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Processing Speed versus Working Memory: Contributions to an Information Processing Task in Multiple Sclerosis

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Abstract

Individuals with Multiple Sclerosis (MS) often experience cognitive impairments in information processing. However, the relative contributions of processing speed abilities and working memory abilities to information processing tasks are not yet fully understood. The current study examined the extent to which processing speed and/or working memory abilities contributed to an information processing task, the Keeping Track Task (KTT). Forty-nine individuals with MS were given tests to assess processing speed and working memory, as well as the KTT. Regression analyses indicated that, in the MS group, processing speed abilities accounted for the majority of the explained variance in KTT performance. The findings suggest that processing speed plays a significant role on KTT performance in MS. Implications for cognitive rehabilitation treatments aimed at improving processing speed abilities in MS are discussed.

Keywords

Processing Speed; Working Memory; Multiple Sclerosis; Keeping Track Task; Cognitive Rehabilitation

Introduction

Multiple Sclerosis (MS) is one of the most common neurologic disorders of young- and middle-aged adults and is characterized by inflammatory demyelination of axons in the central nervous system, as well as axonal degeneration (Bjartmar et al, 2003). Although MS has historically been considered a disease of motor functioning, up to 65% of individuals with MS experience some level of cognitive impairment (Chiaravalloti and DeLuca, 2008).

Over the last decade, overwhelming evidence has suggested that the most fundamental cognitive deficit experienced by individuals with MS is diminished information processing ability (Bergendal et al., 2007; Chiaravalloti and DeLuca, 2008; Genova et al., 2010). Specifically, two components of information processing ability have been the focus of recent examinations in MS: working memory (WM) and processing speed (PS) (e.g., Archibald and Fisk, 2000; Denney et al., 2008; Demaree et al, 1999; Forn et al., 2008). Although impairments have been observed in both WM and PS, there has been some controversy regarding the interaction between these two deficits, and the relative contribution of each to impaired processing ability in MS (e.g., DeLuca et al., 2004; Parmenter et al., 2007).

WM is defined as the ability to maintain information while simultaneously processing and manipulating such information (Baddeley, 1992; Baddeley and Hitch, 1994). WM impairments in MS have been well established in individuals with MS (Diamond et al., 1997; Grigsby et al., 1994a, 1994b; Lengenfelder et al., 2003). Impairments in both the slave systems, required for the maintenance of information in WM, (Litvan et al., 1988; Rao et al., 1993) and the central executive system, required for the manipulation of information in WM (D'Esposito et al., 1996) have been reported in individuals with MS.

Although WM impairments in MS have been well established, it is unclear whether the impairments evidenced are purely due to deficits in WM alone or if they are confounded by PS deficits (c.f. DeLuca et al., 2004). Most studies designed to examine WM in MS have been contaminated by the “speed versus accuracy confound,” which states that as an individual is asked to process information more quickly, accuracy of performance generally decreases. This confound has been studied extensively in aging. For example, Salthouse has demonstrated that the majority of the variance in episodic memory impairment in aging can be attributed to PS deficits (Salthouse, 1996).

Recent studies examining the “speed versus accuracy confound” in MS suggests that PS contributes more to deficient information processing than WM deficits (DeLuca et al., 2004; Kalmar et al., 2004; Kalmar et al., 2008; Lengenfelder et al., 2006). For instance, it has been hypothesized that individuals with MS may not have WM impairments; rather, PS impairments may lead to increased errors on WM tasks (DeLuca, et al., 2004). There is some support for the hypothesis that individuals with MS, when given adequate time, perform at the same accuracy level of healthy adults. Two previous studies (Demaree et al., 1999; Lengenfelder et al., 2006) utilizing different tasks, (the PASAT and the Visual Threshold Serial Addition Test, respectively), found that after allowing for the adjustment of time given to MS and HC subjects to complete these tasks at a 50% accuracy rate, individuals with MS were able to perform these tasks as accurately as healthy individuals. Other studies have found that as information processing time is increased via the interstimulus interval, WM performance improves in individuals with MS (DeLuca et al., 1994; Diamond et al., 1997). Taken together, these studies suggest that contrary to what has been suggested previously (D'Esposito et al., 1996; Grigsby et al., 1994a, 1994b; Litvan et al., 1988; Rao et al., 1993), the primary information processing deficit in individuals with MS may be PS and not WM accuracy. Individuals with MS may require more time to process information before they can utilize their WM systems.

The goal of the current study was to examine whether PS or WM accounts for more of the variance during the performance of an information processing task. In the past, multiple neuropsychological measures have been used to assess information processing abilities in MS. Unfortunately, these measures may not have adequately taxed the WM system. Typically, measures alter WM “load” in order to modulate task difficulty. However, the term “load” is composed of two distinct functions in WM as proposed by Salthouse and Mitchell, (1989): structural load and operational load. *Structural load* refers to the number of informational components that must be maintained during task performance, such as numbers or letters. *Operational load* refers to the number of operations to be processed, such as addition or subtraction, while previously performed operations and their products are maintained in the WM system. Typically, information processing measures allow for the alteration of “structural load,” while “operational load” is rarely altered. Thus, the relative impact of increases in structural vs. operational load on WM performance remains undetermined. For this reason, we have chosen a task which alters both structural and operational load, the Keeping Track Task (KTT).

The KTT is a task which has been used previously in studies of cognitive dysfunction in MS, and it is reported to be sensitive to information processing impairments in MS (Archibald and Fisk, 2000; Archibald et al., 2004). However, it is unclear whether performance deficits in the KTT are related to PS or WM. This question is addressed in the current study. Based on previous research in our lab which indicates that PS impairments underlie WM impairments, it was hypothesized that PS abilities would account for the majority of the variance in KTT performance. Further, it was predicted that PS would make a significant contribution to KTT performance beyond the portion of variance already explained by WM.

Methods

Participants

This work is part of a larger project some of which has been published elsewhere (Leavitt et al., *in press*). The study included 49 individuals between the ages of 18 and 65, with clinically definite MS, determined by the criteria provided by Poser et al. (1983), as well as the McDonald et al. (2001) diagnostic criteria. The majority of the subjects (36/49) were diagnosed with relapsing-remitting MS, while the rest had a diagnosis of a progressive subtype (12/49). One subject’s MS subtype was undetermined. The average time since diagnosis was 9.8 years (SD: 7.3). All subjects were recruited from clinics at UMDNJ, Multiple Sclerosis Comprehensive Care Center at Holy Name Medical Center, Teaneck, New Jersey and the community.

Initially subjects were screened for cognitive impairment using the Cognitive Capacity Screening Exam (CCSE) (Jacobs et al., 1977), a measure of global cognitive functioning. Exclusion criteria included a score of below a 20 on the CCSE, as a score below 20 is indicative a global cognitive impairment. Subjects with a history of head injury, stroke, seizures, significant psychiatric disturbance and drug abuse were also excluded. Substance abuse and psychiatric history was obtained using the Diagnostic Interview Schedule (DIS). All subjects were free from exacerbations and treatments involving steroid/benzodiazepine and/or neuroleptics for at least one month prior to testing. Potential subjects were excluded if their vision was significantly impaired by scotomas, diplopia, or nystagmus. No MS subjects were excluded based on any of these exclusionary criteria.

In addition, 30 healthy controls (HCs) (recruited from the community) were enrolled in the study, matched to the MS group in age, gender and years of education. Exclusionary criteria for the HCs included a history of moderate to severe head injury, stroke, seizures, significant

psychiatric disturbances and drug abuse. Again, the DIS was used to obtain drug abuse and psychiatric history for the HCs. No HC subjects were excluded based on these criteria.

There was no significant difference in terms of age between HCs ($M = 43.7$, $SD = 11.3$) and the MS group ($M = 46.0$, $SD = 9.4$), $t(77) = .952$, $p = .344$. Additionally, there was no difference in terms of education between HCs ($M = 14.6$, $SD = 2.1$) and MS group ($M = 14.7$, $SD = 2.0$), $t(77) = -.200$, $p = .842$. Although there were more women in the MS group (41/49) compared to the HCs (20/30), the gender proportions also did not differ significantly across the MS and HC groups ($\chi^2(1) = 3.059$, $p = .08$).

Procedures

Prior to enrollment, each subject was required to sign an informed consent form approved by the Institutional Review Boards of both Kessler Foundation Research Center and UMDNJ. All procedures were approved by and performed in compliance with the Institutional Review Boards of both Kessler Foundation Research Center and UMDNJ. In addition to the KTT, all subjects were administered a neuropsychological battery assessing a number of cognitive domains including mood, premorbid intelligence, WM, and PS. The neuropsychological battery included the following tests:

Measures

Keeping Track Task (KTT)—The KTT is a computerized test of information processing which allows difficulty levels to be altered by raising structural load, operational load, or both. The KTT uses a 2x2 matrix, and presents numbers (0 to 9) and operations (+ or −) in one quadrant of the matrix at a time (see Figure 1). Subjects are required to perform the operation as it appears in a randomly selected quadrant. Subjects are required to keep the running total for each quadrant throughout a trial. Subjects reported the final sum aloud whenever a question mark appears in a quadrant. All numbers are presented such that the outcome of the operation is a number between 1 and 9.

The difficulty level of the KTT may therefore be varied in two ways. First, the structural load, or the number of distinct informational units to be remembered, may be varied from 1 or 3. Second, the operational load, or the number of processing operations performed while still remembering the products of earlier operations, may also be varied from 1 or 3. This design results in four conditions: structural load of 1 and operational load of 1 (1:1), structural load of 1 and operational load of 3 (1:3), structural load of 3 and operational load of 1 (3:1), and structural load of 3 and operational load of 3 (3:3). Subjects were administered a total of twelve trials of 20 items each, three trials of each of the four “load” conditions. For this study we were interested in only the most difficult condition the 3:3 which places the greatest demands on WM by requiring subjects to remember 3 distinct informational units and perform 3 operations.

Beck Depression Inventory (BDI) (Beck, 1987)—This questionnaire (a measure of mood) consists of 21 multiple choice items which assess depression. Each item of the BDI is given a graded score of 0, 1, 2, or 3, which indicate the degree of severity of depressive symptomatology of the subject. The dependent variable is the total score.

Wide Range Achievement Test 3, Reading Subtest (WRAT-3) (Wilkinson, 1993)—This task has been used as a measure of IQ and premorbid intelligence (Ahles et al., 2003; Strauss et al., 2006) involves the oral reading of a 75-word list. The test is discontinued after ten pronunciation failures. The dependent variable is the number of correctly pronounced words.

Digit Span subtest of the WAIS-III (backward trial) (Wechsler, 1987)—This task of working memory consists of orally presented strings of random number sequences. In the digit span backward trial, the subject is instructed to repeat the string of digits presented by the examiner in the reverse order. The dependent variable is the number of the correct responses.

Symbol Digit Modalities Test (SDMT), – oral version (Smith, 1982)—The SDMT (a measure of processing speed) involves a set of 9 meaningless geometric designs, each of which corresponds to a different Arabic number (1–9). The subject is given the key at the top of the page, which shows which number corresponds to each symbol, as well as a series of symbols, presented randomly, with blank boxes underneath. The subject is required to say out loud what number corresponds to each symbol as the examiner records the response. The subject is told to do this as quickly as possible and continues to make the substitutions until 90 seconds have passed, when they are told to stop by the examiner. The dependent variable is the number of correct substitutions given in the 90-second period.

Letter Comparison (Salthouse et al., 1991)—This task of processing speed requires the subject to determine whether two strings of letters are identical or different. Strings of letters either 3, 6, or 9 characters in length are presented to the subject on a sheet of paper. The subject is required to give a response of “S” for same or “D” for different, and to make this decision quickly and accurately. Two trials of 21 items are presented. The dependent variable is the number of correctly identified items on each trial in a 30 second time span.

Pattern Comparison (Salthouse et al., 1991)—This task of processing speed requires the subject to determine whether two geometric line patterns are identical or different. Patterns are presented to the subject on a sheet of paper. The subject is required to give a response of “S” for same or “D” for different, and to make this decision quickly and accurately. Two trials of 30 items are presented. The dependent variable is the number of correctly identified items on each trial in a 30 second time span.

Data Analysis

Linear regression analyses were conducted to examine the relative contributions of PS and WM to performance on the KTT (Condition 3:3) in the MS sample. Two separate hierarchical linear regression models were conducted using demographics (premorbid intelligence as assessed by WRAT Reading, age and education), PS measures (SDMT, and a composite LC PC score, created by taking the average of the LC and PC scores) and WM measure (DS Backwards). In the first analysis, demographic variables were entered first, then PS variables were entered, followed by WM variables. In the second analysis, demographic variables were entered first, then WM variables were entered, followed by PS variables.

Results

Neuropsychological Performance

For the following tests, degrees of freedom were adjusted due to unequal variance: BDI, PC, and KTT 3:3. Adjusted degrees of freedom were calculated using Welch-Sattuerthwaite equation.

The BDI scores were classified in the following way: subjects scoring 13 and below classified as having “minimal to no” depression; subjects scoring between 14 and 19 were considered to have “mild” depression; subjects scoring between 20–28 were considered to be “moderately” depressed; and subjects scoring 29 and above were considered “severely”

depressed. Of the participants, 37/49 individuals with MS (75.5%) and 29/30 HCs (96.7%) were considered to have “minimal” depression. 8/49 individuals with MS (16.3%) and 1/30 HCs (3.3%) were considered to have “mild” depression and 4/49 individuals with MS (8.2%) were considered to be “moderate.” No HCs were classified as moderately depressed, and individuals from neither group were classified as severely depressed. Although, the MS group had significantly elevated scores on the BDI (Mean: 9.53, SD: 5.8) compared to HCs (Mean: 3.03, SD: 3.86), ($t(76.4) = 5.973$, $p < .001$), the overall mean BDI score was not indicative of significant depressive symptomatology in this sample. In terms of premorbid intelligence, there was no significant difference between the MS group (Mean: 48.92, SD: 5.41) and HCs (Mean: 50.7, SD: 3.5), ($t(77) = -1.786$, $p = .078$).

The MS group performed significantly worse on the SDMT (Mean: 50.78, SD: 11.9) compared to the HC group (Mean: 63.93, SD: 9.9), ($t(77) = -5.064$, $p < .001$). The MS group also performed worse across both trials of LC (Mean: 11.49, SD: 2.75) compared to HCs (Mean: 13.22, SD: 3.07), ($t(77) = -2.589$, $p = .012$) and both trials of PC (Mean: 16.90, SD: 4.66) compared to HCs (Mean: 20.85, SD: 3.50), ($t(73.7) = -4.28$, $p < .001$). Taken together, these results indicate that the MS group demonstrated significantly reduced PS performance compared to HCs.

Regarding WM, the MS group performed significantly worse on DS backward (Mean: 7.06, SD: 2.54) compared to HCs (Mean: 9.00, SD: 2.84), ($t(77) = -3.62$, $p = .002$), indicative of compromised WM relative to the HC group.

KTT performance

KTT performance of HC and MS groups were compared on the KTT trial 3:3. As expected, the MS group had a significantly lower number of correct responses on the KTT 3:3 (Mean: 33.5, SD: 9.74) compared to HCs (Mean: 40.07, SD: 4.31), ($t(71.5) = -4.104$, $p < .001$).

Relative Contribution of PS and WM to KTT Performance

Linear regression analyses were conducted on the MS group to examine the relative contributions of PS and WM to performance on the KTT (Condition 3:3) using the total correct in this condition.

First we examined the demographics (age, education, BDI, and WRAT). A linear regression was performed: the demographic variables were entered first in a stepwise fashion and the WRAT-3 Reading was the only variable to emerge accounting for 28.4% of the variance in KTT performance ($p < .001$). Since WRAT was the only demographic variable to emerge as significant, it was the only demographic variable entered in subsequent regression analyses. Additionally, since neither age nor education significantly differed between groups, we did not expect that they would have a significant effect on our PS and WM measures. Given that the gender effect was marginally significant, a re-analysis with gender as a predictor variable yielded a negligible change, leaving the WRAT to account for 25% with gender included (in contrast to 28.4% without gender included).

The results of the first regression analyses are illustrated in Figure 2. In the first analysis, PS variables were entered into the second block of the model and accounted for 19.0% of the variance ($p = .001$) in KTT 3:3 performance. WM variables were entered into the third block and did not make a significant contribution to this model, adding only an additional 3.8% to the variance ($p = .08$).

In order to further examine the amount of variance in KTT performance accounted for by WM vs. PS performance, we reversed the model. That is, the regression analysis was repeated, entering WM variables before PS variables. Again, WRAT was entered stepwise

into the first block and contributed significantly to the model (27.47%, $p < .001$). In this analyses, WM was entered into the model prior to PS, yet WM, only explained 6.3% of the variance in the KTT performance ($p = .042$). PS variables, entered third, accounted for 16.5% of the variance in KTT performance, a significant contribution ($p = .002$). See Figure 3.

Overall, the results of these analyses suggest that PS accounts for a major proportion of the explained variance in KTT performance (beyond the WRAT score), with WM making a much smaller contribution to this task.

Discussion

In the current study, we utilized a challenging information processing task, the KTT, to determine whether WM or PS makes a greater contribution to performance. It was found that both WM and PS did indeed make a contribution, but as hypothesized, a major proportion of the explained variance in the performance of the KTT was attributable to PS and not WM. Unlike studies performed previously which utilized tasks of WM which minimally challenged the central executive component of the WM system, we utilized a task of complex information processing, which allowed us to alter both structural and operational loads. The findings of the current study suggest that the KTT is sensitive to PS impairments in MS, and therefore may be useful in research focused on PS.

Our findings are consistent with existing investigations in MS which support the notion that PS impairment is the primary consequence in MS, underlying other cognitive impairments, such as WM (i.e. Lengenfelder et al., 2006), executive dysfunction (Drew et al., 2009), and acquisition deficits (DeLuca et al., 2004). Several models have been proposed to help explain the influence of PS on other cognitive domains, including the *Relative Consequence Model* which suggests that impairments in PS result in difficulties in other cognitive processes, such as WM (DeLuca et al., 2004). In other words, impaired PS decreases the ability to acquire new information and complete higher-level cognitive functions (Gaudino et al., 2001; Kail, 1998; Litvan et al., 1988). Additionally, Salthouse has described in detail how slowed processing can affect cognitive processing during task performance: large amounts of resources are dedicated to early task performance so that later on, there are fewer resources available to complete the task (1996). This model can be used to explain cognitive impairment affected by PS in aging, as well as MS.

Although the KTT was originally designed to assess WM, our findings indicate that PS accounted for the majority of the variance in KTT performance in our MS sample. It is therefore conceivable that many tasks thought to assess WM impairment in MS are more affected by PS impairments. This situation confounds the assessment of cognition in MS which could lead to misinterpretation of testing results. For example, the Paced Serial Addition Test (PASAT) is traditionally thought of as a measure of WM abilities (i.e. Parmenter et al., 2006). Impairments in PASAT performance are frequently documented in MS sample (i.e. Achiron et al., 2005). However, a recent study reported that between-group differences on the PASAT between healthy adults and individuals with MS were actually associated with PS scores, and not WM (Forn et al., 2008), even though the PASAT is widely referred to as a task of WM. Such a misattribution of findings to deficits in WM, rather than PS, has a significant impact on both our understanding of cognitive impairment in MS and our ability to appropriately identify potential treatments for cognitive impairments in MS. Thus, the clarification of the source of decrements in processing abilities in MS is essential to improving our ability to care for these individuals.

Given the growing evidence that deficits in PS lie at the source of the cognitive impairment in MS, it is essential for the research and clinical community to focus on means of improving PS in persons in MS. To date, little research has been done to test the effectiveness of cognitive rehabilitation techniques aimed at improving PS in persons with MS (O'Brien et al., 2008). The research that has been done thus far in MS shows improvement in information processing treatments, or treatments that address WM and PS combined, such as computer-based training programs. Such treatment protocols do not specifically address PS (Flavia et al., 2010; Vogt et al., 2009). No studies to our knowledge have focused on treating PS independently of other impairments in MS. Research in other populations however, has shown that one can effectively treat PS impairments through a behavioral intervention. For example, "Speed of Processing Training" has been shown to significantly improves PS abilities in samples of healthy older adults on objective tests of cognitive performance (Edwards et al., 2002; Edwards et al., 2005). In addition, these PS gains have been demonstrated to generalize to everyday life abilities in this population (Edwards et al., 2005). Importantly, cognitive impairments in MS are similar to those seen in aging in that PS impairments have a significant impact on higher-level cognitive functioning (Salthouse, 1996; Salthouse and Coon, 1993; Salthouse and Ferrer-Caja, 2003; Sliwinski and Buschke, 1997). Thus, techniques that have been shown to improve PS in aging are likely to have similar impact in persons with MS.

Given the influence of PS on cognition in MS, as demonstrated in this study, as well as others (DeLuca et al., 2004; Drew et al., 2009; Lengenfelder et al., 2006), this is an essential area of research to advance our ability to improve cognition and everyday life functioning in persons with MS. Until effective treatment for PS deficits in MS are identified, an immediate means of improving cognition in this sample is to provide individuals with MS more time to process information. This will serve to maximize cognitive functioning in other domains, such as learning of new information (Demaree et al., 1999). In fact, it has been demonstrated that the speed of presentation of verbal stimuli significantly impacts one's ability to recall information in persons with MS (Arnett, 2004). That is, slower presentation enabled subjects to recall greater amounts of information on a story learning task (Arnett, 2004). It can be concluded from this research that slowing the presentation of to-be-learned information could significantly improve learning and memory in rehabilitation settings.

The present study had several limitations. Our results indicate that PS abilities demonstrated a greater impact on KTT performance than WM abilities. However, these findings are directly affected by the tasks we used to assess WM and PS impairments. Working memory is a multi-faceted construct and it is therefore unclear whether utilizing a different measure of WM (i.e. letter-number sequencing, or one that challenges the central executive component) would have altered the findings in any way. It is difficult to find a "pure" measure of any cognitive domain, and it is thus possible that PS impacted performance on the WM variable we used as well. Thus replication of these results with different measures is necessary to draw definitive conclusions about the constructs assessed.

Additionally, there was a significant amount of variance in KTT performance that was unaccounted for in our model. It is unclear what other factors might have affected performance on the KTT, but many factors can be explored, including: fatigue, anxiety, depression, cognitive reserve, neuronal and white matter integrity and patterns of cerebral activation. Such variables are prime targets for inclusion in future investigations. For example, cognitive reserve has recently been shown to explain a great deal of variance in episodic memory performance (Sumowski et al., 2010) and cognitive efficiency (Sumowski et al., 2009) in MS. Similar findings may be expected with regard to KTT performance and may help explain the 50% of variance left unexplained in our model. In terms of neuroimaging, an fMRI investigation of PS impairments in MS was recently performed

(Genova et al., 2009) and it was reported that neural networks underlying PS performance in MS differed from HCs, and were correlated in part with lesion load. Investigations of PS using neuroimaging techniques such as fMRI will continue to help researchers understand the effects of disease on cerebral activation and behavior.

In summary, results of the current study demonstrated that although both WM and PS may contribute to performance on a complex information processing task, PS is the key impairment and accounts for more of the variance than WM. This finding has significance not only for future studies of cognitive impairment in MS, but also for the development of effective cognitive rehabilitation techniques for persons with MS.

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Number of Variables:	1	1	3	3
Number of Operations:	1	3	1	3
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	<input type="text" value="-4"/>	<input type="text" value="+6"/>	<input type="text" value="-7"/>	
	<input data-cs="2" data-kind="parent" type="text" value="???"/>	<input type="text" value="+2"/>		
		<input data-cs="2" data-kind="parent" type="text" value="???"/>		
			<input type="text" value="+3"/>	
			<input data-cs="2" data-kind="parent" type="text" value="???"/>	

Figure 1.

The Keeping Track Task is illustrated. The correct responses for the KTT are the following: condition 1:1 is 9, condition 1:3 is 5, condition 3:1 is 7, and condition 3:3 is 4. Condition 3:3, in which 3 operations and 3 variables are manipulated is illustrated in column 4.

Figure 2.
Processing Speed (PS) entered first into regression.

Figure 3.
Working Memory (WM) entered first into regression.