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Cognition in Early Relapsing-Remitting Multiple Sclerosis: Consequences May Be Relative to Working Memory

Lindsay I. Berrigan,[1] Jo-Anne LeFevre,[2,3] Laura M. Rees,[2,4,5,6] Jason Berard,[4,6] Mark S. Freedman,[6,7] AND Lisa A.S. Walker[4,5,6,7]

[1]Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada
[2]Department of Psychology, Carleton University, Ottawa, Ontario, Canada
[3]Institute of Cognitive Science, Carleton University, Ottawa, Ontario, Canada
[4]School of Psychology, University of Ottawa, Ottawa, Ontario, Canada
[5]Neuropsychology Service, The Ottawa Hospital, Ottawa, Ontario, Canada
[6]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[7]Division of Neurology, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

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Abstract

The *Relative Consequence Model* proposes multiple sclerosis (MS) patients have a fundamental deficit in processing speed that compromises other cognitive functions. The present study examined the mediating role of processing speed, as well as working memory, in the MS-related effects on other cognitive functions for early relapsing-remitting patients. Seventy relapsing-remitting MS patients with disease duration not greater than 10 years and 72 controls completed tasks assessing processing speed, working memory, learning, and executive functioning. The possible mediating roles of speed and working memory in the MS-related effects on other cognitive functions were evaluated using structural equation modeling. Processing speed was not significantly related to group membership and could not have a mediating role. Working memory was related to group membership and functioned as a mediating/intervening factor. The results do not support the *Relative Consequence Model* in this sample and they challenge the notion that working memory impairment only emerges at later disease stages. The results do support a mediating/intervening role of working memory. These results were obtained for early relapsing-remitting MS patients and should not be generalized to the broader MS population. Instead, future research should examine the relations that exist at other disease stages. (*JINS*, 2013, *19*, 938–949)

Keywords: Multiple sclerosis, Cognitive functioning, Information processing speed, Working memory

INTRODUCTION

Multiple sclerosis (MS) is a disease in which the myelin that insulates axons of the central nervous system (CNS) is damaged. Because myelin is vital to the rapid conduction of neural impulses, the loss of myelin results in the disruption of these impulses so neuronal transmission slows or never reaches its target. The disease process also results in a loss of axons and neurons. MS is associated with a variety of sensory and motor symptoms, neuropsychiatric disorders, and cognitive deficits. Estimates of the frequency of cognitive dysfunction in MS range from 40% to 60% of patients (Benedict et al., 2006; 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.

Slowed processing speed has been proposed as the primary deficit in MS such that inefficiencies in more complex mental abilities are a consequence of slower processing (Relative Consequence Model: DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). Research examining this hypothesis has used mixed-course samples. Because the prevalence and nature of cognitive deficits may differ between MS subtypes (Amato et al., 2010), results could potentially be affected by the cognitive status of one or more disease types *versus* another. One objective of the present study was to investigate the relations between processing speed and the cognitive functions that are often impaired in MS for individuals with early relapsing-remitting MS. The focus on early relapsing-remitting MS was chosen because physical disability may be mild for many individuals in this subgroup and in some cases

Correspondence and reprint requests to: Lindsay I. Berrigan, Department of Psychiatry, Dalhousie University, 5909 Veterans' Memorial Lane, 8th floor, Abbie J. Lane Memorial Building, QEII Health Sciences Center, Halifax, NS, B3 H 2E2. E-mail: lberrigan@dal.ca

cognitive difficulties can be the most severe symptom (Ruggieri et al., 2003). Also, these individuals are typically attempting to maintain their pre-morbid employment status and, thus, are susceptible to the disability that results from cognitive difficulties (Benedict et al., 2005; Clemmons, Fraser, Rosenbaum, Getter, & Johnson, 2004; Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008; Simmons, Tribe, & MacDonald, 2010). Finally, this group is typically targeted for disease modifying therapies. If we wish to evaluate the effectiveness of therapies for cognitive difficulties, it is important to understand the nature of cognitive dysfunction in this group and to identify the assessment tools most useful for detecting and monitoring cognitive difficulties at this stage of the disease.

Furthermore, we sought to investigate these relations while addressing methodological flaws identified to limit previous research evaluating relations between processing speed and other cognitive abilities [i.e., constructs not operationalized successfully, inadequate statistical methods, and failure to examine other potential mediators (Demaree, Frazier, & Johnson, 2008)]. First, operational confounds were minimized by using multiple measures of the constructs under study and by emphasizing the common, construct-relevant variance among different measures through the use of structural equation modeling. Structural equation modeling also offers an appropriate method for evaluating the mediational hypothesis that slowed processing speed is the mechanism by which MS impairs cognitive functioning. Finally, processing speed was operationalized using measures less likely to be confounded by other intellectual abilities and individual differences than what has been used in previous research.

The conceptualization of processing speed adopted in the present study was the rate at which elementary cognitive operations are executed (Kail & Salthouse, 1994). Salthouse (1996) advised that tasks assessing processing speed should be simple enough such that performance is not overly influenced by the individual's knowledge or other cognitive abilities besides processing speed, but not so simple that the task measures only sensory and motor processes and not the duration of relevant cognitive operations. The majority of the research that has reported significant relations between processing speed and higher-order cognitive processes in MS (e.g., DeLuca, Baarbieri-Berger, & Johnson, 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Litvan, Grafman, Vendrell, & Martinez, 1988) operationalized processing speed using some variation of the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977). A major drawback of using the PASAT in this manner is that successful execution of the task requires numerous cognitive functions besides processing speed and individual differences such as mathematical ability and strategy use may also influence performance (Tombaugh, 2006). Therefore, associations found between performance on this task and measures of other cognitive abilities cannot be ascribed specifically to processing speed.

In the present study, processing speed was assessed using three tasks that meet Salthouse's (1996) criteria: simple, choice, and semantic search reaction time from the Computerized Tests of Information Processing (CTIP; Tombaugh & Rees, 2008)]. The three reaction time tasks are easy enough that healthy participants and neurological patients consistently achieve perfect or near-perfect accuracy and individual differences in intelligence, education, knowledge, and strategy use do not influence performance (Reicker, Tombaugh, Walker, & Freedman, 2007; Tombaugh, Rees, Stormer, Harrison, & Smith, 2007; Wojtowicz, Berrigan, & Fisk, 2012). The three tasks index cognitive processing to different degrees, with previous research conducted with individuals with traumatic brain injury and MS supporting this claim (Reicker et al., 2007; Tombaugh et al., 2007; Wojtowicz et al., 2012). In these studies, patients responded significantly slower than controls on each task and, moreover, the reaction times of the groups became more divergent as task difficulty increased. To allow comparisons with existing research, the PASAT was administered; however, it was not included in the structural equation models because of the issues noted above. Similarly, the Symbol Digit Modalities Test (SDMT; Smith, 1991) was administered because it has frequently been used in previous MS research but it was decided a priori to exclude this task from the structural equation models because of evidence that performance is affected by variability in working memory and learning/memory in addition to processing speed (Benedict et al., 2006; Forn et al., 2011).

A second objective of the present study was to examine whether working memory contributes to the deficits in other cognitive functions experienced by individuals with early relapsing-remitting MS. Working memory is defined as the active maintenance of information in the face of ongoing processing (Conway et al., 2005). Along with processing speed, working memory is one of the most frequently documented areas of cognitive difficulty in MS (Lengenfelder et al., 2006). Working memory was investigated as a potential mediator in the present study because, similar to processing speed, working memory 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, it seems possible that the working memory deficits associated with MS could yield difficulties in other cognitive abilities. Because there is evidence to suggest that central executive dysfunction is the primary working memory impairment in MS (Arnett et al., 1999; D'Esposito et al., 1996; Diamond, DeLuca, Kim, & Kelly, 1997; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003; Parmenter, Shucard, & Schucard, 2007), measures that primarily assess this component of the working memory system were used in the present research.

Because the present study is concerned with the mediational hypotheses of whether processing speed and working memory are a mechanism by which MS diminishes other cognitive functions, the structural equation models include

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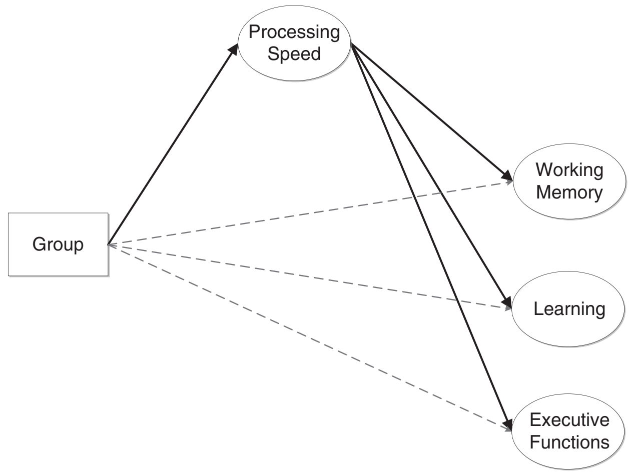

Fig. 1. Structural model tested to evaluate the Original Relative Consequence Model of cognition in multiple sclerosis. The solid lines represent the relations hypothesized to be significant and the dashed lines represent the relations hypothesized to be nonsignificant.

an independent variable representing presence or absence of MS (group), a mediator variable representing processing speed or working memory, and dependent variables representing other cognitive functions frequently impaired in MS (learning, executive functioning). The evaluation of relations between each of processing speed and working memory and the other cognitive functions for the MS patients alone is not sufficient because significant findings would be expected for everyone, regardless of neurological status, and would not inform us if these relations are responsible for the diminished abilities of MS patients. Thus, direct effects of the presence of MS on the potential mediators (processing speed, working memory) and the other cognitive functions were estimated as well as indirect effects of the presence of MS on the other cognitive functions *via* the potential mediators. This pattern is shown in Figure 1 for the Original Relative Consequence Model, with processing speed as the mediator,

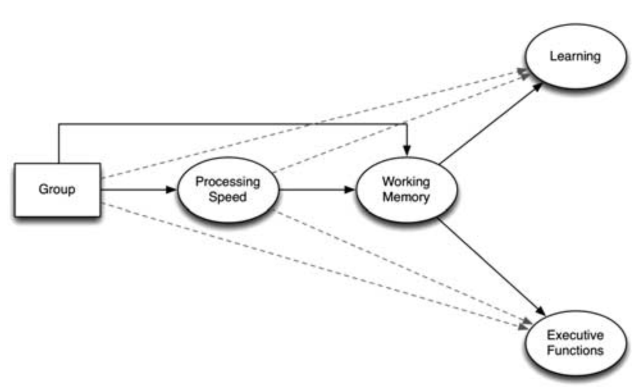

Fig. 2. Structural model tested to evaluate the Expanded Relative Consequence Model of cognition in multiple sclerosis. The solid lines represent the relations hypothesized to be significant and the dashed lines represent the relations hypothesized to be nonsignificant.

and in Figure 2 for the Expanded Relative Consequence Model, with working memory as a mediator.

METHODS

Participants

Seventy adults (57 females, 13 males) with relapsing-remitting MS (McDonald, Compston, & Edan, 2001) and disease duration ≤ 10 years were recruited from regular visits to the MS Clinic of the Ottawa Hospital. Individuals with a history of neurologic disease or injury other than MS, drug or alcohol abuse, or psychiatric disorders other than depression were excluded from participating in the study. Fifty-three MS participants were receiving disease-modifying therapy at the time of testing. The sample was characterized by mild physical disability (Kurtzke, 1983), on average (Table 1).

Seventy-two control volunteers (59 females, 13 males) meeting the same exclusion criteria were recruited through advertisements. Participants were compensated for parking expenses and control volunteers recruited through university classes received course credit for participating in the study. All participants provided informed consent following procedures approved by the Ottawa Hospital and Carleton University Research Ethics Boards.

MATERIALS

Information Processing Speed

Computerized Test of Information Processing (CTIP; Tombaugh & Rees, 2008)

The CTIP includes a: (1) Simple Reaction Time task where participants are asked to press the space bar as soon as a single “X” appears in the center of the screen, (2) Choice Reaction Time task where participants are presented with either the word “DUCK” or “KITE” on each trial and are asked to press the right key (“?”) or the left key (“Z”), respectively, and (3) Semantic Search Reaction Time task where participants are asked to decide if a word belongs to a semantic category. On each trial the name of one of four categories (weapon, furniture, bird, or fruit) is presented at random on the screen for 2.5, 3.0, 3.5, or 4.0 s. The category name remains on the screen while another word appears below 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 it does not. Each task includes 10 practice trials and 30 test trials.

Working Memory

Reading span

The task was based on recommendations of Conway et al. (2005) and stimuli from Engle (2005). The background task

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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
Years of disease duration	–	–	4.37	3.02		
Expanded Disability Status Scale	–	–	1.83	1.18		

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

requires participants to read aloud a sentence presented on a computer screen and verify whether the statement makes sense 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 are administered before the test blocks. The total number of letters recalled in the correct serial position is summed across blocks and recorded. Reading span tasks are a widely used measure of working memory capacity in the field of cognitive psychology and have been proven to be reliable and valid (See Conway et al., 2005 for a review).

Letter-number sequencing subtest from the Wechsler Memory Scale-III (Wechsler, 1997)

Increasingly longer sequences of intermixed letters and numbers ranging in length from two to eight stimuli are presented verbally. Participants are 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 (Schmidt & Tombaugh, 1995)

On each of five learning trials, participants are asked to recall a list of 15 words. Each word belongs to a different semantic category. After the first trial, 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 then a cued recall trial is administered for the missed words (e.g., "Which word was a type of color?"). Correct free recall responses are summed across trials to form the total Free Recall score. Correct cued recall responses are summed across trials and added to the Free Recall score to form the Free Recall + Cued Recall score. The Free Recall scores were analyzed in the present study.

Immediate recall from the Brief Visuospatial Memory Test-Revised (Benedict, 1997)

On each of three learning trials, participants are presented with a matrix of six simple geometric figures for 10 s. Participants are then asked to draw the figures as accurately as possible and in the same location as they remember seeing them. Between zero to two points is allotted for each figure based on the accuracy and placement of the drawing. Points are summed across trials to form a total learning score.

Logical Memory-I subtest from the Wechsler Memory Scale-III (Wechsler, 1997)

Two short stories are presented verbally; each is composed of 25 units or ideas and the second story is presented twice. After each presentation, examinees are immediately asked to recall as many details as they can. One point is awarded for each idea that is correctly recalled and points are summed across trials.

Executive Functions

Sorting subtest from the Delis-Kaplin Executive Functions Systems (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 was recorded and summed across the two card sets.

Phonemic verbal fluency from the Controlled Oral Word Association Test (Benton & Hamsher, 1976)

Examinees are asked to say as many words as possible beginning with "F," then "A," and finally "S." A 60-s interval is used for each letter and the number of correct responses is summed across the three trials.

Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977)

A modified version of the test allowing computer administration was used. Participants are presented with a series of 61 single digit numbers auditorally and 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 and the program tallies the number of correct responses occurring within the 3-s interstimulus interval. Because of well-known practice effects associated with the PASAT (Tombaugh, 2006), a run-in procedure recommended in the Multiple Sclerosis Functional Composite manual was used (Cutter et al., 1999).

Symbol Digit Modalities Test (Smith, 1991)

At the top of the 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 number of correct responses produced within 90 s is recorded.

Data Analysis

The data were evaluated for violations of statistical assumptions using generally accepted methods and any violations that were identified were corrected accordingly. Group comparisons were made using independent samples *t* tests for the demographic and observed cognitive variables and using a χ^2 test for sex. Structural equation modeling analyses were conducted using Amos 18.0 (Arbuckle, 2009) and maximum likelihood estimation was used to estimate all parameters. Because the structural equation models aim to assess relations among latent factors, it is critical that the measurement of each latent construct is psychometrically sound. Thus, an important preliminary step was to first evaluate the validity of the measurement model. Accordingly, a confirmatory factor analysis was performed assessing the relations between the observed variables and the latent factors. Following evaluation of the measurement model, the hypothesized structural models were analyzed. Several fit indices were used to evaluate the models [χ^2 test statistic, comparative fit index (CFI), root mean square error of approximation (RMSEA)]. Bias-corrected bootstrap confidence intervals were used to estimate 95% confidence intervals for all structural model parameters. Tests of significance were based on unstandardized estimates; however, standardized coefficients are also presented and discussed to describe the results of the structural equation model fully. If processing speed or working memory serve as mediators of other cognitive deficits in MS, the indirect effects of group membership on the dependent cognitive factors will be significant.

RESULTS

Characteristics of the Groups

The proportion of females and males was similar between the groups, χ^2 (1, $N = 142$) = .006, $p = .937$. The groups did not differ on age, education, or estimated intelligence although the MS participants exhibited more symptoms of depression and fatigue (Table 1). Accordingly, depression and fatigue were accounted for by adding these variables to the final structural models used to examine the relations among group membership and the cognitive factors.

Descriptive statistics for the observed cognitive variables are presented in Table 2. MS patients responded more slowly than controls on the processing speed tasks, although group differences were not significant for the choice and semantic search tasks. There were no significant differences between the groups on the executive functioning tests. Thus, the MS patients exhibited deficient working memory and learning whereas processing speed and executive functioning were unimpaired.

MS patients made fewer correct responses than controls on the PASAT and SDMT, although group differences were only significant for the PASAT (Table 2). When the commonly used criterion of a score more than −1.5 *SD*s below the mean of the control group was applied, 21.4% of patients were impaired on the PASAT and 12.9% were impaired on the SDMT.

Structural Equation Modeling

Measurement model

Figure 3 illustrates the measurement model, specifying the relations between the observed variables[1] and the hypothesized latent factors. The model fit the data well, $\chi^2(29) = 37.83$, $p = .13$; CFI = .97; RMSEA = .046, 90% CI = .000–.084. All parameter estimates were significant at $p < .05$, except for the covariance between processing speed and executive functioning and between learning and executive functioning ($p = .076$, .098, respectively). The standardized residuals and modification indices did not identify any areas of misspecification in the model requiring adjustment. Figure 3 includes the standardized coefficients; all loadings were significant and, furthermore, the majority of loadings were high suggesting convergent validity.

Original Relative Consequence Model

Figure 1 illustrates the structural model used to test the hypothesis that processing speed functions as a mediator between the effects of MS and other cognitive functions.

[1] See Appendix A for correlations among the observed cognitive variables.

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Table 2. Comparisons between the groups on the observed variables

	Group					
	Control (N=72)		MS (N=70)			
	M	SD	M	SD	t(140)	Cohen's d
Processing Speed (ms)						
CTIP Simple RT	288	41	303	46	−2.17*	−.37
CTIP Choice RT	524	99	545	106	−1.18	−.20
CTIP Semantic Search RT	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						
LAMB 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
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. *$p < .05$; **$p < .01$; ***$p < .001$. The significant result for Simple RT was not observed with depression and fatigue accounted for using an analysis of covariance ($p = .085$). All other significant results remained.
CTIP = Computerized Test of Information Processing; LAMB = Learning and Memory Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; PASAT = Paced Auditory Serial Addition Task.

Because it seemed logical to assume the individual cognitive functions would be related, correlated disturbance terms for the factors without direct effects on one another were also included in the structural models. Four path estimates did not meet the criterion for significance: the direct effects of group on processing speed and executive functioning, the direct effect of processing speed on executive functioning, and the covariance between the disturbance terms associated with learning and executive functioning. Thus, these paths were removed from the final model.[2] The final model fit the data well, $\chi^2(38) = 52.26$, $p = .062$; CFI = .96; RMSEA = .052, 90% CI = .000–.083. The final model including standardized coefficients is illustrated in Figure 4. Table 3 presents the estimated coefficients, standard errors, and confidence intervals for the effects included in the final model. In sum, the hypothesis that processing speed is a mediator of the MS-related effects on other cognitive functions in early relapsing-remitting MS was not supported because of the absence of a significant direct effect of group membership on processing speed. The relations were unaffected in an additional analysis that accounted for depression and fatigue.

Expanded Relative Consequence Model

Figure 2 illustrates the structural model used to determine if working memory mediates the deficits that MS patients show in other cognitive functions. With working memory assigned as a mediating factor, six path estimates did not meet the criterion for significance: the three direct effects of group on the cognitive factors other than working memory, the two direct effects of processing speed on the cognitive factors aside from working memory, and the covariance between disturbance terms for learning and executive functioning. These paths were removed from the final model except for the covariance between the disturbance terms of the learning and executive functioning factors because this path did approach significance ($p = .087$) and removing it actually resulted in slightly poorer fit. The final model fit the data well, $\chi^2(40) = 53.67$, $p = .073$; CFI = .96; RMSEA = .049, 90% CI = .000–.081. The final model including standardized coefficients is illustrated in Figure 5. Table 4 presents the estimated coefficients, standard errors, and confidence intervals for the effects included in the final model.[3] In sum, the findings support the hypothesis that working memory plays a mediating or intervening role in the MS-related effects on

[2] The nonsignificant 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 was removed first. Following this adjustment, the direct effect of processing speed on executive functioning now met the criterion for significance. However, the other nonsignificant parameter estimates still failed to reach significance and, thus, they were removed from the model as well.

[3] The relations between processing speed and other cognitive functions were also evaluated for the MS sample alone by conducting regression analyses on factor scores representing the latent factors from the structural equation models. In terms of the significance of the effects, the results obtained with the MS sample only did not deviate from the results presented for either of the structural equation models that included data from both MS patients and controls.

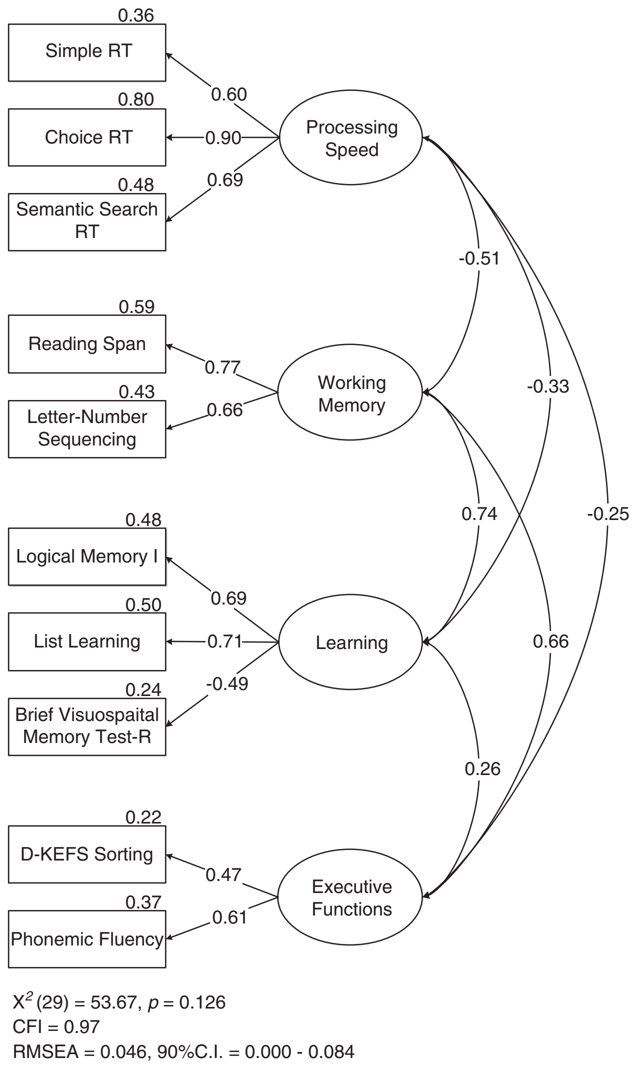

Fig. 3. Measurement model showing standardized solution. The numbers above the single-headed arrows correspond to standardized regression coefficients. The numbers above the observed variables correspond to squared multiple correlations. The numbers above the double-headed arrows correspond to correlations. Error terms are not shown. All path estimates were significant except for the covariance between processing speed and executive functioning and between learning and executive functioning ($p = .076$, $.098$, respectively). RT = reaction time; D-KEFS = Delis-Kaplin Executive Functions Systems.

cognitive functioning in early relapsing-remitting MS. The relations were unaffected in an additional analysis that accounted for depression and fatigue.

DISCUSSION

The primary goal of the study was to test two models of the relation between MS and cognitive functioning for individuals with early relapsing-remitting MS. The results of the Original Relative Consequence Model indicated that group membership did not predict processing speed in the present

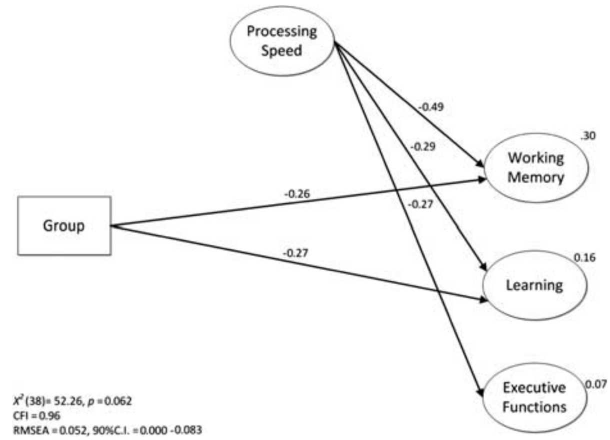

Fig. 4. The final Original Relative Consequence Model including standardized coefficients. The numbers above the arrows correspond to standardized regression coefficients. The numbers to the right of the dependent factors correspond to squared multiple correlations. Error terms and associated correlations are not shown. All path estimates are significant; nonsignificant paths have been removed.

sample, and thus, processing speed could not play any mediating role in the MS-related effects on other cognitive functions. In contrast, group membership did predict working memory and learning such that the presence of MS was associated with poorer ability. Furthermore, a role for working memory as a mediating or intervening factor for cognitive functioning in early relapsing-remitting MS was supported by the results of the Expanded Relative Consequence Model. Through reduced working memory ability, MS was associated with worse learning and executive functioning abilities. In contrast to the results of the Original Relative Consequence structural model, the direct effect of group on learning was not significant when working memory was assigned as a mediator. This finding is strong evidence for the mediating role of working memory in the relation between MS and learning.[4] Because a direct effect of group membership on executive functioning was never observed, the significant indirect path between group and executive functioning indicates that working memory functions as an intervening variable. Specifically, the deleterious effect of MS on working memory is partially transferred to executive functioning but it was not sufficient to produce a significant between group difference (Hayes, 2009).

In contrast to numerous other studies (e.g., Archibald & Fisk, 2000; Demaree, DeLuca, Guadino, & Diamond, 1999; Denney, Lynch, Parmenter, & Horne, 2004; Lengenfelder et al., 2003, 2006), the participants did not experience significant cognitive slowing. Processing speed may be more impaired in individuals with more severe MS or longer

[4] Although an alternative model with learning assigned as the mediator and working memory as a dependent factor showed a significant mediational relation, adequate model fit was not achieved and the original model accounted for more variance in the endogenous factors overall. Furthermore, specification of the original model is supported by theoretical rationale, whereas the alternative model is not.

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Table 3. Path coefficients and confidence intervals for the final Original Relative Consequence Structural Model

	Predictor variables							
	Group				Processing speed			
	B	*SE*	95% CI	β	*B*	*SE*	95% CI	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, −0.66	−.27

Note. B = unstandardized coefficient; *SE* = standard error; 95% CI, 95% confidence interval; β, standardized coefficient; —, nonsignificant and removed from final model.

disease duration. Patients with relapsing-remitting MS exhibit milder processing speed deficits than those with other forms of the disease (Benedict et al., 2006; De Sonneville et al., 2002; Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006; Potagas, et al., 2008), and short disease duration is associated with more subtle cognitive deficits as well (Deloire et al., 2005). Other studies have also used different measures of processing speed that are more likely to be confounded with other cognitive abilities, thereby increasing the likelihood of finding significant group differences. Although our chosen processing speed tasks may have decreased the likelihood of observing group differences in comparison to more complex processing speed measures (Chiaravalotti et al., 2003; Parmenter et al., 2007), this approach helps to avoid the mistake of attributing significant findings resulting from confounds of higher-level cognitive abilities to processing speed. Thus, the absence of impaired processing speed in the present sample may reflect a combination of: (1) a homogeneous sample of patients with relapsing-remitting MS and short disease duration, and (2) use of processing speed measures that are relatively less confounded by other cognitive abilities. Given the absence of impaired processing speed in the present sample, the results should not be generalized to MS patients who do experience substantial cognitive slowing. For such individuals, it is possible that speed may contribute to deficits in other cognitive functions. Consistent with previous research (Fry & Hale, 1996; Kail, 2006), the results of the Original Relative Consequence Model showed that processing speed was a significant predictor of working memory and learning for all participants regardless of neurological status. Therefore, it seems likely that cognitive slowing would impede working memory and learning abilities for those MS patients with impaired processing speed.

Although the reaction time tasks were considered to be relatively less confounded than other measures that have been used, there is no such thing as a pure measure of processing speed. The correlations of the reaction time tasks with some of the other types of variables (Appendix A) may have arisen because of the influence of additional cognitive functions. Although the correlations may also reflect that processing speed is a general ability that influences performance on many different types of tasks (Salthouse & Madden, 2008). Regardless, although some relations with other types of variables were observed, the reaction time tests were more strongly correlated with one another. Thus, the latent processing speed factor identified in the structural equation models will predominantly represent the common processing

Table 4. Path coefficients and confidence intervals for the final Expanded Relative Consequence Structural Model

	Predictor variables											
	Group				Processing Speed				Working memory			
	B	*SE*	95% CI	β	B	*SE*	95% CI	β	B	*SE*	95% CI	β
Learning												
Direct effect	—	—	—	—	—	—	—	—	2.41	.49	1.62, 3.57	.74
Indirect effect	−2.36	.95	−4.62, −.72	−.19	−28.40	10.76	−56.57, −14.41	−.33				
Executive Functioning												
Direct effect	—	—	—	—	—	—	—	—	2.09	.57	1.03, 3.32	.62
Indirect effect	−2.04	.81	−4.31, −.83	−.16	−24.54	10.22	−53.33, −10.06	−.28				
Working Memory												
Direct effect	−.98	.35	−1.80, −.33	−.26	−11.77	4.09	−22.88, −6.16	−.44				

Note. B, unstandardized coefficient; SE, standard error; 95% CI, 95% confidence interval; β, standardized coefficient; —, nonsignificant and removed from final model.

speed variance among the reaction time measures while the influence of other cognitive abilities will be minimized. The results of the measurement model are consistent with this interpretation because a factor identified by the reaction time tasks emerged that was independent and differentiable from the other cognitive factors and it was not necessary to allow any of the reaction time tasks to cross-load on the other factors.[5]

The PASAT and SDMT were also administered in the present study and the proportion of patients identified as impaired on these two measures is similar to other samples of patients with early relapsing-remitting MS (Glanz et al., 2007; Portaccio et al., 2006). Group comparisons revealed that the MS patients performed worse than controls on the PASAT whereas the groups were comparable on the SDMT. Thus, tests that are termed processing speed measures in the neuropsychological literature may form a continuum according to the extent that performance draws on multiple cognitive functions, with the CTIP existing toward one end, the PASAT at the other, and the SDMT falling somewhere in between. In support of this notion, there is evidence that the PASAT requires greater working memory capacity than the SDMT (Forn et al., 2011). This may explain why the MS patients in the present study performed worse than controls on the PASAT but were comparable on the SDMT. Although the multifactorial nature of tasks like the PASAT and SDMT contributes to their sensitivity to general cognitive dysfunction and to their utility as screening measures, any attempt to attribute performance to a single cognitive process, such as speed of information processing, is unwarranted.

Although working memory impairment has been acknowledged as a fundamental cognitive deficit for patients at later stages of the disease course, there are reports that only processing speed is impaired in early stages (Archibald & Fisk, 2000; DeLuca et al., 2004). However, our results are consistent with other studies reporting reduced working memory ability in patients with relapsing-remitting MS (Gmeindl & Courtney, 2012; Parmenter et al., 2007). Working memory demands draw upon a distributed network of brain regions (Baddeley, 2003; Wager & Smith, 2003; Woodward et al., 2006). Thus, working memory ability will be related to both the integrity of the cells comprising the relevant brain regions as well as the connections that allow the regions to function together as a network. Similar to processing speed, working memory performance in MS has been associated with magnetic resonance imaging (MRI) correlates of white and gray matter damage (Covey, Zivadinov, Shucard, & Shucard, 2011; Foong et al., 1997;

[5] In contrast, when we explored including the SDMT, the reportedly less confounded variable of the two multifactorial measures excluded from the structural equation models, on the Processing Speed factor, adequate fit for the measurement model could not be obtained without allowing it to cross-load on another cognitive factor. This supports our claim that measures like the SDMT are more strongly influenced by cognitive functions other than processing speed than the reaction time tasks. Furthermore, the results of the Original and Expanded Relative Consequence structural models did not change with the SDMT included, supporting the reliability of the results obtained when only the reaction time measures were used to represent processing speed.

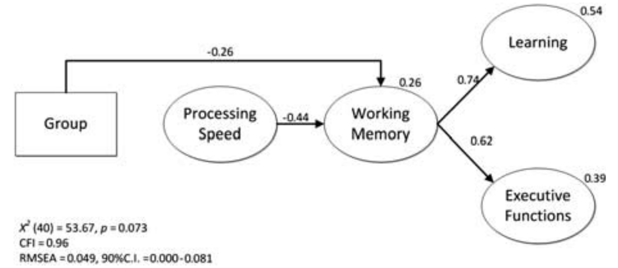

Fig. 5. The final expanded Relative Consequence Model including standardized coefficients. The numbers above the arrows correspond to standardized regression coefficients. The numbers to the right of the dependent factors correspond to squared multiple correlations. Error terms and associated correlations are not shown. All path estimates are significant; nonsignificant paths have been removed.

Sepulcre et al., 2009). Such pathology is present even from the earliest stages of the disease (Audoin et al., 2007, 2010; Chard et al., 2004; De Stefano et al., 2003; Riccitelli et al., 2012). Therefore, it is plausible that working memory deficits can exist for individuals with early relapsing-remitting MS.

In conclusion, the results of the present study suggest that the previously held perception of the pattern and sequence of cognitive deficits in MS may be incorrect. Clinicians and researchers need to consider the possibility that working memory may be impaired in MS and may contribute to dysfunctional cognition early on. Furthermore, clinical and research assessments should include valid measures of working memory ability for all patients. Although the focus on a relatively homogeneous group of individuals with relapsing-remitting MS is a strength of the present study, the homogeneity of the sample also means that the results should not be generalized to all stages and subtypes of MS. Instead, researchers should examine the relations that exist at other disease stages. For patients with more severe forms of MS, it is expected that processing speed will be significantly slowed and that the disease will affect working memory processes in two ways, first, indirectly by slowing cognitive processing and second, directly by affecting the neurological substrates of the working memory system (i.e., Figure 2).

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APPENDIX A

Table A. 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. LAMB 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. *$p < .05$; **$p < .01$; ***$p < .001$. For those variables requiring transformation, the included correlations pertain to the transformed versions. Because a reflect and square root transformation was applied to the BVMT-R, 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.
RT = reaction time; LAMB = Learning and Memory Battery; BVMT-R = Brief Visuospatial Memory Test—Revised; D-KEFS = Delis-Kaplin Executive Functions Systems.

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