# Processing Speed and Working Memory in Multiple Sclerosis:

# Comparison of the *Relative* and *Independent*

# *Consequence Models*

By

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Abstract

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***Objective:*** The relationship between reduced processing speed and impaired working memory commonly noted in patients with multiple sclerosis (MS) is currently unclear. DeLuca et al. (2004) proposed two models to explain this relationship: the *Relative Consequence Model*, which states that impairments in working memory are secondary to reduced processing speed, and the *Independent Consequence Model*, which states that these deficits are independent of one another. Research examining the application of these models has been inconsistent, perhaps due to sex differences complicating this relationship, as well as varying methodologies and statistical techniques used among studies. The present study was designed to employ a novel statistical technique, path analysis, to directly compare these models using the experimental *n*-back task to parse processing speed and working memory abilities. The role of sex in explaining processing speed and working memory impairments in MS was also investigated. Primary hypotheses were that MS patients would demonstrate impaired processing speed and working memory relative to healthy controls, while analyses comparing the models were exploratory. Secondary hypotheses were that relative to women with MS, men with MS would exhibit impaired working memory along with slowed simple and complex processing speed on the *n*-back task. ***Design:*** Forty-five MS patients and 29 healthy controls completed the *n*-back task as part of a larger neuropsychological battery. Questionnaires addressing fatigue and depression were also completed. ***Results:*** After controlling for simple processing speed, MS patients did not demonstrate impaired processing speed or working memory relative to controls. Path models demonstrated that, for MS patients, processing speed both directly and indirectly predicted working memory performance on the *n*-back task. The importance of examining task approach was also demonstrated (i.e., whether people performed the task as instructed), as this partially mediated the relationship between processing speed and working memory. Sex of participant was not predictive of processing speed or working memory performance. ***Conclusions:*** Results of the present study provide support for the *Relative Consequence Model*, as processing speed was found to predict working memory performance. Future research should explore rehabilitative strategies that may help to alleviate problems caused by reduced processing speed in MS patients.

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## Dedication

I would like to dedicate this dissertation to my husband Dustin. He has provided laughter and love on many cloudy days and sacrificed more than I to make this possible. I do not know that I will ever be able to give him the same support and encouragement that he has selflessly given me over the last several years, but I will spend my life trying.

I also wish to dedicate this dissertation to all of the people with MS who participated in this study as well as to all people impacted in some way by MS. I hope that the results of this study can contribute to improved treatment of this disease.

# CHAPTER ONE

# INTRODUCTION

i. Multiple Sclerosis

Multiple sclerosis (MS) is a neurodegenerative, autoimmune disease and demyelinating and inflammatory condition of the central nervous system (CNS). Although MS is not well understood, the disease is characterized by progressive destruction of the myelin sheath of the brain and spinal cord, causing significant motor and cognitive impairments (Keegan & Noseworthy, 2002). While it has been proposed that MS primarily impacts the white matter of the CNS, recent evidence suggests that the disease also impacts cortical and subcortical gray matter of the brain (see Mesaros et al., 2008). The causes of MS are also not well understood; however, there are genetic and environmental factors that are thought to contribute to the development of MS (for review, see Olsson & Hillert, 2008; Kantarci & Wingerchuk, 2006). Regarding genetic influence, MS tends to run in families and several different genes have been identified as possible markers for the disease. Evidence for environmental factors is based on MS being more common in regions farther away from the equator (see Rao, 1986) and more prevalent in northern climates and specific regions of countries (see Vella, 1984). The most current hypothesis of MS etiology suggests that certain environmental factors influence the development of the disease in genetically susceptible individuals (Myhr, 2008).

MS has been classified into four subtypes according to clinical course. The subtypes include: relapsing-remitting (RRMS), characterized by periods of symptom exacerbation and symptom remission; primary-progressive (PPMS), involving a gradual progression of the disease; secondary-progressive (SPMS), distinguished by a gradual progression of the disease following a relapsing-remitting period; and progressive-relapsing (PRMS), exemplified by a gradual progression of the disease with frequent periods of exacerbation of symptoms (Miller, 1996). As discussed by Coyle (2000), the most common type is RRMS as approximately 85% of patients begin with this disease course; however, within ten years nearly 50% of these patients transition to SPMS. PPMS and PRMS are less common, affecting 10% and 5%, respectively. Symptoms of MS are also extremely variable. Symptoms commonly experienced by patients with MS are extremity weakness, sensory symptoms, optic neuritis, diplopia, vestibular symptoms, urinary symptoms, hemiplegia, trigeminal neuralgia, and facial palsy (see Rao, 1986). More recent reports also identify fatigue and cognitive dysfunction as common symptoms of MS (see Parmenter et al., 2007a).

It is currently estimated that between 70-75% of people with MS are female (Coyle, 2005). While more women are commonly affected with the disease, men with MS tend to experience a more severe, progressive course. For instance, men with MS suffer greater mortality and more rapid progression of physical disability (Hawkins & McDonnell, 1999; Weinshenker et al., 1989). MS typically has its onset in the third and fourth decades of life, with onset being rare prior to the age of 15 and after the age of 45 (Rao, 1986), although age of onset for women is different than for men. For instance, RRMS preferentially affects women and shows a typical onset at 28 to 30 years of age, whereas PPMS preferentially affects men and shows a typical onset at ages 38 to 41 (Coyle, 2005). Magnetic resonance imaging (MRI) studies have also shown that men are more susceptible than women to destructive brain lesions (Weatherby et al., 2000; Pozzilli et al., 2003). Finally, men and women with MS have been found to perform differently on measures of cognitive function (Beatty & Aupperle, 2002; Beatty, Goodkin, Hertsgaard, & Monson, 1990; Beatty et al., 1995). Genetic factors, such as the ε2 and ε4 alleles of the APOE gene, have been implicated in sex differences in cognition among MS sufferers (for review see Savettieri et al., 2004; Parmenter et al., 2007a).

ii. Cognition in MS

Cognitive dysfunction affects between 30-70% of patients with MS (Amato et al., 1995; Heaton et al., 1985; Peyser et al., 1980; Rao et al., 1991a). Impairment is typically seen in attention, processing speed, executive functions, memory, and visual spatial perception (Beatty & Aupperle, 2002; Benedict et al., 2002; Prakish et al., 2008; Rao, 1986), as well as learning and verbal fluency (Prakish et al., 2008). Although MS patients have been found to perform more poorly than healthy controls across many cognitive domains, recent literature suggests that the most significant deficits occur in information processing, primarily in working memory and processing speed (Archibald & Fisk, 2000).

According to Baddeley (1992; 2003), working memory is a limited capacity system enabling the storage, processing, and manipulation of information. Working memory consists of a central executive system, which is an attentional control system, and two slave systems, the phonological loop and the visuospatial sketchpad. The phonological loop holds and manipulates speech-based information, and the visuospatial sketchpad performs similar processes for visuospatially presented information (Baddeley & Hitch, 1974; Baddeley & Hitch, 1994).

Processing speed refers to the rate at which cognitive processes can be executed (Krail & Sanan, 1994). There is a careful balance between the rate that information can be processed and the rate at which information becomes unavailable secondary to decay or displacement (Nebes et al., 2000). Two types of processing speed have been discussed in the literature: simple and complex. Simple processing speed refers to the amount of time needed for simple attentional tasks such as target detection. Complex processing speed, on the other hand, is the amount of time necessary to process more complicated tasks, such as those requiring mental manipulation (Chiaravalloti et al., 2003). Research in MS has indicated the importance of assessing both simple and complex processing speed, as MS patients have been found to exhibit more prominent complex processing speed deficits relative to simple processing speed deficits (Parmenter et al., 2007b).

iii. The Relationship Between Processing Speed and Working Memory Impairments in MS

Impairments in both working memory (D'Esposito et al., 1996; Diamond et al., 1997; DeLuca et al., Foong et al., 1999; Lengenfelder et al., 2003; Lengenfelder et al., 2006; Parmenter et al., 2006; Parmenter et al., 2007a; Parmenter et al., 2007b; Ruchkin et al., 1994; Wishart & Sharpe, 1997) and processing speed (Archibald & Fisk, 2000; Archiron et al., 2005; DeLuca et al., 2004; Demaree et al., 1999; Denney et al., 2004; Kail, 1998; Kujala et al., 1995; Lengenfelder et al., 2006; Litvan et al., 1988; Parmenter et al., 2006; Parmenter et al., 2007a; Parmenter et al., 2007b) in patients with MS are widely established. However, it is not known to what extent these deficits are related to one another. For example, DeLuca and colleagues (2004) have explained information processing deficits in terms of two potential models: the *Relative Consequence Model* and the *Independent Consequence Model*. The *Relative Consequence Model* suggests that processing speed is the primary deficit in MS and influences impairments in a range of other cognitive domains, including working memory. More specifically, as the disease progresses and processing speed becomes more and more deficient, a "critical point" is reached, causing poorer performance on tasks assessing additional cognitive domains such as working memory. Thus, according to this model, deficits on tasks of working memory are secondary to deficits in processing speed. In contrast, the *Independent Consequence Model* proposes that, while it is not possible for processing speed and working memory to be mutually exclusive, deficits in processing speed and working memory noted in MS are largely independent from one another. According to DeLuca and colleagues (2004), this model assumes that “the particular pattern of cognitive deficits would then be determined by individual factors such as lesion location in the brain or perhaps depression” (p. 558). While some research findings are consistent with the *Relative Consequence Model* (DeLuca et al., 2004; Demaree et al., 1999), other results support the *Independent Consequence Model* (Landro et al., 2004; Parmenter et al., 2007b).

A potential reason for differential support of the *Relative* and *Independent Consequence Models* may be related to differences in task selection used across studies. For example, many of the studies examining information processing in patients with MS use the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). For this task, numbers are presented at a predetermined speed, such as every two seconds, and the participant is asked to add two consecutive numbers and state the answer before the next number is presented. The main outcome variable is total correct; however, as discussed by Fisk and Archibald (2001), MS patients typically have significant difficulty with the PASAT and have been shown to adapt a strategy that allows them to complete the task more efficiently. This strategy involves skipping numbers intermittently so that the information can be combined into more manageable units or “chunks,” thus reducing the burden on working memory (Fisk & Archibald, 2001). Therefore, researchers have begun to question whether measuring performance by total correct on the PASAT is an accurate reflection of working memory abilities (Fisk & Archibald, 2001). For instance, if total correct is used to indicate overall performance, MS patients perform similarly to controls; however, upon closer examination, it has been shown that MS participants provide more chunking responses and consequently have fewer consecutive correct responses, or “dyads”

(Fisk & Archibald, 2001). These authors also commented that the percentage of correct responses that are dyad responses (percent dyad) is an even more accurate indication of whether participants performed the task as instructed. Therefore, it has been proposed that total number of dyad responses and the percentage of dyad responses are a better indication of working memory performance when comparing MS and control groups (Fisk & Archibald, 2001). However, the PASAT is a speeded task and adequate performance relies not only on working memory, but on processing speed as well. Because the PASAT does not allow for these processes to be examined separately, it is difficult to determine if poor performance on this task is due to impaired processing speed, working memory, or both. It has been proposed that the *n*-back task may be a more accurate measure when attempting to examine working memory and processing speed separately (Parmenter et al., 2006).

The *n*-back task is a computerized experimental test that is traditionally thought to measure executive aspects of working memory (Baddeley, 2003). The task typically includes three conditions of increasing complexity and requires the participant to determine whether a presented letter matches one presented "*n*" trials back, where *n* equals zero, one or two for the first, second and third conditions, respectively. For instance, in the 0-back condition participants simply respond when they see a specified letter, such as "X," whereas for the 1-back condition, participants are asked to decide if the presented letter matches the one immediately preceding it, or one back (see Figure 1). As "*n*" increases, so does the working memory burden. Like the PASAT, working memory performance on the 1- and 2-back conditions can be measured with total correct and total/percentage of dyad responses. However, unlike the PASAT, the *n*-back task provides behavioral indicators of processing speed as measured by reaction time. Reaction time in the 0-back condition can be thought to reflect simple processing speed, whereas more complex processing speed is indicated in the 1- and 2-back conditions, which place higher demands on working memory. Parmenter and colleagues (2007b) argue that because the *n*-back task provides separate measures of processing speed and working memory, it can be used to examine the *Relative* and *Independent Consequence Models*. Indeed, using this task, they found that compared to controls, MS patients exhibited slower processing speed, as measured by longer reaction times on all conditions of the *n*-back task, and impaired working memory, based on fewer total correct and total dyads on the 2-back condition. They interpreted these results as supporting the *Independent Consequence Model* of information processing in patients with MS. While these findings support those of Landro and colleagues (2004), they are in direct contrast to those of DeLuca and colleagues (2004) and Demaree and colleagues (1999).

Another potential reason for differential support of the *Relative* and *Independent Consequence Models* may be related to sex differences in MS. For instance, as previously discussed, although women are more commonly affected with the disease, men with MS tend to have a more severe, progressive course and are more susceptible to destructive brain lesions (Weatherby et al., 2000; Pozzilli et al., 2003). Therefore, considering the *Relative* and *Independent Consequence Models*, sex differences may be interacting with the disease to produce differences in performance on measures of processing speed and working memory. For example, men may have a pattern of cognitive deficits that are more consistent with the *Independent Consequence Model*. In contrast, because women with MS tend to progress more slowly and suffer from less disease-related brain pathology, they may have a pattern of deficits that are consistent with the *Relative Consequence Model*. Within this framework, men would therefore be more likely to suffer from processing speed and working memory difficulties, with no significant relationship between these domains, whereas women would be more likely to suffer from processing speed difficulties only, at least until they reach a more progressive stage of the disease. Thus, this possible interaction between sex and disease-related cognitive deficits may contribute to the current confusion in the literature about which model might best characterize the pattern of deficits in this population (i.e., one model may account for males' deficits while another may account for females' deficits).

Despite the previously noted sex differences in disease factors in MS, only a handful of studies have explored sex differences in cognition in MS. For instance, studies have demonstrated that men with MS tend to perform more poorly than women with MS on measures of memory, information processing, verbal fluency, and higher executive functioning (Beatty &Aupperle, 2002; Beatty, Goodkin, Hertsgaard, & Monson, 1990; Beatty et al., 1995). The inferences that can be made from these studies conducted by Beatty and colleagues (1990; 1995; 2002) are limited, however, as the studies did not include a control group, but used findings from the general population as a reference group. In other words, these researchers compared performances of MS patients against published normative data derived from the general population to establish whether MS patients performed more poorly on cognitive tasks than healthy individuals (although published normative data were not available for all of the tasks). This is a significant limitation of these studies, as a healthy control group can provide information about and allow control for factors outside of the disease process that may be influencing the results (e.g., experimental influence, regional influence, etc.). A study by Parmenter and colleagues (2007b) did use a control group and, although not the primary purpose of the study, also examined sex differences specifically in processing speed and working memory. Using the *n*-back task, the results of this study did not indicate significant sex differences in working memory and processing speed. However, the small sample sizes in this study (N = 5 for one group) may not have been adequate to detect such differences. Therefore, although sex differences in cognition have been minimally investigated, these studies presented with considerable limitations that may have confounded the results. Further exploration of sex differences as well as how they may relate to the *Relative* and *Independent Consequence Models* is warranted.

A final factor that potentially has complicated the investigation of the *Relative* and *Independent Consequence Models* is the type of statistical approach that has generally been used across studies. Previous research has generally employed some form of general linear modeling to examine processing speed and working memory abilities in MS patients relative to controls. This type of statistical technique is limited, however, in that it does not permit the examination of the relationship between these domains. A statistical technique that can be used to address this limitation in MS studies is path analysis, which is a form of structural equation modeling. The basic aim of this type of statistical technique is to estimate presumed causal relationships among observed variables while also examining the covariance among the variables (Kline, 2005). Thus, a researcher specifies a theoretically-driven path model that attempts to explain a causal relationship between variables X and Y, either directly or indirectly, while also controlling for other variables that may confound this relationship. Therefore, this technique is viewed as an extension of multiple regression because it allows for examination of direct causality between variables X and Y but also allows for examination of indirect causality by including paths of potential mediating variables; i.e., X causes Y and Y causes Z. Path analysis includes what has been specified as exogenous and endogenous variables in the model, which can be viewed as similar to independent and dependent variables, respectively; however, it is important to note that while variables can be both independent and dependent in path models, they are viewed as endogenous if they are dependent on any part of the model (Klem, 1995).

The results of a path model indicate parameter estimates that are derived based on the maximum likelihood principle that states, "…the estimates are the ones that maximize the likelihood (the continuous generalization) that the data (the observed covariances) were drawn from this population" (see Kline, 2005; pg. 112). The resulting path coefficients are interpreted similarly to regression coefficients in that they are assumed to be an estimate of a causal relationship after controlling for correlations among the multiple presumed causes (Kline, 2005). However, these parameter estimates can only be interpreted based on the "fit" of the model. When assessing model fit one must consider a variety of statistics including: the model Chi Square, the comparative fit index (CFI), the root mean square error of approximation (RMSEA) with its 90% confidence interval, and the standardized root square mean residual (SRMR). A general way of understanding the model Chi Square is that it tests the difference between the observed data and what would be expected given the specified model; thus, a small, nonsignificant effect indicates a well-specified model. The CFI is directly related to the correlations in the data and assesses the specified model compared with a baseline or null model, which assumes zero population covariances among variables in the model. The RMSEA estimates the error of approximation as well as the error of estimation, which is affected by sample size (i.e., greater error in smaller samples), per model degree of freedom. In other words, this estimate informs us how well the model represents what actually occurs in the population. The SRMR is similar to RMSEA except that it does not take sample size into account; therefore, RMSEA is generally viewed as a better model fit estimate. All of these estimates must be considered when assessing model fit and all must fall into acceptable ranges in order to evaluate the parameter estimates.

This technique allows for the exploration of the direct and indirect effects of group (MS vs. controls) and sex on processing speed and working memory. For instance, if the data are consistent with the *Independent Consequence Model*, group would directly affect processing speed and working memory performance but there would be no relationship between these cognitive domains; conversely, if the data are consistent with the *Relative Consequence Model*, group would directly impact processing speed and also impact working memory, with evidence of processing speed fully or partially mediating this relationship. Also consistent with the *Relative Consequence Model*, it is possible that processing speed directly predicts working memory performance, regardless of group. Thus, a path analysis would allow for examination of these possible paths to explain the relationship between processing speed and working memory to determine which model best explains the deficits seen in MS. This technique would simultaneously allow for the exploration of the influence of sex in a similar manner. To my knowledge, a structural equation modeling technique has never been used to explore the relationship between working memory and processing speed in the MS population; given the recent discrepant findings in the literature, this statistical approach could help to resolve some of this confusion as well as to explore the possible influence of sex in the relationship between processing speed and working memory.

*Goals of the Present Study*

The purpose of the present study was to explore the relationship between processing speed and working memory in MS, as they have been previously noted to be common deficits in this population (Achiron et al.,2005; Archibald & Fisk, 2000; D'Esposito et al.,1996; DeLuca et al., 2004;Demaree et al., 1999; Denney et al., 2004; Diamond et al., 1997; Grigsby et al., 1994; Kail, 1998; Kujala et al., 1995; Lengenfelder et al., 2003; Lengenfelder et al., 2006; Litvan et al., 1988; Parmenter et al., 2006; Parmenter et al., 2007a; Parmenter et al., 2007b; Ruchkin et al., 1994; Wishart & Sharpe, 1997). The primary goal of this study was to use different methods and analyses to test the *Relative* and *Independent Consequence Models* (DeLuca, 2004) as explanations for the relationship between processing speed and working memory impairments in MS. The *n*-back task was used in the present study, as it allows for the parsing of processing speed and working memory performance as well as examination of both simple and complex processing speed. Working memory performance was also more precisely investigated as the *n*-back task allows for the recording of more specific performance variables (e.g., dyad responses). Also, to improve upon the research by Beatty and colleagues (1990, 1992, 2002), the present study used a healthy control group for comparison rather than using normative data as a reference group. In addition, the present study employed a larger and more representative sample than that used by Parmenter and colleagues (2007b) to provide the statistical power needed to examine sex differences in cognition in the MS population.

*Primary Hypotheses*

Several previous studies have shown that relative to controls, people with MS perform more poorly on measures of both speed of information processing (Archibald & Fisk, 2000; Archiron et al., 2005; DeLuca et al., 2004; Demaree, et al., 1999; Kail, 1998; Kujala et al., 1995; Lengenfelder et al., 2006; Litvan et al., 1988; Parmenter et al., 2006; Parmenter et al., 2007a; Parmenter et al., 2007b) and working memory (D'Esposito et al., 1996; Diamond et al., 1997; DeLuca et al., Foong et al., 1999; Lengenfelder et al., 2003; Lengenfelder et al., 2006; Parmenter et al., 2006; Parmenter et al., 2007a; Parmenter et al., 2007b; Ruchkin et al., 1994; Wishart &

Sharpe, 1997). Path analysis allowed us to investigate these group differences by constructing models that included both MS and healthy control groups and comparing them on processing speed and working memory. Consistent with previous research, it was hypothesized that in models constructed for both the 1- and 2-back conditions of the *n*-back, a direct relationship would be observed between both group and processing speed and group and working memory, with MS patients exhibiting slower complex processing speed and reduced working memory on the *n*-back task. Specifically, with regard to complex processing speed, MS patients were expected to have longer mean reaction times on the 1- and 2-back conditions. With regard to working memory, MS patients were hypothesized to have fewer total correct and a smaller percentage of dyad responses on the 1- and 2-back conditions.

Path analysis also allowed us to compare the *Independent* and *Relative Consequence Models*. As stated previously, independent direct relationships between group and processing speed/working memory would be more consistent with the *Independent Consequence Model*. On the other hand, impairment in processing speed that either directly or indirectly predicts the impairment in working memory commonly noted in the MS population would be more consistent with the *Relative Consequence Model*.

*Secondary Hypotheses*

Consistent with previous research demonstrating that compared to women with MS, men with MS perform more poorly across several cognitive domains (Beatty & Aupperle, 2002; Beatty, Goodkin, Hertsgaard, & Monson, 1990; Beatty et al., 1995), it was hypothesized that within the MS group a direct relationship would be observed between both sex and processing speed and sex and working memory. More specifically, compared to women with MS, men with MS were hypothesized to demonstrate slower complex processing speed on the *n*-back task as measured by mean reaction times on the 1- and 2-back conditions. It was also hypothesized that, compared to women with MS, men with MS would exhibit reduced working memory as defined by fewer total correct and a smaller percentage of dyad responses in the 1- and 2-back conditions.

If sex differences emerged on the aforementioned models, then separate models would be used to examine males and females in the MS sample. Considering the *Independent* and *Relative Consequence Models*, we expected to observe path models that applied differently to males and females with MS. More specifically, consistent with the *Independent Consequence Model*, in the male MS group a direct relationship between processing speed (simple or complex) and working memory was not expected (i.e., no evidence of partial or full mediation of processing speed in working memory performance). In contrast, consistent with the *Relative Consequence Model*, in the female group a direct relationship was expected between processing speed and working memory (i.e., evidence supporting partial or full mediation of processing speed in working memory performance).

## CHAPTER TWO

## METHOD

*Participants*

Forty-five MS patients and 29 healthy controls participated in the study. Thirty-four of the MS participants had RRMS (26 females, eight males), five had SPMS (four females, one male), two had PPMS (two males), and four of the participants' MS subtype was unknown. The MS group included 33 female and 12 male participants whereas the control group included 15 female and 14 male participants.

MS participants were recruited primarily through local neurologists in Spokane, Washington, Moscow, Idaho and surrounding areas. Healthy controls were primarily recruited through advertisement in the Washington State University campus newspaper as well as local newspapers and radio stations. Exclusionary criteria included history of prior head trauma with loss of consciousness, vision or hearing problems, or learning disability. Participants were also excluded from the study if they had any other medical, neurologic, or psychiatric conditions besides MS, with the exception of depression in the MS group due to its high comorbidity with the disease.

*Procedure*

All participants were recruited as part of a larger study and the *n*-back task was administered as part of a larger neuropsychological battery that included the Ambulation Index, the North American Adult Reading Test, the Center for Epidemiologic Studies- Depression Scale, the Fatigue Severity Scale, and the Minimal Assessment of Cognitive Functioning in MS (MACFIMS; Benedict et al., 2002) battery. The order of tests was counterbalanced and the *n*-back task was administered at the beginning of the cognitive battery for some participants and at the end of the battery for other participants. The Ambulation Index and the North American Adult Reading Test were always administered at the beginning of the testing battery while the Center for Epidemiologic Studies- Depression Scale and the Fatigue Severity Scale were counterbalanced, with administration at the beginning or end of the testing battery.

*Measures*

*N-back Task*

The *n*-back task is an experimental computerized measure of processing speed and working memory. The *n*-back task had three conditions in the present study: 0-, 1-, and 2-back (see Figure 1) and the conditions were presented in the same order (0-, 1-, and 2-back) for all participants. Practice trials preceded all test trials and were repeated as necessary to allow the participants to adapt to the new demands of the task. For the 0-back condition, participants were asked to identify the letter "X" out of a sequence of letters presented one at a time. For the 1-back condition, participants were asked if the letter presented matched the letter immediately preceding it. The 2-back condition was identical to the 1-back condition except that participants were asked if the letter presented matched the letter presented two before it (see Figure 1). For the 0-back condition, participants used a computer mouse and pressed the left mouse button when they saw the letter "X" and the right mouse button when any other letter was presented. For both the 1-back and 2-back conditions the participants pressed the left mouse button to signify a "match" and the right mouse button to signify a "non-match." The *n*-back task used in the current study was modeled after previously published studies that used this task (see Carlson et al., 1998; Gevins et al., 1996; Segalowitz et al., 2001). Ten lower- and upper-case letters of the alphabet were repeated and case (lower or upper) did not determine correct response. Each trial presented a total of 150 letters, with one-third of the trials being a "match" and two-thirds being a “non-match.” Similar to the task used by Parmenter and colleagues (2006, 2007b), stimulus duration was 400 msec, with a 2000 msec interstimulus interval (ISI).

Total correct responses were recorded for each condition of the *n*-back task separately (i.e., 0-, 1- and 2-back). For the purposes of the current study, total dyad responses were calculated for 1-back and 2-back conditions by the method discussed in Fisk and Archibald (2001) and Shucard and colleagues (2004). Specifically, a dyad was recorded when there were two consecutive correct responses. For each condition, the proportion of total correct answers accounted for by dyad responses was calculated using the following equation: percent dyad = (1-([total correct-total dyads]/total correct)) x 100. Total consecutive responses were recorded in order to examine task approach (i.e., whether participants were responding consecutively, as directed, or skipping responses). Reaction times were averaged across all 150 trials for each condition. Thus three different mean reaction times were calculated for each participant, with reaction time for the 0-back reflecting simple processing speed and reaction times for the 1- and 2-back reflecting complex processing speed.

*North American Adult Reading Test ([NAART]; Blair & Spreen, 1989):* The NAART is a reading test used to predict premorbid intelligence, based on the assumption that reading abilities generally remain stable despite insult to the brain (Blair & Spreen, 1989). The test consists of 60 irregularly spelled words that were read aloud by the participant and scored as correct or incorrect based on pronunciation. A full scale IQ estimate was calculated using the equation proposed by Blair and Spreen (1989; 127.8 - .78[NAART errors]), with full scale IQ estimates ranging from 81 to 127.8.

*Ambulation Index ([AI]; Hauser et al., 1983):* The AI is a measure that assesses physical mobility and disability associated with MS. The participant was asked to walk 25 feet as quickly but as safely as possible and the examiner recorded speed and information about gait, balance, and assistance needed to complete the walk. This information is used to determine a score ranging from 0 (asymptomatic, fully active) to 10 (bedridden).

*The Center for Epidemiologic Studies Depression Scale ([CES-D]; Radloff, 1977):* The CES-D is a self-report measure of depression. This scale consists of 20 items pertaining to four features of depression: depressed affect, positive affect, somatic and retarded activity, and interpersonal issues. Participants were asked to rate each item on a scale from 0 (rarely or none of the time) to 3 (most or all of the time) with reference to how they felt during the past week. The ratings were summed to yield a total score ranging from 0 to 60, with higher scores reflecting a greater level of depression and scores of 16 or greater indicative of clinical depression.

*The Fatigue Severity Scale ([FSS]; Krupp et al., 1984):* The FSS is a self-administered scale consisting of nine items that address the severity of participants' fatigue. The participant was instructed to rate each item on a scale from 1 (strongly disagree) to 7 (strongly agree) according to how strongly they agreed with the item. Summed responses on the FSS were then averaged, with total scores ranging from 1 to 9 and scores greater than 4 indicating significant fatigue.

*Minimal Assessment of Cognitive Functioning In MS (MACFIMS; Benedict et al., 2002):* The MACFIMS is a battery of tests developed by an international panel and recommended for the minimal assessment of cognitive functioning in MS. It consists of seven tests determined to assess domains most commonly impacted by MS (see Benedict et al., 2002; Benedict et al., 2006). These tests included the Controlled Oral Word Association Test (COWAT; Benton et al., 1994) to assess language abilities; the Judgment of Line Orientation Test (JLO; Benton et al.,

1994) to assess spatial processing; the California Verbal Learning Test, Second Edition (CVLT-II; Delis et al., 2000) to assess verbal learning and memory; the Brief Visuospatial Memory Test, Revised (BVMT-R; Benedict et al., 1996; Benedict et al., 1997) to assess visuospatial learning and memory; the Symbol Digit Modalities Test (SDMT; Smith, 1982; Rao et al., 1991b; Rao et al., 1991) to assess processing speed and working memory; the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1997; Rao et al., 1991b; Rao et al., 1991) to assess processing speed and working memory; and the Delis-Kaplan Executive Functioning System Sorting Test (D-KEFS Sorting; Delis et al., 2001) to assess executive functioning.

*Statistical Analyses*

Independent samples t-tests were conducted to compare the MS and control groups as well as to compare males and females within each group on demographic variables such as age, level of education, and estimated premorbid intelligence (i.e., NAART score) and on health characteristics such as depression (CES-D score) and fatigue severity (FSS score). Chi square analysis was used to investigate group differences in proportion of sex, taking into account the different male-female ratios in control vs. MS groups. Within the MS group, a one-way analysis of variance (ANOVA) was conducted to examine differences between males and females in level of physical severity based upon the AI index score. A multivariate analysis of variance (MANOVA) was also conducted to examine differences between MS males and females in level of cognitive severity based upon performance on the MACFIMS.

Mplus (version 5.21, Muthén & Muthén) robust maximum likelihood estimation procedure was used to test the models in Figures1-6. Model fit was evaluated with the Chi Square test (study criteria p value greater than .05), the CFI (study criteria .95 or higher), the SRMR (study criteria .06 or less) and the RMSEA (study criteria of .06 or less) as recommended by Brown (2005). Significance levels of $p < .05$ were used to establish the significance of parameter estimates in the models unless otherwise indicated.

*Models of Study Hypotheses*

Figures 2 and 3 show the proposed models for the analyses of the primary and secondary hypotheses, with separate models for the 1- and 2-back conditions of the *n*-back task. Figures 4-7 are similar to Figures 2 and 3 except that in these models the MS group (Models 3 and 4, Figures 4 and 5, respectively) and the control group (Models 5 and 6, Figures 6 and 7, respectively) are examined separately in order to assess similar or divergent group processes in the relationship between processing speed and working memory and the influence of sex in this relationship. Different models were constructed using total correct and percentage of dyad responses to define the outcome variable of working memory on the 1- and 2-back conditions. Reaction time on the 1- and 2-back conditions was added as an endogenous variable in the respective 1- and 2-back models to examine the potential mediation of complex processing speed in working memory performance. Total number of consecutive responses was also included as an endogenous variable in all respective 1- and 2-back models models in order to examine potential group differences in task approach (i.e., did the participants perform the task as instructed) as well as to explore whether this variable partially or fully mediated the relationship between processing speed and working memory on the *n*-back task. Sex was included as an exogenous variable in all models in order to investigate possible sex differences in processing speed and working memory as well as to explore whether sex of participant contributed to different models used to explain the pattern of impairment in patients with MS. Reaction time on the 0-back condition was also included as an exogenous variable in all models in order to control for simple processing speed impairment and other confounding variables (e.g., upper extremity impairment) that may influence working memory performance. Variables shown to be significantly different between groups were also added as exogenous variables.

# CHAPTER 3

# RESULTS

*Participant Characteristics*

Table 1 presents demographic and health characteristics for MS patients and healthy controls. The two groups did not differ on education [$t(72) = -.427$, n.s.] or estimated intelligence [$t(72) = -.069$, n.s.]. Groups did differ significantly in age [$t(72) = 3.707$, $p = .001$], with MS patients being significantly older than controls ($M = 46.87$, $SD = 9.13$; $M = 36.10$, $SD = 13.81$, respectively). Groups also differed significantly in fatigue severity based on FSS mean scores [$t(72) = 5.062$, $p < .001$], with MS patients reporting significantly higher levels of fatigue ($M = 5.22$, $SD = 1.56$) relative to healthy controls ($M = 3.40$, $SD = 1.43$). Group differences in depression based on CES-D total scores approached significance [$t(72) = 1.851$, $p = .07$], with MS patients self-reporting higher levels of depression ($M = 15.44$, $SD = 10.26$) than healthy controls ($M = 11.21$, $SD = 8.49$).

In terms of sex differences within groups, in the MS group (see Table 2) males and females did not differ significantly in age [$t(43) = 0.344$, n.s.], education [$t(43) = 1.477$, n.s.], estimated intelligence [$t(42) = 1.608$, n.s.], fatigue severity [$t(43) = -0.983$, n.s.], or depression [$t(43) = 1.030$, n.s.]. Males and females in the control group (see Table 3) did not differ in education [$t(27) = -0.021$, n.s.], estimated intelligence [$t(27) = 0.917$, n.s.], fatigue severity [$t(27) = 1.109$, n.s.], or depression [$t(27) = -0.048$, n.s.]; however, differences in age approached significance [$t(27) = 1.833$, $p = .08$] with females being older (M = 40.5 years, SD = 14.7 years) than males (M = 31.4 years, SD = 11.5 years). In terms of physical and cognitive severity within the MS group, males and females did not differ significantly in physical severity based upon the

AI index score [*F*(1,41)=.083, n.s.] or cognitive severity based upon performance on the MACFIMS battery [*F*(11,31) = 1.622, n.s.].

*Models of Study Hypotheses with Additional Covariates*

Different models were constructed for the outcome variables of total correct and percentage of dyad responses on the 1- and 2-back conditions separately; however, only models using percentage of dyad responses are reported for purposes of brevity as these models were often identical. Models 1 and 2 (Figures 2 and 3, respectively) include males and females in both the MS and control groups. Because MS patients and controls differed significantly in age, FSS mean score, and CES-D total score (see Table 1), these variables were added as exogenous variables in Models 1 and 2 in order to control for the potential influence of age, fatigue, and depression, respectively, on working memory performance. Only reaction time on the 0-back condition and sex were included as covariates in Models 3 and 4, as males and females within the MS group did not differ on demographic variables or health characteristics. Because the difference in age between males and females within the control group approached significance, this variable was added as a covariate to Models 5 and 6.

*Analyses of Primary Study Hypotheses*

Figures 2 and 3 address both the primary and secondary hypotheses of the study. The results for the analysis of Model 1 (Figure 2) indicated that the model provided an excellent fit [$\chi^2(6) = 3.307$, p = .77, CFI = 1.000, SRMR = .03, and RMSEA = .000]. This model was shown to account for 50 percent of the variance in working memory performance and 70 percent of the variance in processing speed. The results for the analysis of Model 2 (Figure 3) also indicated that the model provided an excellent fit [$\chi^2(5) = 4.996$, p = .42, CFI = 1.000, SRMR = .05, and RMSEA = .000]. This model was shown to account for 72 percent of the variance in working memory performance and 40 percent of the variance in processing speed. Figures 2 and 3 show the completely standardized parameters for the models, with asterisks denoting statistically significant coefficients (all $p < .05$).

In terms of the primary study hypotheses, a direct relationship was observed between group (MS vs. controls) and percentage of dyad responses on the 1-back condition of the *n*-back task after controlling for the direct effects of simple processing speed, age, fatigue, and depression, with MS patients obtaining a significantly fewer percentage of dyad responses (*M* = 88.65, *SD* = 9.43) than controls [*M* = 92.50, *SD* = 8.14; standardized coefficient = 0.20, (*SE* = .09), p = .02]. The direct relationship between group and percentage of dyad responses was not significant on the 2-back condition [MS: *M* = 75.71, *SD* = 16.40; controls: *M* = 82.13, *SD* = 7.01; standardized coefficient = 0.11, (*SE* = .08), p = .15]. Results also did not demonstrate a significant direct relationship between group and complex processing speed on the 1-back condition [MS: *M* = 627.30 ms, *SD* = 135.96; controls: *M* = 563.06, *SD* = 121.01; standardized coefficient = 0.05, (*SE* = .08), p = .58] or the 2-back condition [MS: *M* = 721.22, *SD* = 178.22; controls: *M* = 679.33, *SD* = 164.85; standardized coefficient = 0.16, (*SE* = .11), p = .16] after controlling for the effects of simple processing speed, age, fatigue, and depression. A direct relationship between group and total consecutive responses also was not observed on the 1-back condition [MS: *M* = 144.80, *SD* = 6.22; controls: *M* = 146.38, *SD* = 4.55; standardized coefficient = 0.09, (*SE* = .09), p = .29] or the 2-back condition [MS: *M* = 137.58, *SD* = 25.45; controls: *M* = 142.10, *SD* = 9.81; standardized coefficient = 0.08, (*SE* = .07), p = .23] after controlling for the effects of simple processing speed, age, fatigue, and depression. To summarize, group was found to significantly predict working memory performance in the 1-back condition, with MS patients performing more poorly than controls, but not in the 2-back condition. Group also did not significantly predict complex processing speed performance in either condition.

Exploratory analyses were conducted to compare the *Relative* and *Independent Consquence Models* in explaining the relationship between processing speed and working memory performance. In Model 1(see Figure 2), which refers to processing speed and working memory performance in the 1-back condition of the *n*-back task for the MS and control groups combined, results demonstrated a significant direct effect of reaction time on the 0-back condition on percentage of dyad responses [standardized coefficient = -0.33, (*SE* = .12), p = .004]) after controlling for age, fatigue, and depression. This result demonstrates that percentage of dyad responses in the 1-back condition decreased by .33 standard deviations for every standard deviation increase in reaction time on the 0-back. Reaction time on the 0-back was also shown to have a significant indirect effect on percentage of dyad responses through reaction time on the 1-back. Specifically, reaction time on the 0-back was shown to be significantly positively associated with reaction time on the 1-back [standardized coefficient = 0.85, (*SE* = .05), p = .000] and reaction time on the 1-back was shown to be positively related to  percentage of dyad responses on the 1-back [standardized coefficient = 0.67, (*SE* = .14), p = .000]. In other words, slower simple processing speed resulted in slower complex processing speed and slower complex processing speed resulted in better working memory. Total consecutive responses on the 1-back was also positively related to percentage of dyad responses [standardized coefficient = 0.59, (*SE* = .011), p = .000], but demonstrated no effect of mediation in reaction time and percentage of dyad responses. To summarize, in the 1-back condition of the *n*-back task, the effect of simple processing speed on working memory performance was partially mediated by complex processing speed. Further, both complex processing speed and total consecutive responses directly predicted working memory performance with no presence of mediation.

Model 2 (see Figure 3), which refers to processing speed and working memory performance on the 2-back condition of the *n*-back task, demonstrated results that were similar to Model 1 but there were also important differences between these models. In this model reaction time on the 0-back did not have a significant direct effect on percentage of dyad responses but did have a significant indirect effect on percentage of dyad responses through reaction time on the 2-back and total consecutive responses on the 2-back after controlling for age, fatigue, and depression. Reaction time on the 2-back was shown to have a significant direct effect on percentage of dyad responses as well as a significant indirect effect on percentage of dyad responses through total consecutive responses on the 2-back after controlling for simple processing speed, age, fatigue, and depression. Specifically, reaction time on the 0-back was shown to be significantly positively associated with reaction time on the 2-back [standardized coefficient = 0.64, (*SE* = .11), p = .000] and reaction time on the 2-back was shown to be positively related to percentage of dyad responses on the 2-back [standardized coefficient = 0.26, (*SE* = .11), p = .03]. Reaction time on the 2-back was negatively associated with total consecutive responses on the 2-back [standardized coefficient = -0.24, (*SE* = .08), p = .002] and total consecutive responses was positively associated with percentage of dyad responses [standardized coefficient = 0.84, (*SE* = .10), p = .000]. In other words, slower simple processing speed was again significantly associated with slower complex processing speed and slower complex processing speed was shown to directly predict better working memory performance. Complex processing speed was also shown to indirectly affect working memory performance as slower complex processing speed predicted fewer total consecutive responses; greater total consecutive responses predicted better working memory performance. To summarize, in the 2-back condition of the *n*-back task, the effect of simple processing speed on working memory performance was fully mediated by complex processing speed and total consecutive responses. Further, the effect of complex processing speed on working memory performance was partially mediated by total consecutive responses.

To examine potential divergent impacts of processing speed on working memory, separate models were constructed for the MS and control groups. Models 3 and 4 (Figures 4 and 5, respectively) refer to processing speed and working memory performance within the MS group on the 1- and 2-back conditions, respectively, while Models 5 and 6 (Figures 6 and 7) refer to the same in the control group. The results for Model 3 (Figure 4) indicated that the model provided an excellent fit [$\chi^2(2) = 1.868$, p = .39, CFI = 1.000, SRMR = .05, and RMSEA = .000]. This model accounted for 44 percent of the variance in working memory and 70 percent of the variance in processing speed. The results for the analysis of Model 4 (Figure 5) indicated that the model provided a very good fit [$\chi^2(2) = 0.923$, p = .63, CFI = 1.000, SRMR = .07, and RMSEA = .000]. This model accounted for 76 percent of the variance in working memory and 31 percent of the variance in processing speed.

The results of Models 3 and 4 indicate an identical process in the MS group that was evident in Models 1 and 2 to explain the relationship between processing speed and working memory performance. In other words, in the 1-back condition, simple processing speed was shown to directly affect working memory performance as well as indirectly affect working memory performance through complex processing speed and total consecutive responses. Specifically, faster simple processing speed predicted better working memory performance; further, slower simple processing speed resulted in slower complex processing speed and slower complex processing speed resulted in better working memory. The only difference between this model and Model 1 is that complex processing speed was significantly associated with working memory directly as well as indirectly through total consecutive responses. In the 2-back condition, the direct relationship between simple processing speed and working memory was not significant, but simple processing speed was indirectly associated with working memory through complex processing speed and total consecutive responses. Again, consistent with results of Model 2, slower simple processing speed resulted in slower complex processing speed and slower complex processing speed resulted in better working memory. The results for Models 5 and 6, which looked specifically at the control group, indicated poor fit as neither model met the study criteria [$\chi^2(3) = 4.265$, p = .23, CFI = 0.998, SRMR = .07, and RMSEA = .12; and $\chi^2(3) = 8.876$, p = .03, CFI = 0.82, SRMR = .08, and RMSEA = .26, respectively]. Therefore, these models were not interpreted.

*Analyses of Secondary Hypotheses*

In terms of secondary hypotheses of the study, no direct relationships were observed between sex and percentage of dyad responses on the 1-back condition [MS – Males: *M* = 88.28, *SD* = 6.46, Females: *M* = 88.79, *SD* = 10.39; Controls – Males: *M* = 90.48, *SD* = 11.29, Females: *M* = 94.38, *SD* = 2.47; standardized coefficient = -0.06, (*SE* = .09), p = .49] or 2-back condition [MS – Males: *M* = 68.80, *SD* = 22.24, Females: *M* = 78.22, *SD* = 13.24; Controls – Males: *M* = 81.67, *SD* = 7.37, Females: *M* = 82.57, *SD* = 6.89; standardized coefficient = -0.02, (*SE* = .07), p = .80], or between sex and reaction time on the 1-back condition [MS – Males: *M* = 693.33, *SD* = 172.45, Females: *M* = 603.29, *SD* = 113.86; Controls – Males: *M* = 530.26, *SD* = 99.54, Females: *M* = 593.66, *SD* = 134.19; standardized coefficient = 0.000, (*SE* = .07), p = .999] after controlling for simple processing speed, age, fatigue, and depression. The relationship between sex and reaction time approached significance on the 2-back condition [MS – Males: *M* = 715.27, *SD* = 210.92, Females: *M* = 723.38, *SD* = 168.41; Controls – Males: *M* = 623.18, *SD* = 151.19, Females: *M* = 731.73, *SD* = 164.42; standardized coefficient = -0.18, (*SE* = .10), p = .07] after controlling for simple processing speed, age, fatigue, and depression. However, because sex was not found to significantly affect processing speed or working memory performance, no additional models were constructed to further examine the secondary hypotheses of the study.

## CHAPTER FOUR

## DISCUSSION

This study was designed to explore the relationship between commonly noted impairments in processing speed and working memory in patients with MS. Similar to work done by Parmenter and colleagues (2006, 2007), this study used the *n*-back task, which allowed for separate examination of these domains. A unique contribution of the current study is the use of path analysis to better determine how processing speed and working memory abilities are related. The influence of sex in processing speed and working memory impairments was also investigated, as recent research has indicated sex differences in both physical and cognitive impairment in MS sufferers.

### *Discussion of Results Related to Primary Hypotheses*

Contrary to what was expected, results of the present study did not demonstrate signficant differences between MS patients and healthy controls in working memory on the 2-back condition or in complex processing speed on either the 1-back or 2-back conditions of the *n*-back task. In the 1-back condition, group was shown to significantly predict working memory performance, with MS patients performing more poorly than controls; however, this effect was notably weaker than the associations between processing speed (simple and complex) and working memory performance. At first glance, these findings appear to contradict the majority of previous studies indicating that processing speed and working memory are the primary deficits in MS; however, it is important to note that the excellent fit of the models for working memory in the MS group and the poor fit of the models in the control group suggests group differences in working memory. Thus, it is also possible that the lack of group differences in Models 1 and 2 (looking at the groups combined) may be related to unequal sample sizes or the need for more control participants to increase the power to detect such differences.

In addition, these results could be related to the statistical analyses used in this study. For instance, while previous research has attempted to remove simple processing speed from more complex measures of processing speed, this has been done by calculating difference scores (Parmenter, 2007b). This is problematic because it restricts the range of reaction times and therefore compresses the variance in complex processing speed. Thus, this restricted variance may in itself produce an effect that otherwise would not be present. In the current study, simple processing speed was included as an exogenous variable in the path models, which allowed us to explore the direct effect of group on complex processing speed and working memory while holding constant, or controlling for, simple processing speed. The lack of group differences in complex processing speed and working memory in the 2-back condition, which places the highest demand on processing speed and working memory, therefore suggests that basic deficits in simple processing speed may account for deficits in complex processing speed and working memory. This finding thus provides support for the *Relative Consequence Model*, which purports that working memory deficits are secondary to impaired processing speed (DeLuca, 2004).

The present study employed path analysis in order to directly compare the *Relative* and *Independent Consequence Models* in explaining the relationship between processing speed and working memory impairments in MS versus healthy controls. Previous research has used general linear modeling (e.g., ANOVA) to examine these impairments in MS, and has generally reported findings of main effects (i.e., group differences in processing speed and working memory performance). To our knowledge, no previous study has used path analysis to examine the relationship between processing speed and working memory in MS, despite the unique ability of this approach to demonstrate causal relationships. The path models examining MS patients separate from healthy controls demonstrated clear direct and indirect paths between processing speed and working memory. More specifically, for MS patients on the 1-back condition of the *n*-back task, which is a simple working memory task, simple processing speed was shown to be directly and indirectly related to working memory performance through complex processing speed and total consecutive responses. Complex processing speed was also shown to be directly related to working memory performance as well as indirectly related to working memory performance through total consecutive responses. Thus, the relationship between simple processing and working memory performance was partially mediated by complex processing speed and total consecutive responses and the relationship between complex processing speed and working memory performance was partially mediated by total consecutive responses. Importantly, complex processing speed was the strongest predictor of working memory performance relative to the other variables in the path model.

Thus, on a simple working memory task, faster simple processing speed (i.e., shorter reaction times) predicted better working memory performance (i.e., higher percentage of dyad responses) and was also associated with faster complex processing speed. However, in this model slower complex processing speed also predicted better working memory performance. The pattern of these coefficients (i.e., positive relationships between simple processing speed and complex processing speed and between complex processing speed and working memory but a negative relationship between simple processing speed and working memory) has the hallmarks of a suppressor variable being present in the model that is impacting the direction of these relationships. No variables in our data set were identified as the suppressor variable; thus future studies may attempt to discover what types of variables could be impacting these relationships.

However, the 1-back condition is a simple working memory task that was not the main focus of this study. These results were not replicated in the 2-back condition which is a better indicator of working memory performance.

The results for the MS group on the 1-back condition were replicated in the 2-back condition except that simple processing speed was not directly related to working memory performance but was indirectly related to working memory performance through complex processing speed and total consecutive responses. In sum, on a more complex working memory task, complex processing speed, although still impacted by simple processing speed, becomes more important in predicting performance. Thus, the findings within the MS group that processing speed, whether simple or complex, significantly predicted working memory performance support the idea of relative consequence put forth by previous researchers (Archibald & Fisk, 2000; DeLuca et al., 2004; Demaree et al., 1999; Lengenfelder et al., 2006). Using these models, support for the *Independent Consequence Model* (DeLuca, 2004) would have necessitated differences between MS patients and healthy controls on both processing speed and working memory with no relationship between these domains, which the results of this study do not demonstrate.

Importantly, the results within the MS group (Figures 3 and 4) were not replicated in the control group (Figures 5 and 6), suggesting divergent group processes to explain the relationship between processing speed and working memory. Although this may suggest a phenomenon that is specific to the MS population, the poor fit of the models in the control group could also be due to a power issue. For example, previous research has demonstrated a large effect size when using the *n*-back task to investigate processing speed (Cohen's d = 1.41) and working memory (Cohen's d = 0.70) in MS (see Parmenter et al., 2006; Parmenter et al., 2007b). These large effect sizes likely contributed to the excellent fit of the models noted in the MS group. On the other hand, the effect sizes for studying processing speed and working memory in healthy controls using the *n*-back task are likely much smaller than those demonstrated in the MS population. Therefore, it is unclear whether similar effects would be noted in the control group with a much larger sample size, or if the effects are specific to the MS population.

The present study also included a novel variable (i.e., total consecutive responses) in the path models to examine the possible mediation of task approach in processing speed and working memory performance. Although percentage of dyad responses has been proposed (Fisk & Archibald, 2000) to better assess working memory than total correct because it takes strategy (e.g., responding consecutively vs. skipping items intermittently to reduce working memory burden) into account, a low percentage of dyad responses can be somewhat misleading. For instance, a dyad was recorded when a participant responded to two consecutive items *correctly*; therefore, a low percentage of dyad responses can be due to either responding incorrectly, which could indicate impaired working memory, or to a lack of responding, which could indicate impaired processing speed as the participant is not able to keep up with the task. Thus, simply examining percentage of dyad responses, or total correct for that matter, does not fully capture working memory performance. Including total consecutive responses was therefore used to assess whether the participants were responding to the task as directed or whether they were skipping responses.

The inclusion of total consecutive responses also permitted the examination of how task approach was related to both processing speed and working memory performance. For instance, within the MS group, a significant direct relationship was noted between complex processing speed and working memory performance in both the 1- and 2-back conditions, with longer reaction times predicting better working memory performance. This result would be expected, given that the challenging nature of the 1- and 2-back conditions of the *n*-back task typically results in longer mean reaction times. However, a significant indirect relationship was also noted between complex processing speed and working memory performance through total consecutive responses, with longer reaction times predicting fewer total consecutive responses, which in turn predicted poorer working memory performance. At first, these direct and indirect findings seem to contradict one another; however, upon closer examination, the results demonstrate the complexity of the relationship between processing speed and working memory as well as the importance of assessing task approach. For instance, if total consecutive responses had not been a variable included in the path model, the direct relationship between complex processing speed and working memory would have been misleading, as we likely would have interpreted this result to be expected given the challenging nature of the working memory task. However, the indirect path indicates a more complex relationship between processing speed and working memory, as poor working memory performance on the *n*-back task within the MS group was not found to be due to impaired working memory but rather slowed processing speed. This conclusion is apparent because poor working memory performance was not caused by a higher number of incorrect responses but rather a lower number of total consecutive responses, or a lack of responding. Further, the inverse of this indirect relationship is also true, as when participants were responding consistently they tended to respond correctly. Overall these findings again provide support for the *Relative Consequence Model* and also emphasize the importance of evaluating task approach when investigating the relationship between processing speed and working memory, as total consecutive responses partially mediated this relationship.

*Discussion of Secondary Hypotheses*

The inclusion of sex as an exogenous variable in the path models did not produce any significant direct or indirect effects on processing speed or working memory performance. Although this finding may indicate no effect of sex on processing speed or working memory in patients with MS, the small sample size of this study may have been limited to detect such an effect. Further, while men with MS have been noted to have a more severe, progressive course than women with MS, the males and females within our sample did not differ significantly in either physical or cognitive severity. Therefore, the males within our MS group may not be representative of other men with MS.

*Limitations and Future Directions*

A potential limitation of this study is the relatively small sample size. The control group included only 29 participants, and as aforementioned, this may have greatly impacted the poor fit of the path models in this group. Although the MS group included only 45 participants, the results of the path models indicated excellent fit and also accounted for a substantial amount of variance in processing speed and working memory performance on the *n*-back task. Therefore, although a larger number of participants is generally recommended to employ a path modeling approach, the few variables included in the models as well as the large effect sizes of these variables likely counteracted the small number of participants in the MS group. Although the sample size in the MS group was large enough to investigate the relationship between working memory and processing speed, its size, along with the even smaller size of the control group, may have limited the ability to detect group differences related to the primary hypotheses of the study. Further, although the overall MS sample was representative of the sex disparity noted in this population, the MS group included only 12 male participants, which may have limited the ability to detect sex differences in processing speed and working memory related to the secondary hypotheses of the study. Conversely, however, the effect size of sex was typically very small, suggesting that even if the sample were increased substantially, significant findings still may not have emerged. This may suggest that sex does not significantly impact processing speed and working memory performance in MS patients. Nonetheless, replication of this study with a larger sample is recommended.

It is important to note that the findings of this study may be limited to the characteristics of the sample. For instance, although subtype of MS was not controlled for in this study, the MS group primarily included RRMS patients and appeared to be high functioning overall. The sample was also well-educated, which may have affected the findings. Therefore, the generalizability of the results may be limited. Replication of this study with a more diverse group of MS patients is thus recommended to evaluate the stability of these findings. It is also recommended that future studies employ path analysis to examine how processing speed and working memory influence performance on tasks of other cognitive abilities (e.g., memory, executive function, etc.).

*Conclusions*

Despite the aforementioned limitations, the present study provides several important contributions to the MS literature. Most importantly, the results of this study provide strong evidence supporting the *Relative Consequence Model* (DeLuca, 2004) in explaining the relationship between processing speed and working memory impairments in MS. Thus, although previous research has been inconsistent and provided differential support for the *Relative* and *Independent Consequence Models* (DeLuca, 2004), the current study expands on previous research by using path analysis to directly compare these models, and results clearly supported the *Relative Consequence Model*.

Similar to how it has been used in previous studies (Parmenter et al., 2006; Parmenter et al., 2007b) the use of the *n*-back task in the current study also allowed for separate examination of processing speed and working memory abilities measured simultaneously in a single task. The use of this paradigm is therefore more advantageous than using separate tasks to examine the relationship between processing speed and working memory because it reduces the potential confounds that are introduced when measuring processing speed and working memory in proposed isolation (e.g., fluctuating attention, fatigue, etc.). The use of the *n*-back was also more beneficial than other tasks that do not allow for the parsing of processing speed and working memory (e.g., the PASAT), as it permitted the creation of separate variables (i.e., reaction time and total correct/percentage of dyad responses) to investigate the relationship between processing speed and working memory using a path analysis approach.

The use of path analysis in the present study was invaluable for two reasons. Most evident, this approach allowed for direct comparison of the *Relative* and *Independent Consequence Models* (DeLuca, 2004) and elucidated the relationship between processing speed and working memory impairments in MS. However, the results of this study also highlight the advantages of using this type of statistical approach over the more commonly used general linear modeling approach when investigating similar types of relationships in the MS population or any other population. Specifically, compared to general linear modeling, path analysis allows for examination of direct and indirect causal relationships between designated variables while also controlling for other potentially confounding variables.

The finding that processing speed influences task approach and predicts working memory performance suggests that processing speed is the more primary deficit in MS, which has important research and clinical implications. For example, future research could focus on establishing strategies that may help patients with MS compensate for slowed processing speed or developing styles of rehabilitation that may diminish the severity of this impairment. Clinicians should also be informed of the potential for slowed processing speed when working with MS patients, as information should be delivered at a slower rate or repeated to ensure that it is conveyed correctly and understood. Clinicians could also work with MS patients to employ such strategies in their daily life in an attempt to reduce the impact that slowed processing speed may have on their overall cognitive functioning.

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APPENDIX

**Table 1. Patient and control group characteristics**

| | MS (n=45) | | Control (n=29) | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **p=** |
| ***Demographics*** | | | | | |
| Age (yrs) | 46.87 | 9.13 | 36.10 | 13.81 | .001 |
| Education (yrs) | 15.04 | 2.20 | 15.28 | 2.39 | n.s. |
| Estimated IQ (NAART) | 110.31 | 7.81 | 110.44 | 6.87 | n.s. |
| ***Health Characteristics*** | | | | | |
| Depression (CES-D) | 15.44 | 10.26 | 11.21 | 8.49 | .07 |
| Fatigue (FSS) | 5.22 | 1.56 | 3.40 | 1.43 | .000 |

**Table 2. Sex differences within MS group**

| | Males (n=12) | | Females (n=33) | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **p=** |
| ***Demographics*** | | | | | |
| Age (yrs) | 46.08 | 7.67 | 47.15 | 9.70 | n.s |
| Education (yrs) | 14.35 | 2.80 | 15.33 | 1.91 | n.s. |
| Estimated IQ (NAART) | 107.09 | 8.29 | 111.39 | 7.46 | n.s. |
| ***Health Characteristics*** | | | | | |
| Depression (CES-D) | 12.83 | 9.48 | 16.39 | 10.51 | n.s. |
| Fatigue (FSS) | 5.51 | 0.90 | 5.12 | 1.74 | n.s. |
| Physical Severity (AI) | 2.09 | 2.30 | 1.88 | 1.88 | n.s. |

**Table 3. Sex differences within Control group**

| | Males (n=14) | | Females (n=15) | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **p=** |
| ***Demographics*** | | | | | |
| Age (yrs)* | 31.43 | 11.46 | 40.47 | 14.74 | .08 |
| Education (yrs) | 15.29 | 3.00 | 15.27 | 1.75 | n.s. |
| Estimated IQ (NAART) | 109.22 | 7.67 | 111.57 | 6.07 | n.s. |
| ***Health Characteristics*** | | | | | |
| Depression (CES-D) | 11.29 | 5.81 | 11.13 | 10.62 | n.s. |
| Fatigue (FSS) | 3.10 | 1.09 | 3.69 | 1.67 | n.s. |

Figure 1. The 1- and 2-back conditions of the *n*-back task.

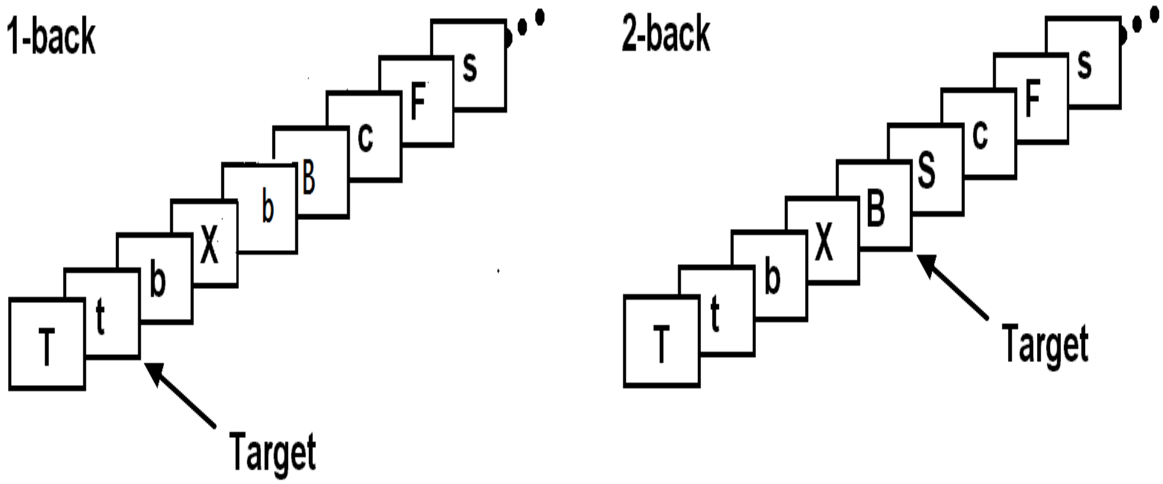
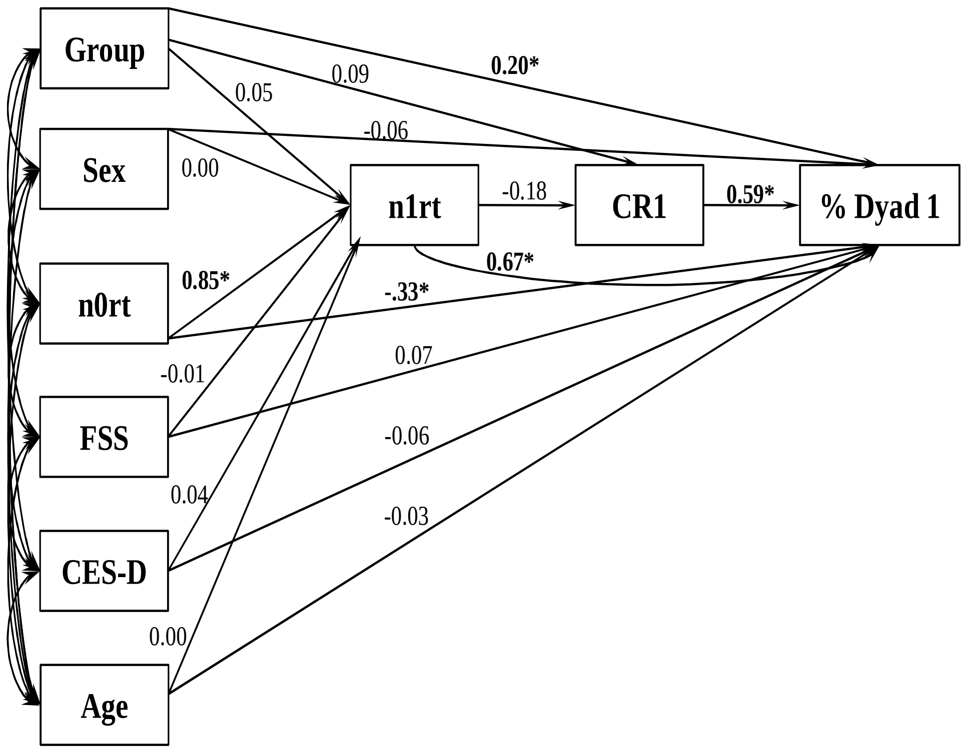
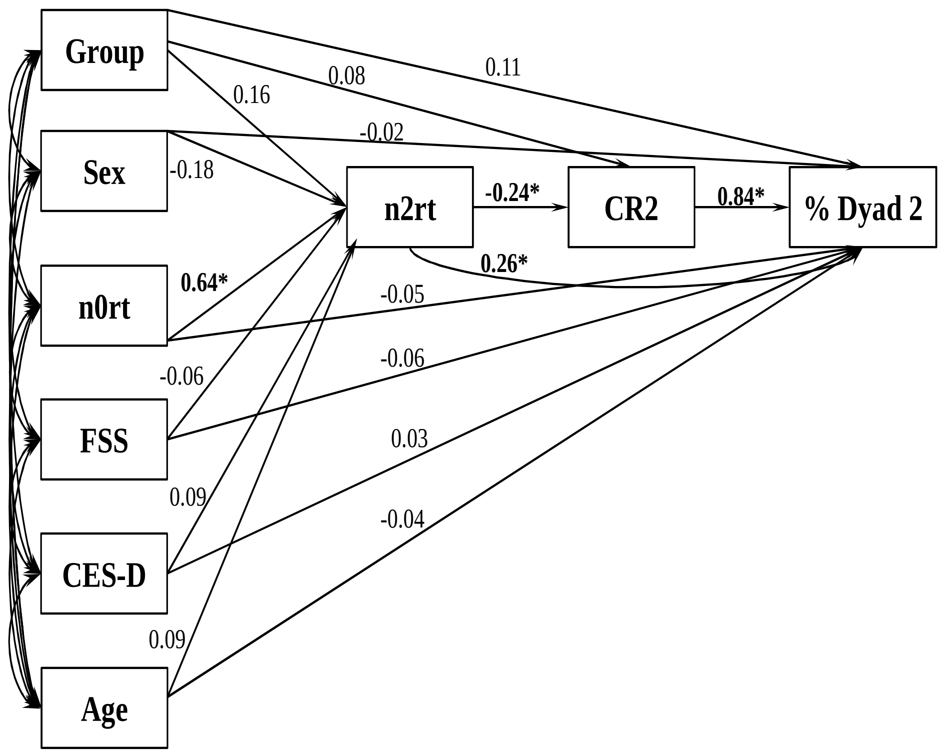


Figure 2. Model 1: Path analysis model comparing MS and control groups and males and females on percentage of dyad responses and complex processing speed on the 1-back condition of the *n*-back task while controlling for simple processing speed, fatigue, depression, and age. Note: All path coefficients are completely standardized.




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **FSS** = mean score on FSS (fatigue); **CES-D** = total score on CES-D (depression); **n1rt** = reaction time on the 1-back (complex processing speed); **CR1** = consecutive responses on the 1-back; **% Dyad 1** = percentage of dyad responses on the 1-back.
***** = p <.05

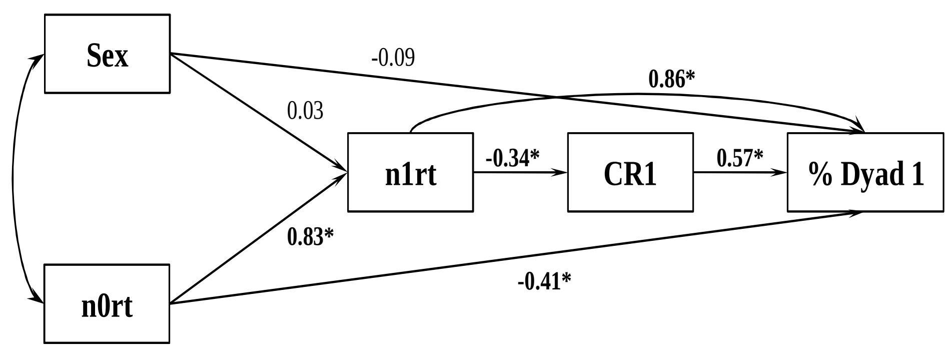
Figure 3. Model 2: Path analysis model comparing MS and control groups and males and females on percentage of dyad responses and complex processing speed on the 2-back condition of the *n*-back task while controlling for simple processing speed, fatigue, depression, and age. Note: All path coefficients are completely standardized.




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **FSS** = mean score on FSS (fatigue); **CES-D** = total score on CES-D (depression); **n2rt** = reaction time on the 2-back (complex processing speed); **CR2** = consecutive responses on the 2-back; **% Dyad 2** = percentage of dyad responses on the 2-back.

***** = p <.05

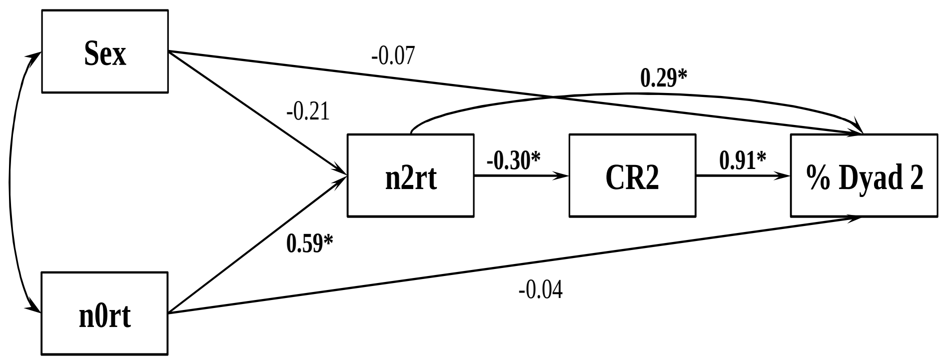
Figure 4. Model 3: Path analysis model comparing males and females within the MS group on percentage of dyad responses and complex processing speed on the 1-back condition of the *n*-back task while controlling for simple processing speed.
Note: All path coefficients are completely standardized.




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **n1rt** = reaction time on the 1-back (i.e., complex processing speed); **CR1** = consecutive responses on the 1-back; **% Dyad 1** = percentage of dyad responses on the 1-back

***** = p <.05

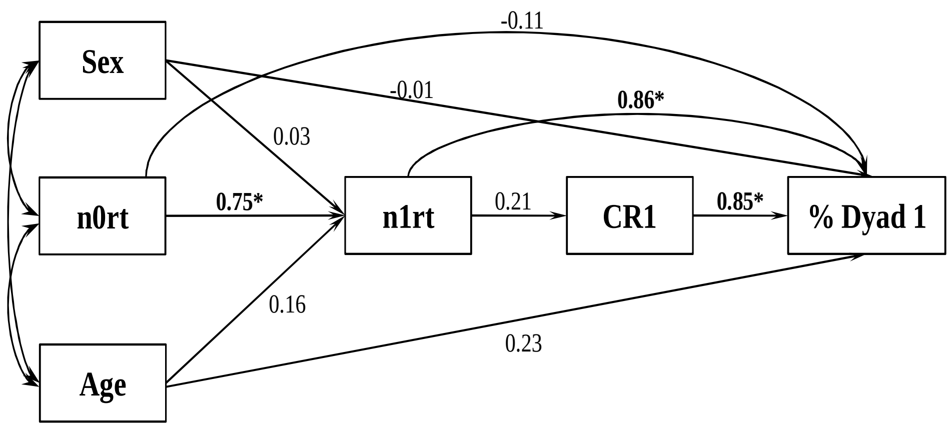
Figure 5. Model 4: Path analysis model comparing males and females within the MS group on percentage of dyad responses and complex processing speed on the 2-back condition of the *n*-back task while controlling for simple processing speed.
Note: All path coefficients are completely standardized.




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **n2rt** = reaction time on the 2-back (complex processing speed); **CR2** = consecutive responses on the 2-back; **% Dyad 2** = percentage of dyad responses on the 2-back

***** = p <.05

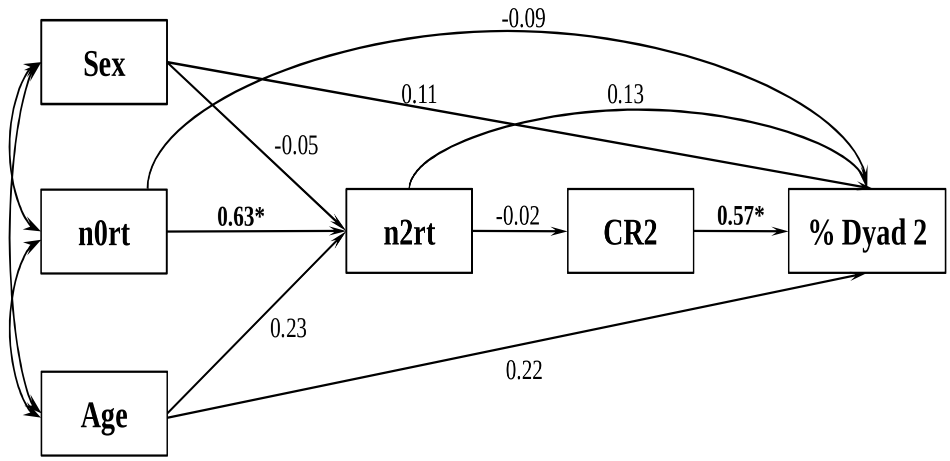
Figure 6. Model 5: Path analysis model comparing males and females within the control group on percentage of dyad responses and complex processing speed on the 1-back condition of the *n*-back task while controlling for simple processing speed and age.
Note: All path coefficients are completely standardized




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **n1rt** = reaction time on the 1-back (complex processing speed); **CR1** = consecutive responses on the 1-back; **% Dyad 1** = percentage of dyad responses on the 1-back

***** = p <.05

Figure 7. Model 6: Path analysis model comparing males and females within the control group on percentage of dyad responses and complex processing speed on the 2-back condition of the *n*-back task while controlling for simple processing speed and age.
Note: All path coefficients are completely standardized.




Note: **n0rt** = reaction time on the 0-back (simple processing speed); **n2rt** = reaction time on the 2-back (complex processing speed); **CR2** = consecutive responses on the 2-back; **% Dyad 2** = percentage of dyad responses on the 2-back

***** = p <.05