path Coefficients and Confidence Intervals for Final Relative Consequence Structural Model.

	Predictor Variables							
	Group				Processing Speed			
	B	SE	95% C.I.	β	*B*	SE	95% C.I.	β
Processing Speed	-	-	-	-				
Working Memory	-3.48	1.25	-5.84, -1.14	-.26	-44.30	10.55	-67.81, -24.69	-.49
Learning	-3.31	1.37	-6.03, -.82	-.27	-24.11	9.22	-41.75, -5.28	-.29
Executive Functioning	-	-	-	-	-22.52	11.28	-46.11, -.66	-.27

Note. B, unstandardized coefficient; SE, standard error; 95% C.I., 95% confidence interval; β, standardized coefficient; -, non-significant and removed from final model.

significantly predict working memory and learning. The unstandardized coefficients indicate that, relative to controls, individuals with MS are expected to be worse by 3.48 units in terms of working memory and worse by 3.31 units in terms of learning. The standardized coefficients indicate that group membership has a comparable degree of importance for predicting both working memory and learning ability.

Processing speed predicted working memory, learning, and executive functioning. Because the processing speed factor was scaled using an observed variable measured in reaction time (with a base 10 logarithmic transformation applied), larger values actually indicate worse processing speed. Thus, the negative coefficients should be interpreted as meaning worse processing speed is associated with worse working memory, learning, and executive functioning. The standardized coefficients indicate that, although processing speed has a comparable degree of importance for predicting learning and executive functioning, it is of greater importance to the prediction of working memory ability.

Squared Multiple Correlations. Regarding the percent of variance in the cognitive functions accounted for by the predictor variables (processing speed and group), 30.3% of the variance in working memory (R^2 = .303, *SE* = .12, 95%C.I. = .12, .56) and 15.5% of the variance in learning (R^2 = .155, SE = .08, 95%C.I. = .03, .33) was accounted for by group membership and processing speed. Furthermore, 7.1% of the variance in executive functioning (R^2 = .071, SE = .10, 95%C.I. = .00, .32) was accounted for by processing speed.

Summary. Group membership did not predict processing speed or executive functioning in the present sample. Because processing speed was not related to group

membership, processing speed could not function as a mediating factor for the MS-related effects on other cognitive functions. In contrast, group membership did predict working memory and learning. Specifically, the results indicated worse working memory and learning abilities for participants with MS relative to controls, with the size of the MS-related effect being very similar for these two cognitive functions. Regardless of the presence or absence of MS, slower processing speed was associated with worse working memory, learning, and executive functioning. Comparisons between the standardized coefficients suggest that slower processing speed had the greatest effect on working memory, whereas the size of the effects on learning and executive functioning were very similar. Furthermore, comparisons of the standardized direct effects between group membership and processing speed suggest that, although both of these variables affect learning to a similar degree, processing speed affected working memory ability to a greater degree than the presence or absence of MS. Between the determinants of group membership and processing speed, moderate amounts of the variance in working memory (30.3%) and learning (15.5%) were accounted for in the final model. With only processing speed able to predict executive functioning, a small amount of the variance in this domain (7.1%) was accounted for. In summary, the results do not support the *Relative Consequence Model* in this sample of patients with early relapsing-remitting MS.

Hypothesis 2 – The Mediating Role of Working Memory

To examine if working memory is also a determinant of cognitive dysfunction in MS, structural equation modeling was used to test the hypothesized model depicted in Figure 4. The model included direct effects of group membership on the cognitive

factors, as well as indirect effects of group membership via working memory. The adequacy of this model was evaluated using the same fit statistics that were examined for the Relative Consequence structural model and the total, direct, and indirect effects were also assessed in the same manner. If working memory contributes to cognitive dysfunction in MS, then similar results as those originally hypothesized for the previous model were also expected for this model.

In addition, the Akaike Information Criterion (AIC), Browne-Cudeck Criterion (BCC), and Bayes Information Criterion (BIC) fit indices obtained for the alternative models used to test Hypotheses 1 and 2 were compared to determine which model fits the data best. Each of these statistics weighs both the badness of fit and complexity of a model such that simple models that fit the data well receive low scores whereas complicated, poorly fitting models receive high scores (Arbuckle, 2009). Burnham and Anderson (1998) have proposed the following criteria for aiding in interpretation of comparisons of the AIC and BCC: (1) differences of 0-2 suggest there is no credible evidence that an alternative model should be ruled out as being the best model for the population of possible samples, (2) differences of 2-4 suggest there is weak evidence that an alternative model is not the best model, (3) differences of 4-7 suggest there is definite evidence that an alternative model is not the best model, (4) differences of 7-10 suggest there is strong evidence that the model is not the best model, and (5) differences greater than 10 suggest there is very strong evidence that the model is not the best model. Raftery (1995) proposed the following criteria for aiding in interpretation of comparisons of the BIC: (1) differences of 0-2 suggest there is weak evidence that an alternative model is not preferred, (2) differences of 2-6 suggest there is positive evidence than an alternative

model is not preferred, (3) differences of 6-10 suggest there is strong evidence than an alternative model is not preferred, and (4) differences greater than 10 suggest there is very strong evidence that an alternative model is not preferred.

Model Assessment. As shown in Table 5, support was found for the hypothesized model. Table 5 also shows that the fit values for the initial structural models developed to test both Hypotheses 1 and 2 are the same. This occurred because the two initial models possess the same number of degrees of freedom and are predicting the same covariance data, but with a different configuration of hypothesized relations. Thus, the initial models for Hypotheses 1 and 2 are equivalent models and, similar to the previous initial model, the current initial model was considered to represent a good fit of the data.

All parameter estimates were judged to be feasible for the hypothesized Working Memory structural model. However, four parameters did not meet the criterion for significance. With working memory assigned as a mediating variable, this occurred for all estimates corresponding to the direct effects of group on the cognitive factors aside from working memory [processing speed: B = -.002, SE = .01, 95%C.I. = -.03, .02, learning: B = -.94, SE = 1.33, 95%C.I. = -3.79, 1.63), executive functioning: B = -2.10, SE = 1.64, 95%C.I. = -.74, 5.77] and for all covariances between disturbance terms of the cognitive factors [processing speed and learning: cov = .02, SE = .04, 95%C.I. = -.06, .11, processing speed and executive functioning, cov = .04, SE = .06, 95%C.I. = -.07, .18; learning and executive functioning, cov = -8.97, SE = 5.53, 95%C.I. = -21.97, .35]. These findings suggest that the parameters just described are unimportant to the model and their removal should be considered.

Model Modification. As before, the residual covariance matrix and the modification indices were examined in order to assess potential modifications that could improve model fit. None of the standardized residuals were larger than 2.58 (the largest value was -2.32). Once again, the modification indices did not suggest any amendments that were judged to be theoretically reasonable or acceptable.

However, because several individual parameters were non-significant, the model required modification before the resulting parameter estimates were to be interpreted. Once again, the non-significant parameters were addressed in a sequential manner beginning with the estimate representing the largest deviation from significance. Following the adjustments, all previously non-significant parameters continually failed to meet the criterion for significance and were removed from the final model except for the covariance between the disturbance terms of the learning and executive functioning factors. Because this parameter did approach significance ($p = .083$) and removing it actually resulted in slightly less good fit, the covariance was retained in the final model. The resulting solution did not possess any unfeasible parameter estimates.
Regarding model fit, removal of the non-significant parameters resulted in improved model fit compared with the original model (see Table 5). Once again, no modification indices were deemed to be worthwhile. In sum, it was judged that the current structural model represented a good fit of the data and no further modifications were necessary. The final structural model including standardized coefficients is illustrated in Figure 7. Table 7 presents the estimated coefficients, standard errors and confidence intervals corresponding to the decomposition of all total, direct, and indirect effects included in the final model.

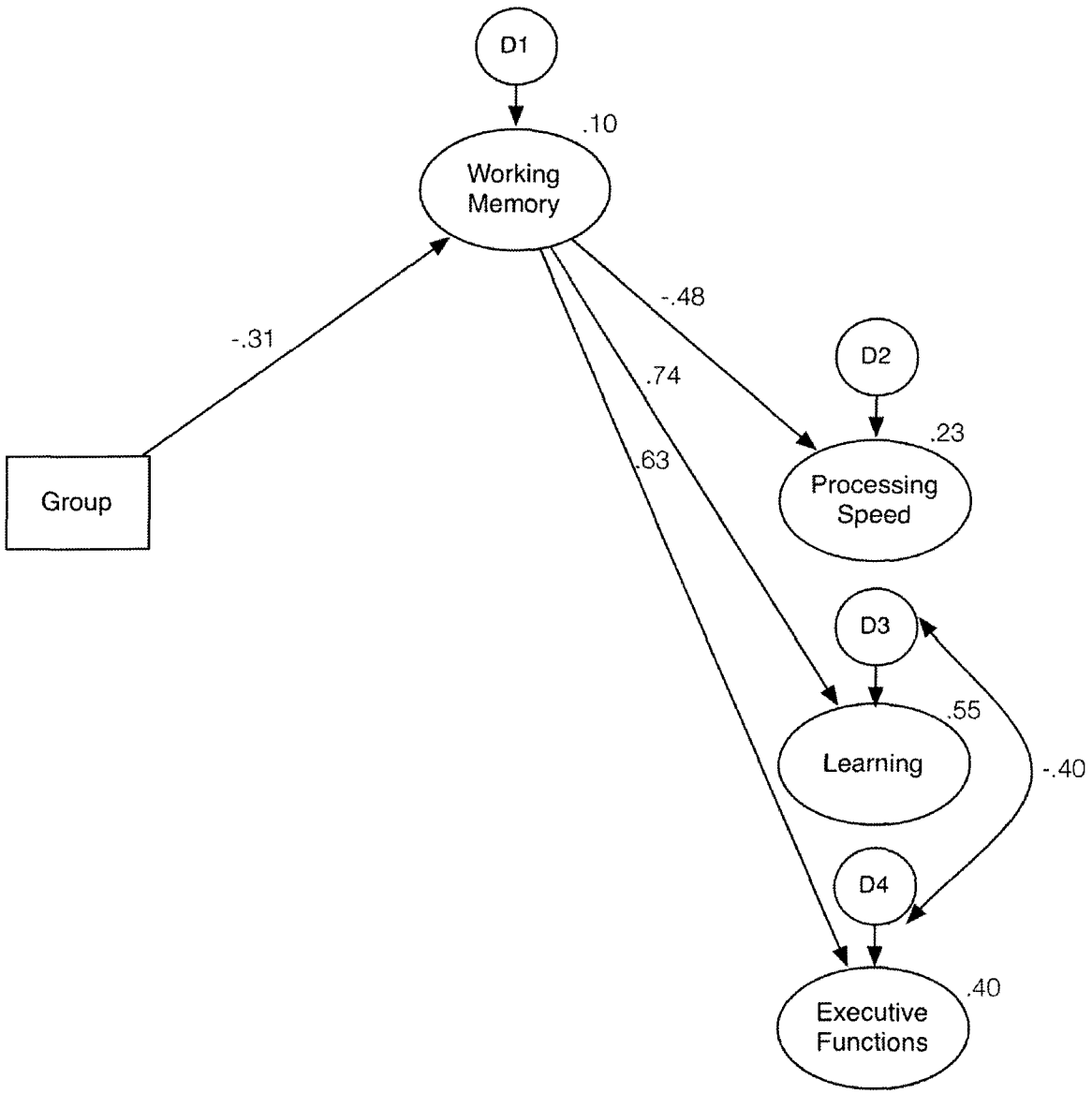

Figure 7. Final Structural Model for Hypothesis Two – the Working Memory Structural Model.

Note. Measurement model not shown.

Table 7. Effects Decomposition for Final Working Memory Structural Model 2.

	Predictor Variables							
	Group				Working Memory			
	B	SE	95% C.I.	β	*B*	SE	95% C.I.	β
Processing Speed								
Direct effect	-	-	-	-	-.02	.00	-.03, -.01	-.48
Indirect effect	.02	.01	.01, .04	.15				
Learning								
Direct effect	-	-	-	-	2.42	.47	1.56, 3.41	.74
Indirect effect	-2.84	1.07	-5.26, -1.00	-.23				
Executive Functioning								
Direct effect	-	-	-	-	2.09	.59	.99, 3.30	.63
Indirect effect	-2.45	.93	-4.76, -1.00	-.20				
Working Memory								

Direct effect	-1.18	.38	-1.95, -.46	-.31

Note. B, unstandardized coefficient; SE, standard error; 95% C.I., 95% confidence interval; β, standardized coefficient; -, non-significant and removed from final model.

Direct Effects. Group membership directly predicted working memory. As noted in the assessment of the originally hypothesized structural model, the path corresponding to the direct effects of group membership on processing speed, learning, and executive functioning were not significant and were removed from the final model. Working memory is expected to be worse by 1.18 units for individuals with a diagnosis of MS relative to Controls.

Working memory predicted processing speed, learning, and executive functioning. Processing speed is expected to get better by .02 logarithmic transformed units, learning is expected to get better by 2.42 units, and executive function is expected to get better by 2.09 units for each unit increase in working memory ability. Working memory is of greatest importance for predicting learning, followed by executive functioning, and then processing speed.

Indirect Effects. The indirect effects of group on the cognitive constructs via working memory were significant for processing speed, learning, and executive functioning. We know from the results of the first structural equation model that group membership does not significantly predict processing speed or executive functioning. Because no direct effects of group membership on these two cognitive factors exist, it would be inappropriate to refer to the significant indirect effects on these factors found in the current model as mediation effects. In such cases, the terms indirect effects and intervening variables are used in place of mediation effects and mediating variables (Preacher & Hayes, 2004). The results suggest that, although group membership did not directly predict processing speed or executive functioning, group membership is related to these cognitive factors through its association with working memory. Specifically, via

the influence of MS on working memory, processing speed is expected to be worse by .02 logarithmic transformed units and executive functioning is expected to be worse by 2.45 units for individuals with MS relative to controls.

In contrast to processing speed and working memory, the results of the first structural equation model indicated that group membership had a significant direct effect on learning. However, with working memory controlled for in the present model, the direct effect of group membership on learning was not significant. The significant indirect effect of group membership on learning suggests that group membership indirectly influences learning through its association with working memory. Specifically, via the MS-related influence on working memory, learning is expected to be worse by 2.84 units for individuals with MS. Kline (2005) notes that the pattern of results characterized by statistically significant indirect effects but not direct effects represents the strongest demonstration for a mediator effect. The indirect effect of group membership has a comparable degree of importance for predicting learning and executive functioning but has less importance for predicting processing speed.

Squared Multiple Correlations. Regarding the percent of variance in the cognitive functions accounted for by the predictor variables (working memory and group), 9.7% of the variance in working memory was accounted for by group membership (R^2 = .097, *SE* = .06, 95%C.I. = .015, .22). Furthermore, 23.3% of the variance in processing speed (R^2 = .233, *SE* = .10, 95%C.I. = .078, .454), 54.8% of the variance in learning (R^2 = .548, *SE* = .12, 95%C.I. = .307, .779), and 39.6% of the variance in executive functioning (R^2 = .396, *SE* = .20, 95%C.I. = .142, .889) was accounted for by group membership and working memory.

Comparison of the Models. The AIC, BCC, and BIC values obtained for the final Relative Consequence structural model were 108.26, 113.47, and 191.03, respectively. The AIC, BCC, and BIC values obtained for the final Working Memory structural model were 103.15, 107.99, and 180.00, respectively. Thus, each of these indices was smaller for the Working Memory structural model compared with the Relative Consequence structural model. As mentioned previously, smaller values are preferred. According to Burnham and Anderson's (1998) criteria, the difference of 5.11 between the AIC values and the difference of 5.48 between the BCC values for the two models should be interpreted as definite evidence that the Relative Consequence structural model is not the best model given the present data. According to Raftery's (1995) criteria, the difference of 11.03 between the BIC values for the two models should be interpreted as very strong evidence that the Relative Consequence structural model is not preferred in comparison to the Working Memory structural model.

Therefore, in absolute terms, the Working Memory structural model outperforms the Relative Consequence structural model according to each of the statistics examined. It should be kept in mind that when considering the meaning of the magnitude of the differences, in addition to assessing badness of fit, each statistic also takes into account the complexity of a model by forming a weighted sum of the two. The degree of penalty corresponding to complexity differs across the three statistics with the BCC imposing a slightly greater penalty for model complexity than the AIC and the BIC imposing a greater penalty for model complexity relative to both the AIC and BCC (Arbuckle, 2009). Because one fewer parameter was included in the final Working Memory structural model, this model is less complex in comparison with the final Relative Consequence

structural model. However, a difference of one parameter is slight and, therefore, it is not likely that this difference contributed substantially to the smaller values obtained by the Working Memory structural model vs. the Relative Consequence structural model, especially in the case of the AIC and BCC.

In terms of the parameter estimates obtained between the two models, the path coefficient for the direct effect of group on working memory in the Working Memory structural model was significant whereas the path coefficient for the direct effect of group on processing speed in the Relative Consequence structural model was not. Therefore, a relationship between group membership and working memory was found to exist whereas there was not sufficient evidence for a relation between group membership and processing speed. Indeed, this is supported by the results of the comparisons between groups on the observed variables presented in Table 2. The MS participants performed significantly worse than Controls on both measures of working memory whereas the MS participants only performed significantly worse than Controls on one measure of processing speed (Simple RT).

When the variance in the endogenous cognitive constructs accounted for by the predictor variables is considered, it can be seen that the combination of the indirect effect of group and the direct effect of working memory in the Working Memory structural model accounted for substantially more of the variance in the learning construct than did the combination of the direct effects of group and processing speed in the Relative Consequence structural model (.55 vs. .16). Also, the combination of the indirect effect of group and the direct effect of working memory in the Working Memory structural model accounted for substantially more of the variance in the executive functioning construct

than did processing speed alone in the Relative Consequence structural model (.40 vs. .07). However, more of the variance in working memory was accounted for by the combination of the direct effects of group and processing speed in the Relative Consequence structural model than was accounted for by group alone in the Working Memory structural model. The combination of the indirect effect of group and the direct effect of working memory in the Working Memory structural model accounted for 23.3% of the variance in processing speed whereas the direct effect of group alone in the Relative Consequence structural model did not significantly predict processing speed.

Summary. Group membership predicted working memory. Specifically, the results indicated worse working memory ability for the MS participants relative to Controls. Worse working memory ability was associated with slower processing speed and worse learning and executive functioning abilities. Reduced working memory ability had the greatest effect on learning, followed by executive functioning, and then processing speed. Via the influence on working memory, group membership also predicted processing speed, learning, and executive functioning. Specifically, slower processing speed and worse learning and executive functioning abilities were indicated for MS participants relative to controls, with the individual cognitive functions affected to similar degrees. Working memory ability itself affected processing speed, learning, and executive functioning ability to a greater degree than did the presence or absence of MS via its influence on working memory ability. Furthermore, the significant direct effect of group on learning observed in the Relative Consequence structural model with no mediator present was rendered non-significant once working memory ability was accounted for. This is strong evidence for the mediating role of working memory in the

relation between MS and learning. Because no direct effects of group membership on processing speed and executive functioning were observed in the Relative Consequence model without a mediator present, the significant indirect effects in the present model indicate working memory functions as an intervening variable such that group membership is related to these cognitive factors through its association with working memory. The presence or absence of MS could only account for a small amount of the variance in working memory (9.7%). Between the determinants of group membership and working memory, moderate amounts of variance in processing speed (23.3%) and executive functioning (39.6%) and a large amount of variance in learning (54.8%) were accounted for in the final model. Comparisons of the two models clearly showed that the final Working Memory structural model fit the data better and accounted for more of the variance in learning and executive functioning than the final Relative Consequence structural model. In sum, the results do support the mediating or intervening role of working memory on cognitive functioning in early relapsing-remitting MS.

Hypothesis 3 – Controlling for Depression and Fatigue

In order to account for possible effects of depression and fatigue on cognitive functioning, the final structural equation models from Hypotheses 1 and 2 were modified to include observed depression and fatigue covariates (i.e., the Beck Depression Inventory-Fast Screen and Fatigue Impact Scale, respectively). Paths linking the depression and fatigue variables to all cognitive factors were included. With these paths included in the models, the relations investigated in the previous two structural models were once again assessed but this time the possible effects of depression and fatigue on the relations were controlled for. If depression and fatigue do contribute to cognitive

dysfunction in MS then the pathways between these variables and the cognitive factors were expected to be significant and the path coefficients representing the relations between MS and the cognitive constructs were expected to be altered.

Initial runs of the models revealed that fit was not acceptable and it was clear that this was due to the absence of correlations between the group, depression, and fatigue variables. The results yielded substantial modification indices pertaining to such correlations and large standardized residuals between these variables were also observed. Because it is logical for symptoms of depression and fatigue to be related to one another and because individuals with MS are known to commonly experience both depression and fatigue, the original models were modified to include correlations between these variables.

Model Assessment. For the Relative Consequence structural model including the covariates, none of the parameters estimates for the paths between the depression covariate and cognitive factors met the criterion for significance. Therefore, the depression covariate and all paths leading from it were removed in the final covariate Relative Consequence structural model. These results suggest that depression is not an important covariate for the relations represented in the final Relative Consequence structural model. Also, the paths between the fatigue covariate and the working memory and executive functioning factors were not significant and were removed from the final covariate Relative Consequence structural model as well. All other paths were significant and were retained in the final model.

The final covariate Relative Consequence structural model (Figure 8) was judged to possess adequate fit and all parameter estimates were feasible (see Table 5).

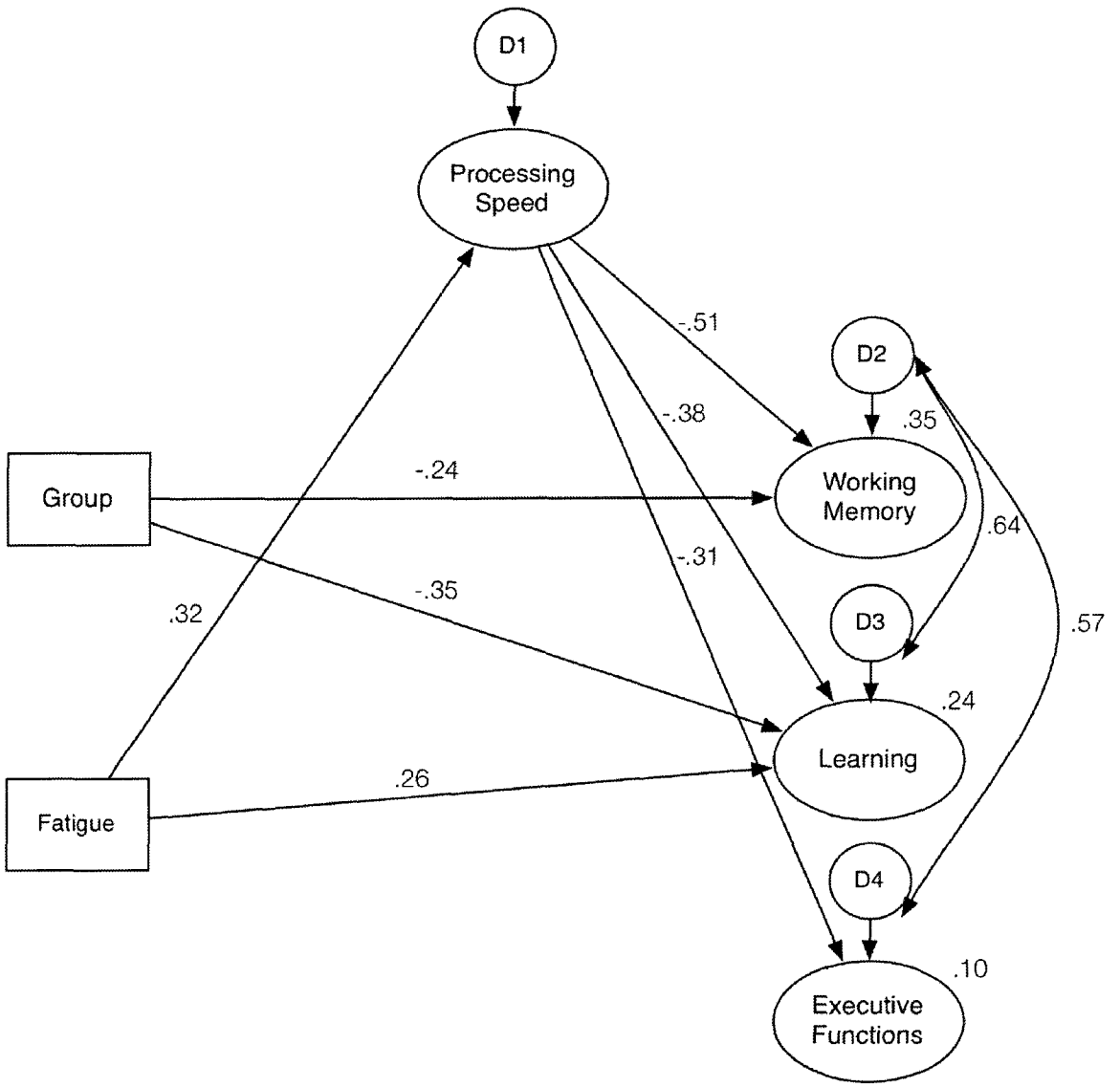

Figure 8. Hypothesis Three – the Relative Consequence Structural Model with Covariates.

Note. Measurement model not shown.

Examination of the standardized residual covariance matrix failed to show any values larger than 2.58 (the largest value was 2.27). The remaining modification indices were not judged to be logical or acceptable.

Table 8 presents the estimated coefficients, standard errors, and confidence intervals corresponding to the effects included in the final structural model. Although the effects of the fatigue covariate had not been significant for the working memory or executive functioning constructs, the fatigue covariate was significant for the processing speed and learning constructs. However, the direct effects of group on the working memory and learning constructs and the direct effects of processing speed on the working memory and learning constructs remained significant with fatigue taken into account.

For the Working Memory structural model including the covariates, the effects of depression on the working memory, processing speed, and executive functioning constructs did not meet significance and these paths were removed in the final covariate Working Memory structural model (Figure 9). Also, the effects of the fatigue covariate were not significant for the working memory, learning, or executive functioning constructs and were removed from the final covariate Working Memory structural model as well.

The Working Memory structural model including the covariates possessed only marginal fit, $\chi^2(59, N = 142) = 94.14, p = .002$, CFI = .92, AIC = 158.14, BCC = 165.20 and BIC = 252.73. The RMSEA was .065 with a 90% confidence interval of .039-.089. All parameter estimates were feasible no standardized residuals exceeded 2.58 (the largest value was 2.27). However, eight additional modification indices were yielded for this model compared with the final Working Memory structural model without

Table 8. Path Coefficients and Critical Ratios for Final Covariate Model 1.

	Predictor Variables											
	Group				Processing Speed				Fatigue			
	B	SE	95% C.I.	β	*B*	SE	95% C.I.	β	*B*	SE	95% C.I.	β
Processing Speed	-	-	-	-					.01	.004	.003, .02	.32
Working Memory	-3.32	1.26	-5.71, -.84	-.24	-45.46	10.01	-67.53, -27.01	-.51	-	-	-	-
Learning	-4.52	1.55	-7.48, -1.44	-.35	-31.37	9.34	-49.71, -13.00	-.38	.66	.28	.09, 1.19	.26
Executive Functioning	-	-	-	-	-24.45	10.73	-47.20, -3.57	-.31	-	-	-	-

Note. B, unstandardized coefficient; SE, standard error; 95% C.I., 95% confidence interval; β, standardized coefficient; -, non-significant and removed from final model.

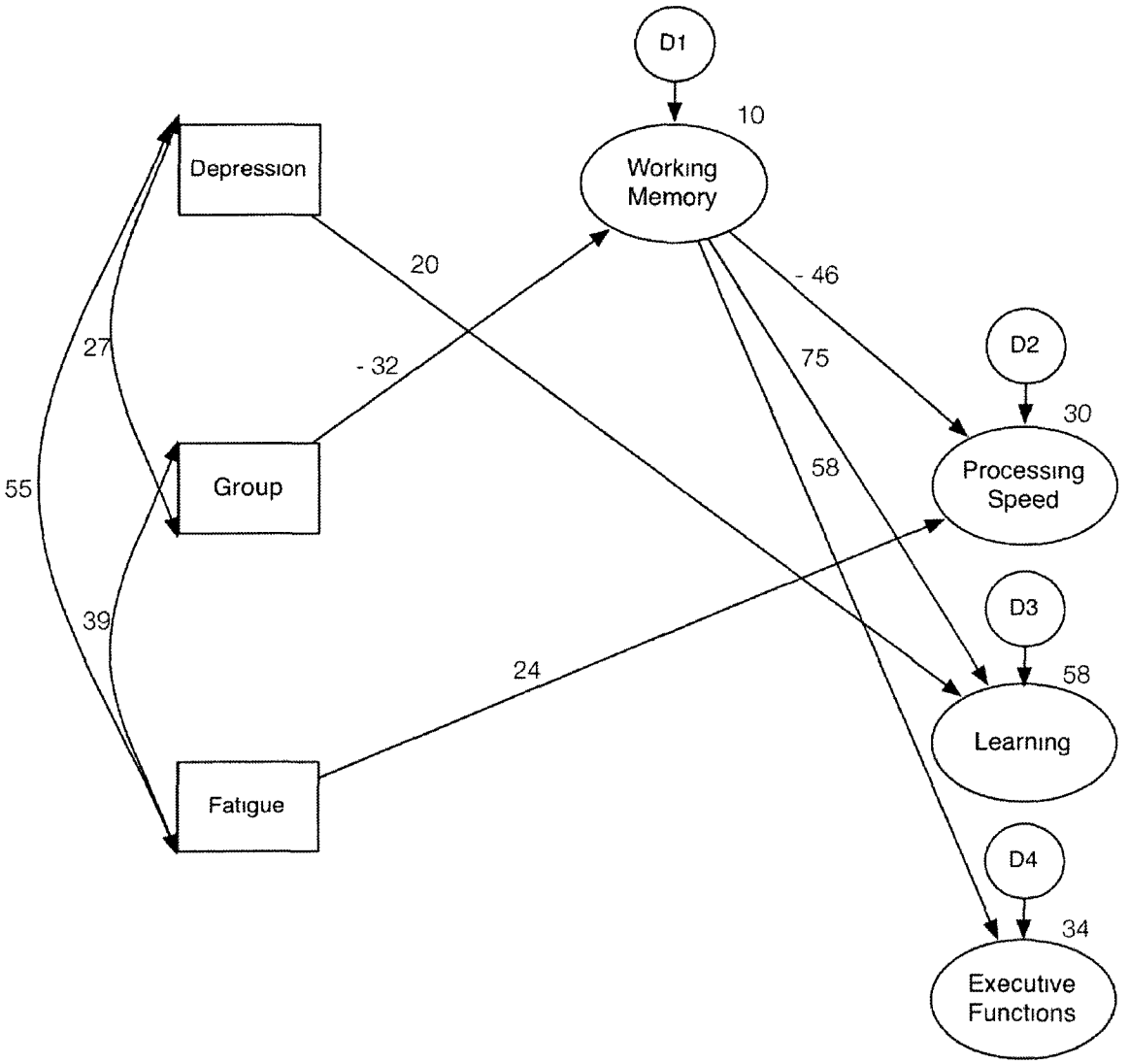

Figure 9. Hypothesis Three – the Working Memory Structural Model with Covariates.

Note Measurement model not shown.

covariates. The majority of these additional modification indices pertained to links between the covariate variables and error terms associated with the observed cognitive variables. Had the model been respecified to include these links, model fit would have improved. But because the suggested modifications were not judged to be logical or acceptable, the model was not modified to include them.

Table 9 presents the estimated coefficients, standard errors and confidence intervals corresponding to the decomposition of all total, direct and indirect effects included in the final model. Although the effects of the depression covariate had not been significant for the working memory, processing speed, or executive functioning constructs, depression was related to the learning construct. However, the indirect effect of group and the direct effect of working memory on the learning construct remained significant with depression accounted for. Similarly, the indirect effect of group and direct effect of working memory remained significant even with the effect of the fatigue covariate on the processing speed construct accounted for.

Summary. Fatigue predicted processing speed and learning in the final covariate Relative Consequence structural model. Specifically, more fatigue was associated with slower processing speed and, surprisingly, better learning. Depression predicted learning and fatigue predicted processing speed in the covariate Working Memory structural model with more depressive symptoms, again surprisingly, associated with better learning and more fatigue associated with slower processing speed. Of most importance, all of the significant results from the final Relative Consequence and Working Memory structural models remained even after the effects of depression and fatigue were accounted for, indicating that these variables were not responsible for the relationships

Table 9. Effects Decomposition for Final Covariate Model 2.

	Predictor Variables											
	Group				Working Memory				Covariates			
	B	SE	95% C.I.	β	*B*	SE	95% C.I.	β	*B*	SE	95% C.I.	β
Processing Speed												
Direct effect	-	-	-	-	-.02	.004	-.03, -.01	-.46	.01[a]	.003	.002, .012	.24
Indirect effect	.02	.01	.01, .04	.15								
Learning												
Direct effect	-	-	-	-	2.43	.46	1.60, 3.51	.75	1.43[b]	.02	.13, 2.73	.20
Indirect effect	-2.96	1.14	-5.41, -.94	-.24								
Executive Functioning												
Direct effect	-	-	-	-	1.93	.54	.96, 3.07	.58	-	-	-	-
Indirect effect	-2.35	.90	-4.64, -.96	-.18								
Working Memory												

Direct effect	-1.22	.40	-2.01, -.45	-.32	-	-	-	-

Note. B, unstandardized coefficient; SE, standard error; 95% C.I., 95% confidence interval; β, standardized coefficient; -, non-significant and removed from final model. [a]Effect of fatigue on processing speed; [b]Effect of depression on learning.

observed previously. Therefore, overall, the depression and fatigue covariates were not important to the relations in the previous structural equation models.

Hypothesis 4 – The Contributions of Different Cognitive Functions to Multifactorial Measures

Because the 3s PASAT and the Symbol Digit Modalities Test were also administered as part of the larger longitudinal project, the multifactorial nature of these tests, which have been used extensively to assess cognitive decline in MS, could be assessed. As outlined in the introduction, the PASAT and the Symbol Digit Modalities Test both are used as measures of processing speed and working memory and the Symbol Digit Modalities Test may also assess learning. Hierarchical regression analyses were used to evaluate the contributions of the cognitive functions defined in the structural equation models to performance on these two measures. Comparisons between the performances of the groups on these measures are presented in Table 10. MS patients had fewer correct responses than controls on the PASAT and Symbol Digit Modalities Test, although group differences were only significant for the PASAT.

3 Second PASAT. In an attempt to delineate the contributions of processing speed and working memory to PASAT performance, a hierarchical regression analysis was conducted using the following predictor variables: group and factor scores summarizing the observed variables used to indicate the processing speed and working memory factors in the structural equation models. The individual independent variables were entered on the first block, followed by all possible two-way interactions (i.e., group X processing speed, group X working memory, processing speed X working memory) on the second block, and the three-way interaction on the last block (i.e., group X processing

Table 10. Comparisons Between the Groups on the Multifactorial Measures.

	Group					
	Control (N=72)		MS (N=70)			
	Mean	SD	Mean	SD	$t(140)$	Cohen's d
3s PASAT	51.83	8.31	48.01	10.83	2.37*	.40
Symbol Digit Modalities Test	63.71	9.25	61.14	11.19	1.49	.25

Note. *$p<.05$.

speed X working memory). Because interactions composed from the group variable were tested, group was first centred. The factor scores representing processing speed and working memory were in standardized form and, thus, did not require centering. The *t*-tests associated with the regression coefficients were examined to determine whether the independent variables made a significant contribution to predicting PASAT performance and the zero-order and part (i.e., semipartial) correlations were used to evaluate the quantity of overall and unique variance accounted for by each independent variable. The *F Change* associated with the block where the three-way interaction was entered into the model was not significant ($p < .05$), thus, data are not reported for this model/variable.

The results of the hierarchical regression analysis are presented in Table 11. The model containing the group, processing speed, and working memory variables was significant and the R^2 value indicated that 32% of the variance in PASAT performance was predicted by the variables. Of the three, only processing speed and working memory significantly contributed to prediction. Because a reflect and square root transformation was applied to the PASAT variable, higher PASAT scores should be interpreted as worse performance and vice versa. Therefore, the coefficients indicate that individuals with slower processing speed and lower working memory ability perform worse on the PASAT. The squared zero-order correlations show that, separately, processing speed predicts 23% and working memory predicts 20% of the variance in PASAT performance. Together (including group), the model accounted for 32% of the variability in PASAT performance. Furthermore, the squared semipartial correlations show that, with the overlapping or common variance between the predictors removed, processing speed uniquely predicts 10% and working memory uniquely predicts 7% of

Table 11. Hierarchical Regression Analysis for the 3s PASAT.

	R^2 *Change*	*F Change*	*df*	*B*	*t*	Correlations	
						Zero-order	*Part*
Block 1	.32	21.22***	3, 138				
Group				.16	.75	.19	.05
Processing Speed				.51	4.61***	.48	.32
Working Memory				-.43	-3.81***	-.45	-.27
Block 2	.06	4.23**	3, 135				
Group X PS				.36	1.66	.14	.11
Group X WM				.09	.39	.04	.03
PS X WM				-.28	-2.65**	-.15	-.18

Note. *B* = unstandardized coefficient; PS = Processing Speed; WM = Working Memory. Model 2: $R^2 = .37$, $F = 13.47$, $p < .001$.
*$p<.05$; **$p<.01$; ***$p<.001$.

the variance in PASAT performance. Thus, processing speed and working memory together predict a significant amount of variance in PASAT performance and each factor makes a comparable unique contribution.

The block including the two-way interactions accounted for an additional 6% of the variance in PASAT performance over and above the first-order effects of the predictors. However, only the processing speed by working memory interaction significantly contributed to prediction, accounting for 3% of the variance. In order to understand the form of the interaction, a simple slopes analysis was conducted using Preacher, Curran, and Bauer's (2006) online calculator to evaluate the relationship between processing speed and PASAT performance at high, average, and low levels of working memory ability (i.e., scores corresponding to +1SD, the mean, -1SD on working memory). See Figure 10 for an illustration of the relation between processing speed and PASAT performance at different levels of working memory ability. The relation between processing speed and PASAT performance was not significant for individuals with high working memory ability ($B = 0.22$, $t = 1.47$, $p = .14$). However, for individuals with average and low working memory ability, slower processing speed resulted in significantly worse PASAT performance. Individuals with low working memory performance showed the largest effects of processing speed, $B = 0.79$, $t = 5.24$, $p < .001$, but those with average working memory also showed effects, $B = 0.50$, $t = 4.76$, $p < .001$.

In sum, both processing speed and working memory ability are related to performance on the PASAT. However, the degree to which each of these resources influences performance depends on the level of the other. The PASAT performance of individuals with high working memory ability was not related to how quickly they

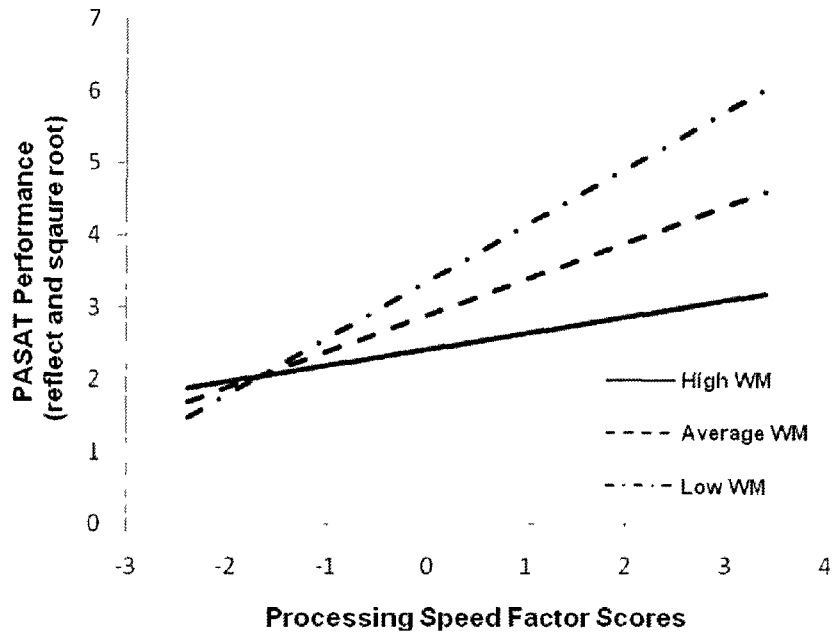

Figure 10. The Relationship between Processing Speed and PASAT Performance at Different Levels of Working Memory Ability.

Note. WM, working memory.

process information. In contrast, for individuals with lower levels of working memory ability, the rate at which information can be processed becomes increasingly more important to successful execution of the task. Individuals with slowed processing speed and low working memory ability would be expected to perform the worst and individuals with fast processing speed and high working memory ability would be expected to perform the best.

Symbol Digit Modalities Test. A hierarchical regression analysis similar to the one described above was conducted for the Symbol Digit Modalities Test but the contribution of learning was investigated as well. The *F Change* associated with the blocks where the three-way interactions and the four-way interaction were entered into the model was not significant, thus, data is not reported for these models/variables. The results of the hierarchical regression analysis are presented in Table 12. The model (block 1) containing group, processing speed, working memory, and learning accounted for 36% of the variance in PASAT performance. Group was the only variable that did not significantly contribute to prediction. The coefficients indicate that individuals with slower processing speed and lower working memory and learning ability performed worse on the Symbol Digit Modalities Test. The squared zero-order correlations show that, separately, processing speed predicts 20%, working memory predicts 21%, and learning predicts 23% of the variance in Symbol Digit Modalities Test performance. The squared semipartial correlations show that processing speed uniquely predicts 7%, working memory uniquely predicts 3%, and learning uniquely predicts 7% of the variance in Symbol Digit Modalities Test performance. Thus, processing speed, working memory, and learning together predict 22% of shared variance in Symbol Digit

Table 12. Hierarchical Regression Analysis for the Symbol Digit Modalities Test.

						Correlations	
	R^2 Change	*F Change*	*df*	*B*	*t*	*Zero-order*	*Part*
Block 1	.36	19.53***	4, 137				
Group				.04	.58	-.13	.04
Processing Sped				-.28	-3.79***	-.45	-.26
Working Memory				.21	2.45*	.46	.17
Learning				.30	3.79***	.48	.26
Block 2	.07	2.74*	6, 131				
Group X PS				-.19	-2.55*	-.22	-.17
Group X WM				.10	1.18	.07	.08
Group X Learning				-.04	-.46	.04	-.03
PS X WM				.10	1.19	.10	.08
PS X Learning				-.03	-.29	.16	-.02
WM X Learning				-.03	-.31	-.10	-.02

Note. *B* = unstandardized coefficient; PS = Processing Speed; WM = Working Memory. Model 2: $R^2 = .43$, $F = 10.057$, $p < .001$.
*$p<.05$; **$p<.01$; ***$p<.001$.

Modalities Test performance and each factor makes a significant unique contribution separate from the other. This pattern strongly supports the view that the Symbol Digit Modalities Test is a good discriminating measure for cognitive dysfunction in multiple sclerosis because it is sensitive to three cognitive functions that often are affected.

Further, the two-way interactions accounted for an additional 7% of the variance in Symbol Digit Modalities Test performance. However, only the group by processing speed interaction contributed to prediction, accounting for 3% of the variance. This pattern suggests that the relation between processing speed and Symbol Digit Modalities Test performance is different for MS patients than it is for controls. Once again, a simple slopes analysis was conducted in order to understand the form of the interaction and was carried out by evaluating the relation between processing speed and PASAT performance for MS patients and controls (Figure 11). The relation between processing speed and Symbol Digit Modalities Test performance was not significant for controls (B = -1.02, t = -.97, p = .34). However, for patients with MS, Symbol Digit Modalities Test performance declined as processing speed decreased (B = -4.97, t = -4.07, $p < .001$).

In sum, processing speed, working memory, and learning ability all positively contribute to performance on the Symbol Digit Modalities Test. However, the degree to which processing speed influences performance differs depending on whether an examinee is a patient with MS or a non-clinical control. The performance of individuals without MS is not affected by how quickly they can process information. In contrast, for patients with MS, the rate at which information can be processed is important to successful execution of the task.

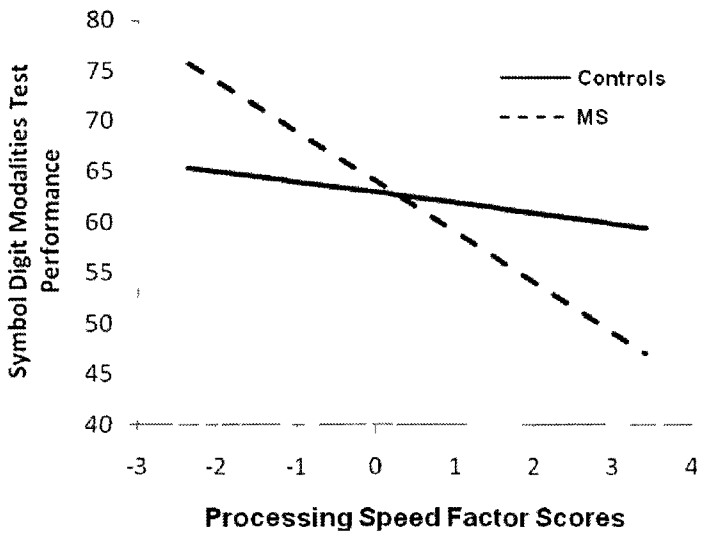

Figure 11. The Relationship between Processing Speed and Symbol Digit Modalities Test Performance for Controls and Patients with MS.

CHAPTER FOUR: DISCUSSION

The primary goal of the present research was to test two models of the relation between MS and cognitive functioning. A substantial sample of controls and MS patients completed a broad range of tasks that assessed four cognitive functions: processing speed, working memory, learning, and executive functioning. Unexpectedly, a structural equation model analysis revealed that group membership did not predict processing speed in the present sample, and thus, processing speed could not play any mediating role in the MS-related effects on other cognitive functions. Accordingly, the present results do not support the *Relative Consequence Model*. However, processing speed was important to higher-level cognitive functions in general, with slower processing speed most detrimental to working memory. In contrast to processing speed, group membership did predict working memory and learning such that MS participants performed worse on measures of these cognitive functions than controls. Furthermore, a second structural equation model analysis supported a role for working memory as a mediating or intervening factor for cognitive functioning in early relapsing-remitting MS. Through reduced working memory ability, MS was associated with slower processing speed and worse learning and executive functioning abilities. Neither depression nor fatigue could account for the relations between MS and the cognitive functions studied in the structural equation models.

A second goal of the present study was to evaluate the contributions of different cognitive functions to performance on multifactorial measures that have commonly been used to assess cognitive decline in MS. Processing speed and working memory both contributed to performance on the PASAT. However, the degree to which processing

speed influenced performance differed depending on the level of working memory ability. Specifically, the performance of individuals with high working memory ability was not influenced by processing speed whereas, in contrast, processing speed became increasingly more important to the successful execution of the task as working memory declined to average and low levels. Processing speed, working memory, and learning all contributed to performance on the Symbol Digit Modalities Test. However, when the contribution of processing speed was evaluated for the groups individually, it was found that processing speed was only associated with the performance of patients with MS and not controls.

In the remainder of the discussion, I present the two most likely explanations for a lack of processing speed deficits (i.e., the improved operationalization of processing speed and the mild and short disease course characterizing the MS sample). The potential interpretation that the results indicate intact simple processing speed in the face of impaired complex processing speed will be addressed, as well as the general importance of processing speed to higher-level cognitive functions. In addition, the nature of working memory dysfunction in MS, the discrepancy between the present results and previous claims that working memory impairment only occurs at more advanced stages of the disease, and the possible mechanisms by which working memory relates to other cognitive functions will be considered. The results concerning the contribution of different cognitive functions to multifactorial measures will be compared with findings from previous work. Finally, the limitations of the present research and potential future directions will be presented, followed by a discussion of the practical implications of the results.

Absence of Impaired Processing Speed in the MS Sample

One of the most commonly observed cognitive impairments in individuals with MS is a reduced ability to process information quickly (e.g., Archibald & Fisk, 2000; Demaree et al., 1999; Denney et al., 2004; Kail, 1997c, 1998; Lengenfelder et al., 2003; 2006). However, processing speed was not impaired in the present sample of patients with MS. Group membership did not predict the latent processing speed factor in the structural equation model and the groups did not differ on the individual Choice RT, Semantic Search RT, or Symbol Digit Modalities Test variables. The groups did differ on the Simple RT and 3s PASAT variables. However, these differences may have arisen due to other factors besides processing speed, such as perceptual and motor processes or working memory ability.

Operationalization of Processing Speed

Although processing speed deficits were expected in this study because they are commonly found, as noted in Chapter One, not all studies examining processing speed in MS have found evidence of deficits. For instance, although some researchers have reported worse Sternberg memory scanning speed for patients with MS (Archibald et al., 2004; Archibald & Fisk, 2000; Janculjak et al., 2002; Rao et al., 1989b), other studies have found worse initial response speed but no difference on memory scanning speed (Drew et al., 2009; Janculjak et al., 1999; Litvan et al., 1988b). In addition, Santiago et al. (2007) reported relapsing-remitting MS patients with mild to moderate disability showed no deficits in processing speed relative to non-clinical controls on the Stroop test. However, other studies have found deficient processing speed on the preliminary trials of

the Stroop (Bodling et al., 2008, 2009; Denney et al., 2004, 2005; Jennekens-Schinkel, et al., 1990; Kujala et al., 1995; Lynch et al., 2010).

One plausible explanation for the observed lack of processing speed deficits among MS patients in the present research and in other studies is that processing speed was operationalized differently than in the studies where deficits were found. As noted by Archibald and Fisk (2000), although slowed processing speed in MS has been consistently found when researchers have used clinical neuropsychological measures, experimental measures of processing speed have not yielded consistent findings. Interestingly, the present study and those discussed above all employed what would be considered experimental measures of processing speed. Therefore, clinical neuropsychological measures of processing speed may share certain characteristics, increasing the likelihood that performance deficits will be observed for individuals with MS. Specifically, one commonality among clinical neuropsychological measures is that they often tap multiple cognitive functions. Such multidimensionality may facilitate detection of cognitive dysfunction but hinder the ability to identify the specific cognitive function(s) affected. I presented analyses of two commonly used measures, the PASAT and Symbol Digit Modalities Test, and found that these tasks are sensitive to variability in both processing speed and working memory, with the Symbol Digit Modalities Test related to learning as well.

Although the evidence is mixed, the results of the present study and those studies described above are consistent with the interpretation that the use of multifactorial measures may have led to conclusions that processing speed was impaired when, in actuality, poor performance may have resulted from working memory or learning

deficits. It is not my intention to suggest that processing speed impairments do not exist *at all* in patients with MS. Indeed, given that the disease pathology directly affects the efficiency with which neural impulses are conducted in the central nervous system, it is reasonable to think that speed of cognitive processing would also be affected. Furthermore, previous research employing the Computerized Test of Information Processing has shown significantly reduced processing speed for patients with relapsing-remitting MS compared with controls (Tombaugh, Berrigan, Walker, & Freedman, 2010). Instead, I intend to imply that processing speed may not be significantly reduced in all patients with MS. For instance, the average disease duration of the patient sample tested by Tombaugh et al. (2010) was about twice as long as the average disease duration of the present sample. Therefore, the absence of impaired processing speed in the present MS sample may be due to patient characteristics such as disease duration.

Prevalence of Cognitive Dysfunction and Impaired Processing Speed in MS

In line with the above proposal, research estimating the prevalence of cognitive dysfunction in MS indicates that not all patients with MS are expected to have cognitive impairments. Although the frequency of cognitive dysfunction in MS is estimated to range from 40% to 60% of patients (Benedict et al., 2006; Heaton et al., 1985; McIntosh-Michaelis & Roberts, 1991; Peyser et al., 1990; Rao et al., 1991), such statistics imply that at least 40% of patients will not show cognitive dysfunction. Further, the frequency with which patients will have cognitive impairments is probably linked to the form of the disease. For example, although Benedict et al. (2006) reported that in a sample of 291 mixed-course patients, just over 50% had impaired processing speed, the relapsing-remitting patients performed better than secondary-progressive patients on all measures

composing the MACFIMS battery, with the largest effect size obtained for processing speed. Hence, although the prevalence of impaired processing speed was not reported for the relapsing-remitting patients specifically, presumably it would be even less than the 50% estimated for the overall sample. Therefore, although reduced processing speed is common in MS, not all patients will experience processing speed deficits and these deficits are less prevalent for individuals with the relapsing-remitting form of the disease. This variability may explain why the present sample did not show deficits in information processing speed.

In addition to only including relapsing-remitting patients, the average disease duration of the present sample was about four years. These characteristics indicate that the present sample was composed of patients from the mild end of the disease continuum. Research focusing on patients with short disease duration has been conducted previously. Deloire et al. (2005) reported that 45% of patients with relapsing-remitting MS diagnosed in the previous six months exhibited some form of cognitive impairment. Correspondingly, 55% of patients did not show cognitive dysfunction. The authors also noted that cognitive impairment early on in relapsing-remitting MS remains subtle and does not significantly affect quality of life. In other work examining cognition early in the disease course, impairment has been reported to occur in 25-57% of patients with probable MS or clinically isolated syndrome (CIS; Achiron & Barak, 2003; Feuillet et al., 2007; Potagas et al., 2008; Zipoli et al., 2010). CIS is the first episode of a demyelinating and inflammatory disease of the central nervous system and a proportion of CIS patients will later be diagnosed with definite MS (Anhoque, Domingues, Teixeira, & Domingues, 2010). The wide variability in prevalence of cognitive impairments across samples of

patients with CIS is likely due to the different neuropsychological tests and criteria for defining impairment employed between the studies. When stringent criteria are implemented, approximately 30% of CIS patients experience some form of cognitive impairment (Potagas et al., 2008; Zipoli et al., 2010). This conclusion is in line with a systematic review by Anhoque et al. (2010) stating that cognitive impairment in CIS seems to be less frequent and intense than in definite MS.

In sum, not all patients with MS experience slowed processing speed or overall cognitive impairment. Furthermore, the frequency and degree of impairment appears to be less in relapsing-remitting patients and patients early on in the disease course compared with the general MS population. This pattern is logical given that such characteristics indicate non-progressive disease pathology and less time for pathology to have manifested and exerted its effects on the neurological substrates of cognitive functions. Thus, processing speed may have been unaffected in the present sample because participants had the relapsing-remitting form of the disease and short disease duration.

Simple versus Complex Processing Speed

Some researchers have made the distinction between simple and complex processing speed in the MS literature (e.g., Chiaravalotti et al., 2003; Parmenter et al., 2007a), leading others to interpret their results within this framework (e.g., Drew et al., 2009). Consequently, some may interpret the MS group performing worse on the PASAT but comparably to controls on choice reaction time, semantic search reaction time, and the Symbol Digit Modalities Test as indicative of impaired complex processing speed but intact simple processing speed.

Chiaravalloti and colleagues (2003) distinguish between simple and complex processing speed because of the pattern of results they found in a factor analysis of a large group of speed-related measures. The factor analysis was conducted with data from a mixed sample consisting of 29 non-clinical controls, 45 patients with Chronic Fatigue Syndrome, and 18 patients with Rheumatoid Arthritis. They included a variety of tests that have been used to assess processing speed in the factor analysis, including auditory and visual simple reaction time, auditory and visual choice reaction time, PASAT, Auditory Threshold-Serial Addition Test, Visual Threshold-Serial Addition Test, as well as measures of verbal and visual learning, and measures identified as verbal and visual working memory. The authors reported that the simple and choice reaction time tasks loaded together on a factor they labeled simple speed/reaction time. The various versions of the PASAT and the learning tests loaded on another factor termed complex information processing and new learning. The working memory tasks loaded on a separate factor. However, the PASAT and the Visual Threshold-Serial Addition Test cross-loaded on the working memory factor (-.49 and .47, respectively) and the Auditory Threshold-Serial Addition Test had a moderate loading on the working memory factor as well (.32). The authors concluded that information processing speed is not a unitary construct, with simple and complex processing speed considered to be distinct constructs that are indexed by different neuropsychological tests. The authors also stated that reaction time tasks measure basic elements of attention and concentration, whereas, the various versions of the PASAT measure more complex attention and concentration and require both processing speed and working memory.

I agree with Chiaravalloti and colleagues' (2003) interpretations that the PASAT, in its traditional and modified versions, taxes working memory. However, the results of the study and the conclusions based on them are problematic. First of all, the sample size was small (N=92) relative to what is considered appropriate for factor analysis. In general, a sample size of 100 is considered poor whereas a sample size of 300 or more is preferable when implementing factor analytic techniques (Tabachnick & Fidell, 2007). Use of small samples can result in unreliable estimates of correlation coefficients and thus, questionable validity of any factors that are derived. Second, the participants were drawn from very different populations, none of which was MS, and it is possible that factorial structures vary across different populations, which would also diminish the reliability and validity of the results. For instance, the present study showed that the relation of processing speed to performance on the Symbol Digit Modalities Test differs between patients with MS and persons without any neurological disorder. Similar differences may exist for the variables and populations sampled in the Chiaravalloti et al. study. Finally, the conclusions drawn by Chiaravalloti et al. seem inconsistent with both their data and interpretation that the PASAT requires both processing speed and working memory. The authors attributed the shared variance that was found to exist between the measures labeled as complex processing speed and learning measures to the influence of processing speed on learning. Therefore, after having reported that "complex processing speed" measures require substantial working memory involvement, the authors attributed the shared variance to information processing speed specifically when it may have just as well resulted from working memory.

Statements such as these are inappropriate and serve to perpetuate confusion regarding the nature of cognitive impairment and the relations between different cognitive functions in MS. A plausible alternative interpretation of Chiaravalloti et al.'s (2003) results is that the various versions of the PASAT do not represent good measures of processing speed because they are confounded by working memory abilities. Furthermore, research reporting that one group of individuals performs worse on the PASAT than another group or that PASAT performance is associated with some other cognitive ability does not allow one to determine why such differences or relations exist. In sum, I would interpret the present results that the MS group performed worse on the PASAT but comparably to controls on choice reaction time, semantic search reaction time, and the Symbol Digit Modalities Test as indicative of impaired working memory, not impaired "complex processing speed".

General Importance of Processing Speed to Other Cognitive Domains

Although the present results did not support processing speed as a mediator of the MS-related effects on other cognitive functions, the results did support the general importance of processing speed to higher-level cognitive functioning. Processing speed predicted working memory, learning, and executive functioning such that slower processing speed was associated with worse performance on these constructs. Furthermore, the relation between processing speed and other cognitive constructs was stronger for working memory compared with learning and executive functioning. The strength of the relations between processing speed and these two other cognitive constructs was comparable.

The finding that processing speed is important to higher-level cognitive functions, regardless of group membership, is consistent with several theories pertaining to cognitive functioning in the general population that were described in Chapter One. Kail and Salthouse (1994) provided one account of how processing speed is thought to contribute to general cognitive ability. They proposed that (a) processing speed is an important resource because time is a limiting factor and therefore, the faster that processing is performed, the better the cognitive performance; (b) people differ in the speed at which processing operations can be executed; and (c) the advantages of increased speed are that more operations can be performed in a given amount of time and later operations can be carried out before the products of earlier operations have decayed (Salthouse, 1985). Alternatively, the *Developmental Cascade Model* proposed that, as children's information processing becomes faster, this leads to improvements in working memory which, in turn, yields increased fluid intelligence (Fry & Hale, 1996). Fry and Hale found that the same cascade model could explain individual differences in cognition.

The link between processing speed and working memory capacity emphasized in the *Developmental Cascade Model* is consistent with the present finding that processing speed was particularly important for working memory. Other researchers have posited that processing speed may facilitate working memory ability because faster processing speed enables faster rehearsal which is expected to yield improved creation and maintenance of working memory stores (Demaree et al., 2008), or because of the rapid execution of processes that refresh information in the slave systems of working memory (Kail, 2008). In the present study, although processing speed was strongly related to

working memory, only 30% of the variance in working memory was accounted for in the Relative Consequence structural model. This finding indicates that, although the two functions are related, working memory ability and processing speed are by no means equivalent constructs and there is more to working memory capacity than just the rapid processing of information.

Although the present results do not provide any insight regarding the mechanism by which processing speed influences higher-level cognitive functions, they do support the contention that processing speed contributes to cognitive ability in general. In addition, the present results indicate that the contribution of processing speed to individual cognitive domains is not equal and that processing speed is especially important to working memory ability.

Presence of Impaired Working Memory in the MS Sample

Although processing speed was not impaired, there was strong evidence for impaired working memory in the present sample. Group membership predicted the latent working memory factor in the structural equation models that were tested and group differences corresponding to medium effect sizes were observed on the individual Reading Span and Letter-Number Sequencing variables. Working memory impairment is considered to be common in MS, thus, the current findings are consistent with past research in the field (Lengenfelder et al., 2006).

Components of Working Memory Affected in MS

As discussed in Chapter One, working memory deficits in MS have been reported for the phonological loop (Hillary et al., 2003; Litvan et al., 1988a, b; Rao et al., 1993; Ruchkin et al., 1994) and the central executive (Arnett et al., 1999; Grigsby et al., 1994a,

b; D'Esposito, 1996; Lengenfelder et al., 2003; Parmenter et al., 2007a). Furthermore, there is evidence that central executive dysfunction is the primary working memory impairment in MS (Arnett et al., 1999; Lengenfelder et al., 2003; Parmenter et al., 2007a).

The results of the present study are consistent with the argument for central executive dysfunction in MS in that patients were found to perform worse on a reading span task. Reading span has been widely used in the cognitive psychology literature to measure working memory capacity and considerable evidence points to the ability to control attention and thought (i.e., central executive functioning) as the central construct measured by reading span (Engle & Oransky, 1999; see Conway et al., 2005).

The other working memory measure used in the present research, Letter-Number Sequencing, is also thought to require the central executive. Several studies have shown that performance on the test cannot be explained by simple storage alone (Crowe, 2000; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Kalmar, Bryant, Tulsky, & DeLuca, 2004). A functional imaging study using positron emission tomography (PET) also provides support for central executive involvement in Letter-Number Sequencing performance. For verbal working memory tasks, the different components of the working memory system are associated with different areas of neural activation in the brain. Specifically, premotor cortex is involved in subvocal articulatory rehearsal, the posterior parietal cortex is involved in temporary storage, and the dorsolateral prefrontal cortex is involved in the active processing of information (Smith, Jonides, Marshuetz, & Koeppe, 1998). The observation of activation in dorsolateral prefrontal cortex in addition to the areas of premotor cortex, orbital frontal cortex, and posterior parietal cortex during

performance of the Letter-Number Sequencing test supports the central executive component of the task (Haut, Kuwabara, Leach, & Arias 2000). Finally, Hill et al. (2010) investigated the ability of different Wechsler Adult Intelligence Scale-III subtests to predict a working memory criterion construct operationalized as factor scores derived from a factor analysis of three commonly-used experimental measures: automatic operation span task, listening span task, and a modified lag task. Letter-Number Sequencing was part of a combination of subtests found to predict the working memory construct and, of all the tests, it contributed the second most to prediction. Because the working memory construct represents shared variance among a number of tasks identified to involve the central executive in the cognitive psychology literature, the present finding that the MS group performed worse than controls on Letter-Number Sequencing is also consistent with the interpretation of impaired central executive in MS.

Previous Claims that Working Memory is Intact in Early MS

The finding that processing speed was not impaired whereas working memory was impaired in the current (early disease course, relapsing-remitting) sample is in disagreement with claims that only processing speed is impaired in early stages of the disease and that working memory deficits do not manifest until later stages (Archibald & Fisk, 2000; DeLuca et al., 2004). For instance, Archibald and Fisk (2000) administered measures of processing speed and working memory capacity to patients with relapsing-remitting and secondary progressive MS and non-clinical controls. The authors reported that, regardless of disease subtype, all patients exhibited worse memory scanning speed relative to controls on the Sternberg Test. In contrast, only the secondary-progressive patients performed worse on working memory capacity measures. Archibald and Fisk

concluded that slowed processing speed manifests early in the disease course but that deficient working memory capacity may only occur after the disease has progressed.

In addition, DeLuca et al. (2004) compared the frequency of impairment on the Processing Speed and Working Memory Indices of the Wechsler Memory Scale-III (Wechsler, 1997b) between groups of patients with relapsing-remitting and secondary-progressive MS. They found that the relapsing-remitting group only exhibited impairment on the Processing Speed Index whereas the secondary-progressive group exhibited impairment on both the Processing Speed and Working Memory Indices, although less so on the Working Memory Index. Similarly to Archibald and Fisk (2000), DeLuca et al. also concluded slowed processing speed may be present early in the disease course (i.e., relapsing-remitting MS), whereas working memory deficits only emerge with disease progression (i.e., secondary-progressive MS). Furthermore, the combination of findings that (a) the magnitude and frequency of impaired processing speed was greater for secondary-progressive patients and (b) secondary-progressive patients also showed impaired working memory led the authors to hypothesize that as the disease progresses a critical level of processing speed impairment is reached that will, in turn, influence working memory. This hypothesis represents the essence of the *Relative Consequence Model.*

Although the present finding of deficient working memory in relapsing-remitting MS patients is opposite to the findings of Archibald and Fisk (2000) and DeLuca et al. (2004), it is consistent with a more recent study. Parmenter et al. (2007a) examined processing speed and working memory abilities in patients with relapsing-remitting MS using the n-back task. The n-back task allowed the researchers to separately assess

processing speed and working memory because reaction time on the 0-back condition offers an index of processing speed without a working memory component whereas accuracy on the 2-back condition offers an index of working memory. The MS group had longer reaction times than controls on the 0-back condition, suggesting reduced processing speed. The MS group also produced fewer correct responses on the 2-back condition, suggesting working memory deficits. Parmenter et al. stated that slowed processing speed could not account for working memory deficits in the relapsing-remitting patients because the mean response times for all participants were always less than the two seconds allotted to respond. For example, the average reaction time was 1.02 seconds (SD = .24) on the 2-back condition and the longest reaction time of any participant was noted to be 1.51 seconds. Therefore, even though the patients had adequate time to perform the task, their performance was still worse than controls, indicating working memory deficits could not be explained by slowed processing speed. This study supports the conclusion that there are both processing speed and working memory deficits in relapsing-remitting patients.

The results of the present study and those of Parmenter et al. (2007a) contradict the hypothesis that working memory deficits are absent in the early stages of MS and only manifest after disease progression has taken place. The results also challenge DeLuca and colleagues' (2004) notion that the emergence of working memory deficits is due to the magnitude of processing speed deficits having increased to reach a critical point where working memory is now influenced as well. In the present study, processing speed was not significantly reduced in the patients with MS yet working memory ability was impaired. Similarly, the MS patients assessed by Parmenter et al. had more time than

was necessary to respond yet they still displayed reduced working memory ability. Therefore, the working memory deficits found in the present study and by Parmenter et al. cannot be attributed to impaired processing speed.

Working Memory as a Mediator of Higher-Level Cognitive Functioning

In addition to finding working memory deficits in patients with relapsing-remitting MS, the present results also indicated that MS-related working memory deficits mediated the relation between MS and learning. Furthermore, although a significant direct relationship between MS and both processing speed and executive functioning was not observed, MS was related to these functions through its detrimental effect on working memory.

Although the potential for impaired working memory to account for dysfunction in other cognitive domains has not typically been investigated in MS, the results of Arnett et al. (1999) are consistent with the findings of the present study. As noted previously, that study reported deficient central executive functioning of MS patients on a reading span task. In addition, lower reading span scores were associated with worse performance of the depressed MS patients on capacity-demanding cognitive tasks, including the Visual Elevator test which requires cognitive flexibility. In contrast, simple span scores did not significantly correlate with the measure. These results also indicate a relation between reduced working memory capacity and executive functioning in MS.

The idea that working memory is related to higher-level cognitive functioning is not novel. In the cognitive psychology literature, central executive ability is predictive of higher order cognition in the general population on a wide variety of complex tasks such as reading comprehension, mathematics, episodic memory, problem solving, and

reasoning (see Conway et al., 2005; DeStefano & LeFevre, 2004; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). Thus, the relations found between working memory and various complex cognitive tasks in the present study are consistent with this line of research but also extend those conclusions by showing that working memory can account for MS-related effects on other cognitive functions. A relevant and interesting question that follows from this finding is: how do working memory deficits in MS patients cause difficulties in other cognitive functions?

Sub-clinical slowed processing speed. The patients with MS responded more slowly than controls on all of the reaction time tasks, although the groups only significantly differed on Simple RT. Thus, overall, processing speed was not impaired in the present MS sample. However, the consistent absolute differences may indicate that the patients with MS had minor or sub-clinical processing speed deficits. When multiple, concurrent maintenance and processing operations had to be executed in the working memory tasks, minor or sub-clinical processing deficits may have accumulated or compounded resulting in a significantly worse performance for the MS patients. Research extending from the *Developmental Cascade Model* provided evidence that working memory is a determinant of individual differences in reasoning ability and the relation between working memory and reasoning ability was attributed to processing speed. Thus, it is possible that the mediational/intervening role of working memory in MS may be explained by the consequences of slowed processing, as suggested by research stemming from the *Developmental Cascade Model.*

However, the *Developmental Cascade Model* was conceived to explain cognitive development in children. Jensen (2006) suggested that a mirror-image of what happens

during cognitive development is responsible for age-related cognitive decline in adulthood such that deterioration of brain structures reduces processing speed leading to reduced working memory capacity and, thus, diminished reasoning. Recent work has investigated whether such a reversed "cascade" can explain age-related cognitive decline in older adults (Gregory, Nettelbeck, Howard, & Wilson, 2009; Nettelbeck & Burns, 2010). The results indicate that a simple mirror-image of what has been found for children is not a sufficient explanation. Although a significant indirect relation between age and reasoning ability via speed and working memory was found, as proposed in the *Developmental Cascade Model*, in addition, a direct relation between age and working memory was observed for the older adults. Thus, age-related changes in working memory ability and reasoning occur for older adults that are independent of processing speed. The authors concluded that relations between age, processing speed, working memory, and reasoning ability are more complex in the elderly population than in children.

Nettelbeck and colleagues' results suggest relations among age, working memory, and reasoning in older adults that do not include processing speed. Theoretical accounts of cognition in MS have borrowed heavily from the aging literature such that the effects of MS on cognitive functioning have often been compared with the cognitive decline experienced by older adults. For example, DeLuca et al. (2004) discussed how the limited time and simultaneity mechanisms proposed by Salthouse (1996) to explain the relation between processing speed and cognitive decline in older adults may also account for the relation between processing speed and higher-level cognitive functioning described in the *Relative Consequence Model*. Similarities have also been drawn between the pathological effects of MS on the brain and deterioration associated with old age. Specifically, both

MS and old age are primarily associated with white matter damage and this white matter damage has been proposed to account for the effects of both conditions on processing speed (Genova, Hillary, Wylie, Rypma, & DeLuca, 2009). Therefore, because recent developments in the aging literature suggest an age-related effect on working memory and, in turn, on other cognitive functions that is independent of processing speed, it is possible that such a relational path extends to cognition in MS as well.

Thus, the meditational/intervening role of working memory found in the present study could be a result of the effects of MS on working memory independent of sub-clinical slowed processing speed. The results of Archibald and Fisk (2000) also offer evidence that working memory can account for learning and memory functioning independent of processing speed. Both relapsing-remitting and secondary-progressive patients exhibited slowed processing speed whereas only the secondary-progressive patients also showed deficient working memory capacity. Furthermore, because only the secondary-progressive patients obtained worse verbal learning and delayed recall scores, Archibald and Fisk suggested it is deficient working memory that underlies the impairment of new learning in patients with MS.

In sum, the results yielded by the present study and by Archibald and Fisk (2000) suggest that working memory can explain functional abilities in other cognitive constructs for individuals with MS independent of processing speed. However, it may be possible that the MS patients included in these studies experienced minor processing speed deficits that led to deficient working memory processes. This question could potentially be addressed in the future using neurophysiological measures, such as

functional magnetic resonance imaging (fMRI), that may reveal differences in functional activity that are still too subtle to manifest as deficits on behavioural measures.

The link between working memory and learning. The possibility that deficient working memory capacity may be responsible for impaired learning in MS has been suggested previously. In addition to Archibald and Fisk (2000), Lengenfelder et al. (2006) reported that a subset of MS participants demonstrating both impaired processing speed and working memory performed worse on verbal and visual learning tasks than MS participants with impaired processing speed only. Fuso, Callegaro, Pompeia, and Bueno (2010) found that patients with relapsing-remitting MS showing "clear episodic memory impairment" performed worse on a measure of working memory capacity than patients who did not exhibit such impairment and controls. Taken together, the results of these studies suggest working memory may contribute to deficits in learning and memory.

Although several studies have reported both deficient working memory and learning/memory in MS, attempts to explain how impaired working memory causes learning difficulties in the population are largely absent. The relation between working memory and learning/memory is not unique to MS; individual differences in working memory capacity are also related to performance on free recall tasks in the general population (Unsworth & Spillers, 2010). To explain the link between individual differences in working memory and learning/memory, Unsworth, Brewer, and Spillers (2011) suggested that performance on immediate free recall tasks results from the joint contribution of short- and long-term stores and the control processes that an individual applies to information held within the two stores. The short-term store is presumed to have a limited capacity and, thus, only a small proportion of information can be actively

maintained (e.g., Atkinson & Shiffrin, 1968, 1971). Because the amount of information composing the immediate free-recall tasks employed in the present study would exceed the capacity of the short-term store, anything aside from this limited amount of activated information would be encoded to and retrieved from long-term store. When it is time to retrieve the information, a controlled search of the contents of long-term store is conducted. Unsworth et al. (2011) noted that the flow of information between short- and long-term stores is considered to be under the control of processes such as rehearsal, coding decisions, and retrieval strategies. The execution of such processes would fall within the domain of the central executive in Baddeley's model of working memory.

Returning to the relation between working memory and learning, researchers have suggested that variation in working memory capacity reflects variation in the control processes just described. Convergent evidence indicates that individuals with high working memory capacity are better at executing encoding strategies (e.g., rehearsal, imagery, grouping) and retrieval strategies (e.g., activating contextual cues) during free-recall performance (Bailey, Dunlosky, & Kane, 2008; Unsworth, 2007; Unsworth & Spillers, 2010). Thus, the ability to better execute encoding and retrieval strategies appears to underlie the relation between individual differences in working memory capacity and episodic free-recall in the general population. Patients with MS have exhibited both impaired working memory and impaired learning in comparison with healthy individuals. Therefore, impaired learning in MS may arise specifically due to central executive deficiencies in the ability to engage in strategic processes, such as rehearsal during encoding and use of contextual cues during retrieval, as well.

The notion of an impaired ability to execute encoding strategies is consistent with the results of research studies reporting that self-generated learning, as opposed to didactic presentation, improves recall in patients with MS (Chiaravalotti & DeLuca, 2002; Basso, Ghormley, Lowery, Combs, & Bornstein, 2008; Basso, Lowery, Ghormley, Combs, & Johnson, 2006). Didactic and self-generated learning procedures have been compared by asking patients to recall the last word of sentences when the entire sentence was presented to them versus when they had to make up the last word or when they were provided with both words of word-pairs versus when they had to make up the second word based on a specified rule. Self-generated learning procedures may provide externally-controlled facilitation of effective encoding strategies, such as meaningful grouping, imagery, or rehearsal, that individuals with high working memory capacity are internally capable of. Thus, encoding strategy may explain the improved recall of patients with MS during self-generated tasks as compared with didactic learning tasks.

In addition, results from the comparison between free-recall and cued-recall performance on the list learning task employed in the present study are consistent with the notion of deficient contextual-retrieval. Although the patients with MS recalled significantly fewer items than controls when engaging in both free- and cued-recall, a significant interaction was found such that the difference between groups was larger for free-recall than for cued-recall. During cued recall, contextual cues (e.g., one of the words was a colour) were provided to participants and did not need to be internally generated. This would provide an externally-controlled focus; such focus is thought to benefit individuals with high working memory capacity by reducing irrelevant items in the search set (Unsworth, 2007; Unsworth & Spillers, 2010). Therefore, the present MS

sample may have showed greater impairment on free-recall relative to cued-recall performance because they were unable to execute contextual-retrieval strategies during free-recall.

The link between working memory and the neuropsychological construct of executive functioning. As noted in Chapter One, the neuropsychological construct of executive functioning can refer to a variety of cognitive processes such as reasoning, problem-solving, planning, sequencing, resistance to interference, utilization of feedback, multitasking, and cognitive flexibility (Chan et al., 2008). The combination of these various abilities has been justified in the sense they can be encompassed within the common theme of goal achievement. Executive functioning has been conceptualized as a series of abilities that are implemented to achieve a goal as they make it possible for us to do such things as formulate goals and plans, maintain these goals over time, choose and initiate actions to achieve these goals, and monitor and adjust our behaviour accordingly (Aron, 2008; Chan et al., 2008). Although a link between working memory and learning has previously been suggested and examined in individuals with MS, to my knowledge, the same linkage has not been proposed for working memory and executive functioning in MS. However, this omission may be a result of the widely-encompassing nature of the executive functioning construct and the fact that working memory is even sometimes included as a component of the construct (McCabe et al., 2010).

McCabe and colleagues (2010) recognized that an executive construct responsible for coordinating goal-directed behavior exists in both neuropsychology and cognitive psychology but that the executive construct has been conceptualized in different ways between the two disciplines. The executive construct has been studied within the

framework of working memory in cognitive psychology (e.g., Baddeley, 1986), whereas neuropsychologists have viewed the construct in a broad, all-encompassing manner as described above. Neuropsychological theorizing also often ascribes the various abilities as being under the control of frontal lobe functioning. McCabe et al. investigated the relation between the different conceptualizations of the executive construct and examined the degree of common variance between the two across the lifespan.

Multiple measures of working memory capacity and executive functioning were administered to 206 adults ranging in age from 18 to 90 years in order to form latent factors. The working memory capacity and executive functioning factors were almost perfectly correlated (r = .97), suggesting that tests of working memory capacity and executive functioning measure a common underlying construct. McCabe et al. proposed that the common underlying construct is an attentional ability that they labeled executive attention. Executive attention was described as "the ability to maintain a goal in an active state during task performance" (p. 235) and the ability to "resolve interference, particularly when there is conflict between a prepotent response and task demands" (p. 235). The authors noted that these abilities are considered to be important for both working memory capacity and executive functioning.

Therefore, the ability of working memory to significantly predict executive functioning in the present study may be a result of the executive attention component that is common to both of these constructs. However, although McCabe et al. (2010) observed an almost perfect relationship between the two factors, this was not the case in the present study. Furthermore, although a significant direct effect of MS on working memory was observed, this did not occur for executive functioning. Instead, executive functioning was

only indirectly affected by MS via the detrimental effects of the disease on working memory. Although McCabe and colleagues found evidence for a component common to working memory and executive functioning, they also clarified that

> "The data presented here do not suggest that each executive function task measures only a single common factor, but simply that performance on each executive function task is at least partly dependent on a single common factor, which we refer to as executive attention, in addition to other factors." (p. 236).

The authors further noted that although the individual executive functioning tasks shared common variance they also possessed substantial amounts of unique variance that did not contribute to the latent factor. A portion of this unique variance is likely a result of distinct executive functioning processes not attributable to the common executive attention construct, thus, signifying the distinct nature of individual abilities conceptualized as executive functioning in addition to the unified nature.

Both the working memory and executive functioning factors were represented using four measures in the McCabe et al. (2010) study. Only two measures represented the latent factors in the present study. The inclusion of more observed variables likely results in a greater opportunity for shared or common variance amongst the observed variables to occur. Therefore, the common executive attention component was most likely better represented in the McCabe et al. study than in the present study. This difference may explain why the relation between the working memory and executive functioning factors was not as strong in the present study and why MS was observed to have a direct effect on working memory but not on executive functioning.

Depression and Fatigue

Overall, the relations found among MS, processing speed, working memory, and complex cognitive functions could not be explained by self-reported depression or fatigue. Numerous studies have failed to find a significant relation between either depression or fatigue and neuropsychological performance even though MS and control groups typically differ on these factors (e.g., Archibald & Fisk, 2000; Benedict et al., 2006; Deloire et al., 2005; Glanz et al., 2007; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Kalmar et al., 2004; Krupp & Elkins, 2000; Potagas et al., 2008). In contrast, other studies have reported that either depression or fatigue influences cognition in MS (e.g., Arnett et al., 1999; Arnett et al., 2001; Denney et al., 2004; Thornton & Raz, 1997) and even relations between individual cognitive domains (Diamond et al., 2008). There is evidence that the ability of depression to influence cognitive functioning in MS may differ depending on the domain (Denney et al., 2005) and that the association of fatigue and cognition may be more likely when based on objective measures versus subjective measures of fatigue (Chiaravalloti & DeLuca et al., 2008). Thus, as DeLuca and Chiaravalloti (2008) note in their review of cognitive impairment in MS, the relation between these factors and cognitive functioning is not clear.

Although the MS group obtained significantly higher depression scores than controls, only 31% of the MS sample would be classified as depressed according to criteria provided in the Beck Depression Inventory-Fast Screen manual. Furthermore, of these individuals, 19 would be classified as mildly depressed, 3 would be classified as moderately depressed, and none would be classified as severely depressed. Thus, clinical depression was not prevalent in the present sample, perhaps because the sample was

composed of relapsing-remitting patients with short disease duration. Although the present study did not find that depression substantially influences cognitive functioning, the relation between depression and cognitive functioning may be stronger for patients experiencing greater levels of depressive symptoms. Classification criteria are not available for the Fatigue Impact Scale, thus, the prevalence of different levels of severity could not be considered for fatigue as they were for depression. However, converting the patients' scores to z-scores using the mean and standard deviation of the control group revealed that only 3% of patients' scores were more than 1 SD above the control group and none of the patients' scores were 1.5 or more SDs above the control group. This information suggests that, similar to depression, the fatigue experienced by the MS sample was also mild and the absence of more severe symptoms may explain the minimal influence of fatigue on cognitive functioning in the present study. Further research is necessary to determine at what levels symptoms of depression and fatigue impact cognition in MS and the relative degree different domains may be affected by these factors.

Contributions of Processing Speed and Working Memory to Performance on the PASAT

The present results showed that both processing speed and working memory ability contribute to performance on the PASAT. These findings are similar to those of Kalmar et al. (2004), who reported that working memory accounted for 29% of the variance in PASAT performance in a sample of patients with MS. The present study found a similar amount of variance (20%) was accounted for in the performance of both MS patients and controls. After controlling for working memory, Kalmar et al. reported

processing speed also contributed to performance and accounted for an additional 26% of the variance not already accounted for by working memory. However, the present study found that processing speed only accounted for 10% of the variance in PASAT performance when working memory was controlled for. The difference among results may have arisen because only the performance of patients with MS was evaluated by Kalmar et al. whereas both patients and controls were included in the present study. However, group membership was not predictive of performance in the present study. The difference may be best explained by differences in the processing speed measures used in the two studies. Kalmar et al. used the threshold score from the Visual Threshold-Serial Addition Test whereas the present study used a factor summarizing the data from three different reaction time measures. Because the Visual Threshold-Serial Addition Test is a modified version of the PASAT, this may have led to a greater amount of shared variance between processing speed and PASAT performance.

Kalmar et al. (2004) concluded that when the effects of working memory are accounted for, processing speed still accounts for significant additional variance in PASAT performance. The results of the present study indicate, however, that the relations amongst processing speed, working memory, and PASAT performance are more complex than that. Processing speed and working memory were found to interact. Specifically, how quickly one can process information was not important to performance for individuals with high working memory ability. In contrast, as working memory ability declined to average and low levels, information processing speed became increasingly more important to successful task performance. These findings suggest that high working memory ability can compensate for slowed processing speed when adults perform the

PASAT but, when working memory ability is only average or low, processing speed cannot be compensated for and speed will substantially influence performance. These results applied to both the MS and control groups, and therefore suggest a general link between levels of working memory ability and levels of processing speed.

Contributions of Processing Speed, Working Memory, and Learning to Performance on the Symbol Digit Modalities Test

The present results showed that processing speed, working memory, and learning ability all contribute to performance on the Symbol Digit Modalities Test. The findings that processing speed and learning influence performance is consistent with Benedict et al. (2006), who reported that the Symbol Digit Modalities Test loaded on both processing speed and learning/memory factors when a factor analysis was conducted using data from patients with relapsing-remitting MS. Glanz et al. (2007) also found that the Symbol Digit Modalities Test correlated with performance on measures of processing speed/working memory and retrieval from memory. Furthermore, Benedict et al. (2005) reported that the Symbol Digit Modalities Test was correlated with temporal lobe atrophy, thereby providing physiological evidence for the contribution of learning/memory to performance in addition to processing speed or working memory, and posited that performance may be enhanced by remembering new associations between symbols and numbers.

Taken together, there is substantial evidence that performance on the Symbol Digit Modalities Test is affected by variability in the cognitive functions of processing speed, working memory, and learning/memory. The results of the present study extend findings by showing that the degree to which processing speed influences performance

differs depending on whether an examinee has MS or not. For individuals without MS, processing speed does not influence performance on the Symbol Digit Modalities Test whereas for MS patients, slower speed results in worse performance. The MS group also exhibited worse performance on measures of working memory and learning in comparison with controls. Therefore, deficiencies in working memory and learning functions may have resulted in the significant influence of processing speed on Symbol Digit Modalities Test performance for the patients with MS.

Limitations and Future Directions

Although the choice to examine cognitive functioning specifically in individuals with relapsing-remitting MS is a strength of the present study, this focus does limit the generality of the findings. In addition to only including patients with the relapsing-remitting form of the disease, the present sample was also characterized by a relatively short disease duration. Therefore, the results of the present study may not apply to patients with other disease sub-types (i.e., secondary progressive and primary progressive MS) or to patients with longer disease durations. It will be important to conduct similar research with other groups of patients in the future in order to determine the nature of the relations among processing speed, working memory, and other cognitive domains at different stages of the disease. Because the MS participants were recruited from a clinic, the results may also not generalize to the larger MS community/population.

Recruitment bias has been identified more generally as a factor affecting research on cognitive functioning in MS. Participants experiencing cognitive difficulties may not have volunteered for the study because they anticipated performing poorly or experiencing frustration and this may have resulted in a minimally disabled sample. The

early disease course characterizing the MS sample could have been a result of newly diagnosed patients being especially motivated to find out more about the disease and contribute to research efforts compared to patients who have lived with the disease longer.

As discussed above, there were issues relating to the construct validity of the unified executive functioning factor included in the structural equation models. Although the individual tasks representing the factor were significantly correlated, the amount of variance common to the tasks was modest. The factor proposed before the data were collected included other variables (e.g., total achievement score from the D-KEFS Tower Test). However, these variables could not be included in the structural equation modeling analyses because they did not significantly correlate with the measures that were used. Issues such as these reflect the problematic aspects of how executive functioning has been conceptualized in the field of neuropsychology, specifically, the varying nature of different abilities and tasks that have been combined under the umbrella term. In contrast to the unified approach adopted in the present study, other researchers have chosen to focus on a few specific executive functioning abilities. For example, Miyake and colleagues (2000) administered multiple measures of shifting, updating, and inhibition and have used factor analytic methods to study these executive functioning abilities concurrently. Given the modest correlations among different executive functioning tasks that were observed in the present study, it appears that this alternative approach should be adopted in future studies designed to examine latent executive functioning factors.

Practical Implications

Although working memory impairment has been acknowledged as a fundamental cognitive deficit for patients at later stages of the disease course (i.e., secondary progressive MS), slowed processing speed has been suggested as the primary deficit in earlier stages of MS (e.g., relapsing-remitting MS). However, the results of the present study suggest that this perception of the pattern and sequence of cognitive deficits is incorrect. Therefore, it is important for clinicians and researchers to consider the possibility that working memory may be impaired and may underlie cognitive dysfunction early in the disease course. Furthermore, clinical assessments and research batteries should include valid measures of working memory ability.

The present results support the interpretation that the PASAT and the Symbol Digit Modalities Test, two measures commonly used for clinical and research purposes in the MS field, are multifactorial and that performance involves several different cognitive functions. Both of these measures are valued for their sensitivity to cognitive dysfunction and their utility as screening measures. Their usefulness in this regard may be a result of their multifactorial nature. That is, if a patient is experiencing difficulty in any of the functions involved in these tasks, they may score poorly and be identified as cognitively impaired.

Although both measures provide an assessment of multiple cognitive domains, there are differences between them that may affect their relative usefulness as screening measures. As discussed in Chapter One, the PASAT suffers from several critical flaws, most importantly, that patients find it aversive and frustrating. In contrast, although the Symbol Digit Modalities Test is not aversive, it failed to differentiate between patients

with MS and controls in the present study even though working memory and learning impairments emerged for the patients on other measures. Therefore, the Symbol Digit Modalities Test may not be sensitive enough to detect cognitive deficits that are present early on in the disease course.

Thus, although the multifactorial nature of the PASAT and the Symbol Digit Modalities Test makes them useful screening measures, this characteristic and the limitations that have been identified in the present analyses also means that the tests are inappropriate for other clinical and research purposes. Because they index several cognitive functions, it is impossible to attribute impaired performance to any one function in particular. If a clinician or researcher wishes to know the specific cognitive functions affected for a given patient or sample, these measures will not be sufficient. Instead, other measures known to possess better specificity should be used. Furthermore, the results of research studies utilizing these measures should be interpreted with caution. If a significant relationship is found between some construct and performance on either the PASAT or the Symbol Digit Modalities Test, it is inappropriate for researchers to attribute that relation to processing speed. The field will progress more quickly, both in terms of theoretical development and in terms of assessment protocols, if appropriate and specific measures of the central constructs are routinely adopted.

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APPENDIX A: GENERAL OVERVIEW OF MS

MS is thought to be an immunological, or autoimmune, disorder in which the myelin of the central nervous system is incorrectly identified as foreign and is attacked. This process can result in inflammation, demyelination, and the formation of lesions, also known as sclerotic plaques. For the most part, damage is considered to be randomly distributed throughout the central nervous system but some evidence of a tendency for lesions to form in peri-ventricular areas has been found. Myelin is vital to the normal transmission of neural impulses. Thus, 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 (i.e., the extreme south and north of the globe) than others (i.e., near the equator), an environmental agent may be involved in the contraction of the disease (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).

It is estimated that there are 55,000-75,000 Canadians living with MS. Prevalence rates range from one MS case per 500 people to one in 1,000 across the country (Multiple Sclerosis Society of Canada, n.d.). More than 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 (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 potentially debilitating symptom experienced 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 (dysphagia), and tremor. These symptoms are quite variable in their nature. This variability is associated with lesions being diffuse and variable in their location in the central nervous system. 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 (McDonald, Compston, & Edan, 2001).

The course of the disease is highly variable; some patients may experience few or no exacerbations in their lifetime whereas 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 for 20 to 25 years following onset (Rao, 1990). Severity of the disease is typically assessed using a clinical measure known as the Expanded Disability Status Scale (Kurtzke, 1983). Scores on the Expanded Disability Status Scale are based on the neurological examination of eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other. Scores on the Expanded Disability Status Scale range from zero to ten, with zero indicating a normal neurological examination for all systems and ten indicating death due to MS. In the past, the Expanded Disability Status Scale 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), though the Expanded Disability Status Scale remains a useful tool for classifying MS patients by disease severity (Cutter et al., 1999).

APPENDIX B: RECRUITMENT FORM

Multiple Sclerosis and Speed of Information Processing

Recruitment Notice For Permission to Forward Names

Drs. Lisa Walker, Laura Rees, and Mark Freedman are studying how Multiple Sclerosis affects a person's ability to process information. In order to achieve these goals, a series of computerized tests have been developed that measure how fast people can perform a series of mental tasks. In this respect, Drs. Walker, Rees and Freedman are seeking your help. If you volunteer it will require approximately 3 hours of your time on three occasions. The tests will be administered at the Ottawa Hospital at a time that is convenient for you. It should be noted that ethical review boards of The Ottawa Hospital and Carleton University have approved this research project.

If you would like to participate in this research program or find out more about it, I will forward your name to Drs. Walker or Rees. They will contact you and provide you with further information. However, I cannot forward your name to them without your permission. If you decide that you don't want to participate, or if you decide not to participate after being contacted, it will NOT affect your care now, or in the future, at the MS Clinic.

I AGREE TO BE CONTACTED BY DR. LISA WALKER AND/OR DR. LAURA REES.

Participant's Name & Phone Number:

Participant's Signature:

Date:

APPENDIX C: INFORMED CONSENT

Patient Information Sheet and Informed Consent

The Ability of the Computerized Tests of Information Processing (CTIP) to Detect Cognitive Impairments in Multiple Sclerosis Patients

Researchers

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Sponsor
Multiple Sclerosis Society of Canada

Background of the Study

Multiple sclerosis (MS) often compromises a person's ability to attend to or concentrate on what is going on around them. Even though attention/concentration deficits are common, very few reliable measures are available in clinical neuropsychology to measure them. In view of this, a series of computerized tests have been developed to measure attention, particularly the speed at which MS participants process information. Previous research has determined how individuals without any injury/illness perform on these tasks. Now we would like to know how people with MS perform on these measures.

Purpose and Procedures

The purposes of this study are (1) to determine how sensitive the tests are to the types of thinking difficulties experienced by people with MS, (2) to further increase knowledge about how MS affects attention/concentration and information processing, and (3) to determine how deficits in information processing speed might impact other thinking abilities. In order to accomplish these goals, 70 people with MS and 70 individuals without MS will take three newly developed computerized tests. These tests measure how quickly and accurately a person can respond when different kinds of words are presented on the computer screen. The results from these tests will be compared to those obtained with a series of neuropsychological tests that are commonly used to study thinking. This study requires that you perform to the best of your ability on all tasks.

Description of Tests

The first three computerized tests require you to rapidly press a key under 3 different conditions: (1) when an "X" appears in center of the screen, (2) when one of two words is

presented on the screen, and (3) when a word (e.g.,"robin") matches a category (e.g "bird"). The other tests require you to perform a variety of thinking tasks such as, remembering verbal and visual information, adding numbers, sorting cards, and reading sentences, to name a few.

Length and Place of the Experiment

Tests will be administered in three sessions that will take approximately 2 to 3 hours each. The first two sessions will occur approximately 1 week apart. The last session will be used to assess the potential progressive effects that MS has and will occur 3 years after the second session. The tests will be administered at the Ottawa Hospital.

Potential Harms, Injuries or Discomfort

The neuropsychological tests may be lengthy and tiring but it will be possible to have rest periods during the evaluation or to conduct the testing on separate days within the same week. If cognitive difficulties are identified that, in the opinion of Drs. Walker or Rees, could potentially impact driving safety, this issue will be discussed with you and then with Dr. Freedman. It would then be at the discretion of Dr. Freedman as to how to proceed (i.e. seek further testing in a clinical setting, inform the Ministry of Transport).

Potential Benefits

You will probably obtain no direct benefit for yourself from your participation in this study. However, you will assist the researchers in furthering knowledge of attention/concentration and information processing in people with MS. The results of this study will also lead to the further development of potentially useful tests of attention/concentration that can be utilized with people with MS. Eventually, it is hoped that these tests can be used to monitor someone's rehabilitation.

Voluntary Participation and Withdrawal

You understand that you are under no obligation to participate in the study and that you can withdraw from the study at any time without providing the investigator with a reason. Should you elect to withdraw from the study, it will not affect the care that you receive at the Ottawa Hospital at this time or in the future.

Study Expenses and Compensation

You will be reimbursed for parking expenses. In the event of a research-related injury, you will be provided with appropriate medical treatment. You are not waiving your legal rights by agreeing to participate in this study. The study investigator and hospital still have their legal and professional responsibilities.

Confidentiality

Information (data) obtained from this study will be electronically stored in an anonymous database and processed for the purpose of scientific evaluation. Your name will not appear on any study document, but a study number (assigned to you) might. Apart from the investigators of this study, only the Ottawa Hospital Research Ethics Board will be allowed to look at your study data and medical records in order to check

that the study is being performed properly and that you have given your full informed consent. If the results of the study are published, your identity will remain confidential. No records bearing your name will leave TOH without your/the substitute decision maker's written consent. If you have any questions or require further information about this study, do not hesitate to ask the investigators or research personnel. They will be more than willing to discuss any of your questions or concerns.

Questions about the Study

If you have any questions about the study, or would like of copy of the study results, you can contact either Dr. Walker or Dr. Rees at (613) 737-8039. You can also contact the Chairperson of the Ottawa Hospital Research Ethics Board, at (613) 798-5555 x14902

Consent

I have read this Patient Information Sheet and Consent Form and have had an opportunity to ask the research investigator any questions I had about the study. My questions and/or concerns have been answered to my satisfaction and I agree to participate in this study. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

A copy of the Information Sheet and Consent Form will be provided to me should I want to review the information at a later date, if I need to contact someone about the study or my participation in the study, or simply for my records.

_____
Name of Participant (printed)

_____
Signature of participant or delegate

_____
Date

_____
Participant Number

_____
Name of Investigator/Delegate (printed)

_____
Signature of Investigator/Delegate

Valid until _____

APPENDIX D: STRUCTURED INTERVIEW

Date Administered _____
Subject Number _____
Gender _____
Age _____
Date of 1st Diagnosis _____

Handedness: R L
Education in Years:

grade school	0 1 2 3 4 5 6 7 8
High school	9 10 11 12
Trade/College	13 14
University	13 14 15 16
Master's level	17 18
Ph.D. level	19 20 21

Are you employed? Yes No If so, what is your occupation:
Full-time or part-time: How many hrs/week:
If not, why (e.g., retired, disability, let go, by choice):

Approximate date of first symptoms of MS: (month/year) _____
What were your first symptoms?

Approximate date of first diagnosis of MS: (month/year) _____

Are you currently experiencing an exacerbation yes no
Date of last exacerbation?
Frequency of exacerbations?

Difficulty with vision? _____
Difficulty with hearing? _____

Medications:

Medical History (get details from all that are checked):

- seizures/epilepsy
- diabetes
- depression
- learning disability
- previous seen Psychiatrist, Psychologist, Counselor
- Motor Vehicle Accident
- Falls leading to Unconsciousness
- Head Injury
- Hand/Arm injury

Type of MS

- Primary Progressive _____
- Remitting-Relapsing _____
- Secondary Progressive _____

EDSS

- Score _____
- Date of evaluation _____

Multiple Sclerosis Information Sheet

Which of the following best describes your ability to walk?

1. I can walk without any problem.
2. I have some difficulties with walking but I can walk without aid for 500 meters or more (approximately the length of 5 football fields or one third of a mile).
3. I have some difficulties with walking but I can walk without aid for less than 500meters (approximately the length of 5 football fields or one third of a mile).
4. I require an aid (cane, crutch, walker etc) to walk 100 meters.
5. I require an aid (cane, crutch, walker etc) to walk less than 20 meters.
6. I use a wheelchair for almost all activities.
7. I am confined to bed most of the time.

When you move about, what percentage of the time do you:

1. Walk without aid? _____
2. Use a cane, a single crutch, or hold onto another person? _____
3. Use a walker? _____
4. Use a wheel chair? _____

Which of the following best describes your functional abilities?

1. I am able to carry out my usual activities without limitation.
2. I have limitations but can carry out most of my usually daily activities, even though I may need some type of special provision such as altered work hours or naps.
3. I am able to carry out about only half of my usual daily activities, even with special provisions.
4. I am severely limited in my ability to carry out my usual daily activities.
5. I require assistance with even my basic care activities.

Which of the following best describes your strength or power?

	Normal	Mildly Weak	Moderately Weak	Severely Weak
1. Right arm	_____	_____	_____	_____
2. Left arm	_____	_____	_____	_____
3. Right leg	_____	_____	_____	_____
4. Left leg	_____	_____	_____	_____
5. Face	_____	_____	_____	_____

Which of the following best describes your sensation or feeling?

	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired
1. Right arm	_____	_____	_____	_____
2. Left arm	_____	_____	_____	_____
3. Right leg	_____	_____	_____	_____
4. Left leg	_____	_____	_____	_____
5. Face	_____	_____	_____	_____

Which of the following best describes your corrected visual acuity (using glasses if necessary)?

	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired
1. Right eye	_____	_____	_____	_____
2. Left eye	_____	_____	_____	_____

Which of the following best describes your double vision?

1. I don't experience double vision.
2. I experience double vision only occasionally.
3. I experience double vision moderately often.
4. I experience double vision most of the time.

Which of the following best describes your coordination.

	Normal	Mildly Uncoordinated	Moderately Uncoordinated	Severely Uncoordinated
1. Right arm	_____	_____	_____	_____
2. Left arm	_____	_____	_____	_____
3. Right leg	_____	_____	_____	_____
4. Left leg	_____	_____	_____	_____

Which of the following best describes your ability to speak?

Normal	Mildly Impaired	Moderately Impaired	Severely Impaired

Which of the following best describes your balance?

No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty

Which of the following best describes your spasticity (stiffness) and/or spasms (brief involuntary contractions) of your muscles?

	No Spasticity or Spasms	Mild Spasticity or Spasms	Moderate Spasticity or Spasms	Severe Spasticity or Spasms
1. Right arm	_____	_____	_____	_____
2. Left arm	_____	_____	_____	_____
3. Right leg	_____	_____	_____	_____
4. Left leg	_____	_____	_____	_____

Which of the following best describes your cognitive (thinking) abilities?

1. I have had no change in my cognitive (thinking) abilities.
2. I have had a mild impairment in my cognitive (thinking) abilities.
3. I have had a severe impairment in my cognitive (thinking) abilities.
4. I am unable to handle my affairs because of my severe cognitive problems.

Which of the following best describes your mood since getting MS?

1. My mood has been unchanged since getting MS.
2. I have beome depressed or more depressed since getting MS.
3. Although I am not pleased to have MS, I have become a more cheerful person since getting it.

Which of the following best describes your ability to swallow?

No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty

Which of the following best describes your dizziness or vertigo (i.e., a sense or feeling of motion)?

No Vertigo	Mild Vertigo	Moderate Vertigo	Severe Vertigo