Variability in speed of information processing: A new measure of cognitive impairment in individuals with multiple sclerosis

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Abstract

Cognitive slowing has been firmly established as one of the few primary cognitive deficits associated with multiple sclerosis (MS). Numerous studies have documented impairments in speed of information processing for MS patients relative to healthy controls, but the present study was the first to investigate individual variability in speed of information processing in persons with MS. Thirty-nine patients with relapsing-remitting or secondary progressive MS and 32 healthy control participants completed a series of RT tests, the Stroop Test and the Rey Auditory Verbal Learning Test. MS patients performed more poorly than control participants across measures of speeded processing, responding more slowly and with greater trial-to-trial variability relative to healthy controls. The most robust group differences were observed on tests posing the greatest burden on rapid processing, with effect sizes for measures of individual variability on the most demanding tasks rivaling those of traditional measures of processing speed.

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Introduction

Slowing of cognitive processing in patients with multiple sclerosis (MS) has been consistently reported in the literature (Brassington & Marsh, 1998; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Denney, Lynch, Parmenter, & Horne, 2004; Hoffmann Tittgemeyer, & von Cramon, 2007; Kalmar, Bryant, Tulsky, & DeLuca, 2004; Kail, 1998; Legenfelder, Bryant, Diamond, Kalmar, Moor, & DeLuca, 2006; Schulz, Kopp, Kunkel, & Faiss, 2006), and many researchers now regard impairments in information processing speed as a fundamental cognitive deficit associated with MS (e.g., Archibald & Fisk, 2000; Bergendal, Fredrikson, & Almkvist, 2007; Bodling, Denney, & Lynch, 2008, 2009; de Sonneville et al., 2002; Demaree, DeLuca, Gaudino, & Diamond, 1999; DeLuca et al., 2004; Denney, Lynch, & Parmenter, 2008; Denney et al., 2004, Denney, Sworowski, & Lynch, 2005; Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Kail, 1998; Kalmar et al., 2004; Legenfelder et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991; Reicker, Tombaugh, Walker, & Freedman, 2007). Data clearly reveal that impairments in processing speed emerge early in the course of the disease (Archibald & Fisk, 2000; Achiron et al., 2005; Bergendal et al, 2007; Bodling et al., 2009; DeLuca et al, 2004; Grigsby et al, 1994; Santiago, Guardia, Casado, Carmona, & Arbizu, 2007; Schulz et al., 2006), predict future cognitive decline (Bergendal et al., 2007), and negatively impact performance in a variety of other cognitive and functional domains (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca et al., 2004; Demaree et al., 1999; Goverover, Genova, Hillary, & DeLuca, 2007; Henry & Beatty, 2006; Kail, 1998; Kalmar, Gaudino, Moore, Halper

& DeLuca, 2008; Kessler, Cohen, Lauer, & Kausch, 1992; Legenfelder et al., 2006; Litvan, Grafman, Vendrell, & Martinez, 1988).

Processing speed in MS patients has generally been assessed with neuropsychological tests such as the Stroop Color-Word Interference Test, the Paced Auditory Serial Addition Test (PASAT), the Symbol Digit Modalities Test (SDMT) and basic reaction time tests. Across studies MS patients give fewer responses per time interval and exhibit slower reaction times on these tests relative to healthy partcipants (e.g., Bergendal et al., 2007; Bodling et al., 2008, 2009; DeLuca et al., 1994; Denney et al., 2004, 2008; Kalmar et al., 2004; Kujala, Portin, Renvonsuo, & Ruutiainen, 1995; Litvan et al., 1988; Parmenter, Shucard, & Schucard, 2007; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Rao, St. Aubin-Faubert, & Leo, 1989; Santiago et al., 2007; Steiger, Denney, & Lynch, 2008; Vitkovitch, Bishop, Dancey, & Richards, 2002; Wishart & Sharpe, 1997). Despite data confirming the existence of cognitive slowing in MS patients, existing studies may not entirely characterize the deficit in information processing speed in this population.

Fewer responses per time interval and slower average reaction times both reflect impairments in overall speed or "level" of performance. To date, analyses of processing speed in MS have been confined to these overall scores; yet level of performance is only one element of the broader construct of information processing speed. Processing speed deficits may additionally be operationalized in terms of consistency or variability in response rate (Dixon, Garrett, Lentz, MacDonald, Strauss, & Hultsch, 2007; Hultsch, MacDonald, & Dixon, 2002; Hultsch, Strauss, Hunter, & MacDonald, 2008). Traditionally, fluctuations in performances on cognitive tests have been attributed to error or disregarded as "noise" in the data (Fjell, Ostby, & Walhovd, 2007). However, recent studies suggest that variability is a sensitive marker of

cognitive impairment and may contribute unique information concerning the nature and underlying causes of cognitive dysfunction (Fjell et al., 2007; Hultsch et al., 2008; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; MacDonald, Hultsch & Dixon, 2003; Ram, Rabbit, Stollery, & Nesselroade, 2005). Studies evaluating variability in cognitive functioning have become increasingly common in several literatures; yet this study is the first to extend investigations of individual variability to persons with MS.

Cognitive variability has been conceptualized in a number of ways, all of which capture differences either between or within individuals' performances on cognitive tests (Hultsch et al., 2002). Inconsistency is one distinct type of within-individual variability that is defined as measureable fluctuations in an individual's performance either across trials or across sessions of a single cognitive test (Hultsch et al., 2002). While fluctuations in both accuracy and latency of responding have been used to study inconsistency, these measures tend to be highly correlated (Hultsch et al., 2000), and the majority of investigations have focused on fluctuations in speed (MacDonald et al., 2003). Evaluations of inconsistency in speeded processing seem particularly relevant to studies of MS-related cognitive dysfunction because of the primacy of impairments in average speed of processing in this population, as well as because of the proposed link between inconsistency and neurological dysfunction and the potential utility of inconsistency as a screening measure for cognitive impairment (Bunce, Anstey, Christensen, Dear, Wen, & Sachdev, 2007; Hultsch et al., 2000, 2008; Lovden, Li, Shing, & Lindenberger, 2007).

Within-person variability measures, and specifically inconsistency, have been considered by many as behavioral markers of central nervous system functioning (Bunce et al., 2007; Bruhn & Parsons, 1977; Hultsch et al., 2000, 2008; Li & Lindenberger, 1999; MacDonald, Nyberg, & Backman, 2006). Individuals with dementia (Burton, Strauss, Hultsch, Moll & Hunter, 2006;

Dixon et al., 2007; Duchek, Balota, Tse, Holtzman, Fagan & Goate, 2009; Hultsch et al., 2000), Parkinson's disease (Burton et al., 2006; deFrias, Dixon, Fisher, & Camicioli, 2007), traumatic brain injury (Collins & Long, 1996; Hetherington, Stuss, & Finlayson, 1996; Stuss, Murphy, Binns, & Alexander, 2003) and epilepsy (Bruhn & Parsons, 1977) have all been found to perform more inconsistently on cognitive tests than healthy individuals. Additionally, patients with non-neurological illnesses such as arthritis do not show greater inconsistency than control participants, suggesting that inconsistency is not only *sensitive* to disease but is also *specific* to neurological dysfunction (Hultsch et al., 2000; Strauss, MacDonald, Hunter, Moll, & Hultsch, 2002).

Healthy older adults without evidence of pathology also perform more inconsistently across trials of cognitive tests relative to healthy younger adults (Anstey, 1999; Bunce et al., 2007; Bunce, MacDonald, & Hultsch, 2004; Deary & Der, 2005; Dixon et al., 2007; Ducheck et al., 2009; Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994; Hultsch et al., 2002; MacDonald et al., 2003, 2006). Both cross-sectional and longitudinal investigations confirm that healthy adults begin to show greater performance variability in mid-life (MacDonald et al., 2003) and that performance becomes increasingly inconsistent with advanced age (Dixon et al., 2007; Hultsch et al., 2002; MacDonald et al., 2003, 2006; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). This developmental trajectory closely parallels age-related changes in the central nervous system (e.g., decreases in white matter volume; Fjell et al., 2007; Hultsch et al. 2008) and may substantiate theories linking behavioral inconsistency with neuronal functioning.

Findings of increased inconsistency in healthy older adults are additionally noteworthy with respect to cognitive functioning in MS patients. MS researchers frequently liken MS-related cognitive impairment to age-related cognitive decline, particularly in terms of the

"primacy" of slowed processing in the overall profiles of cognitive dysfunction (e.g., Bodling et al., 2009; DeLuca et al., 2004; Denney et al., 2004; Kail, 1997, 1998; Kalmar et al., 2004; Reicker et al., 2007). Yet to date, these comparisons have been confined to measures of overall speed. Extending analyses of speeded processing in MS patients to include measures of inconsistency is a necessary step towards determining the extent of the similarities in speed of information processing between MS patients and older adults.

The exact neural underpinnings of cognitive inconsistency remain unclear, although many researchers have broadly referred to increased "neural noise" as the causal link (Dixon et al., 2007; Fjell et al., 2007). One theory attributes behavioral inconsistency to breakdown in neurotransmitter functioning, and more specifically to dysfunction in the modulation of dopamine (Li & Lindenberger, 1999). Others have implicated myelination of neurons as the causal connection between nervous system functioning and inconsistency; extensive myelination provides better isolation of the neuron, yielding more stable transmission of action potentials which is ultimately reflected by greater consistency of cognitive performance (Bunce et al., 2007; Fjell et al., 2007).

Preliminary support for this latter conceptualization is provided by a recent neuroimaging study. Bunce et al. (2007) reported on neuroimaging and neuropsychological data collected from a large sample of older adults ages 60 to 64. In this sample, the degree of white matter lesioning was significantly correlated with trial-to-trial variability in cognitive performance such that greater lesioning was associated with greater variability. Interestingly, lesioning was not correlated with average response time or with performance on any other cognitive test (e.g., verbal memory, word knowledge, etc.). The authors concluded that "neurobiological disturbance is characterized by more erratic responding that is captured by measures of within-person

variability, but not mean RT" (p.2013; Bunce et al., 2007). These findings are particularly intriguing in the context of MS which is characterized by a breakdown of white matter. If inconsistency measures continue to prove sensitive to this specific neuronal change, they may hold significant clinical utility in terms of evaluating the extent and progression of underlying pathology.

Findings from several behavioral studies corroborate Bunce's results by documenting the greater sensitivity of inconsistency (relative to other cognitive measures) in the detection of neurological dysfunction. For example, Dixon et al. (2007) evaluated overall level and variability of speeded performance in samples of older adults with varying degrees of cognitive impairment (i.e., not impaired, mild impairment, moderate impairment). Measures of mean level speed and inconsistency each differentiated between cognitive status groups; however, inconsistency tended to be a stronger predictor of cognitive status, accounting for additional unique variance, relative to mean level performance (Dixon et al., 2007). Similar data were reported in a study of individuals with traumatic brain injury (TBI). Mean level speed most accurately discriminated between persons with a history of TBI and healthy control participants. However, measures of inconsistency afforded greater sensitivity (relative to level of performance) in differentiating control group participants from "cognitively recovered" TBI patients, suggesting that measures of inconsistency were particularly sensitive to the more subtle cognitive effects of TBI (Collins & Long, 1996).

Additional behavioral studies have demonstrated that inconsistency may not only index current cognitive impairment, but may also predict future cognitive decline. For example, MacDonald et al. (2003) evaluated cognitive functioning longitudinally in a sample of healthy older adults, and reported that baseline inconsistency in reaction time significantly predicted six-

year change in cognitive performance. In fact, baseline inconsistency was associated with change in performance for each of the assessed cognitive domains (e.g., verbal memory, vocabulary, fluid reasoning, working memory; MacDonald et al., 2003). Lovden and colleagues (2007) replicated these findings using structural equation modeling to demonstrate that increased inconsistency in cognitive performance predicted future cognitive decline.

In sum, data compiled from patient samples and from healthy older adults validate the existence of increased inconsistency in individuals with compromised neurological functioning and suggest that measures of inconsistency may be particularly sensitive to current cognitive dysfunction and future cognitive decline. However, the present study was the first to extend evaluations of within-individual variability to the MS population. MS patients and healthy control participants completed a series of reaction time (RT) tests of graded complexity which yielded measures of average reaction time and trial-to-trial variability. Participants also completed an established measure of processing speed (i.e., the Stroop Test) to provide a comparison for the newly constructed RT tests, as well as a verbal memory task to permit analyses of this additional cognitive domain. It was hypothesized that MS patients would evidence impairments in both elements of speeded processing, achieving slower average reaction times and responding with greater inconsistency relative to control participants.

Methods

Participants

Forty-one individuals with clinically definite MS were recruited for this study. All patients were under the care of the same neurologist at the University of Kansas Medical Center (Sharon G. Lynch). Recruitment was limited to individuals between the ages of 30 to 60, those

with diagnoses of relapsing-remitting or secondary progressive MS, and those with a length of diagnosis of at least one year duration. Patients were excluded from participation based on the presence of any of the following: neurological disorder other than MS, history of drug or alcohol abuse, premorbid psychiatric disorder, severe visual impairment (including visual acuity greater than 20/50 or impaired color vision), or severe cognitive impairment that would interfere with ability to comprehend testing instructions. Two female participants met criteria for the study, but were excluded from the analyses due to difficulty completing tasks as instructed. The resulting MS sample consisted of 39 patients (35 females, 4 males).

Thirty-four control participants between the ages of 30 and 60, with no history of neurological illness were also recruited for the present study. Control participants were required to meet the inclusion criteria previously outlined for patients. Two control participants who completed the study were excluded from analyses; one had difficulty comprehending testing instructions, and another confessed history of neurological dysfunction after testing was complete. Thus, the final control sample consisted of 32 individuals (28 females, 4 males).

Measures

Simple Reaction Time Test (SRT): In this computerized RT test, a warning stimulus ("O") was presented in the center of the computer screen and was then replaced with a target stimulus ("+"). Participants were instructed to press a key as quickly as possible when the target appeared. The time interval between the warning and target stimuli varied throughout the test, with ten trials completed in random order at each of five interstimulus intervals (ISI = 500ms, 750ms, 1000ms, 1250ms, 1500ms). Ten practice trials were administered before proceeding to the 50-trial test. Response times for each of the 50 test trials were recorded.

Choice Reaction Time Test (CRT-2; CRT-4): Two versions of a computerized choice RT test were included in this study. In CRT-2, two warning stimuli ("O") appeared simultaneously on the screen, one located to the left and one to the right of center. In CRT-4, four warning stimuli ("O") appeared in a horizontal row centered on the screen. In each task, after a random delay interval (ISI = 500ms, 750ms, 1000ms, 1250ms, or 1500ms) one of the warning stimuli changed to a plus sign. Participants were instructed to respond as quickly as possible by pressing the designated button on a keyboard which corresponded to the location of the plus sign. For each test, participants completed 10 practice trials, and then proceeded to the 50-trial test. Accuracy and reaction time for each test trial were recorded.

One-Back Reaction Time Test (1-BRT): The basic format of this test was comparable to that of the CRT-4; four "O"'s appeared in a horizontal row centered on the screen, and after a randomly selected ISI, one "O" changed to a plus sign. However, on this test, participants were instructed to press the button on the keyboard corresponding to the location of the plus sign from the previous trial. Ten practice trials were administered first, followed by 51-test trials. Accuracy and reaction time of each response were recorded for 50-test trials (no response was given on the first trial).

Stroop Color-Word Interference Test: This test is a computerized version of the original Stroop test (Stroop, 1935) consisting of three trials. Trial 1 (word reading) required individuals to read color words (RED, BLUE, YELLOW, GREEN) presented singly and centrally on a computer screen. Trial 2 (color naming) required naming of colors (i.e., 'XXXX' presented in red, blue, yellow, or green ink) appearing singly and centrally on the computer screen. And Trial 3 (color-word naming) required participants to name the color of ink used to print one of four

words (RED, BLUE, YELLOW, GREEN). For each stimulus in Trial 3, the word and the color of its letters were incongruent (e.g., BLUE presented with red letters).

For each of the three trials, participants gave a verbal response and the examiner pushed a button on the keyboard to display the next stimulus. Participants were asked to respond to each stimulus as quickly as possible and to minimize errors. An 8-item practice session was completed prior to each full 60-second test. The total number of items completed in 60 seconds was recorded.

Rey Auditory Verbal Learning Test (RAVLT): This is a computerized version of the RAVLT (Schmidt, 1996) designed to assess verbal memory. In this test, participants were asked to listen to aurally presented words. Fifteen unrelated words were read aloud by the examiner a total of five times. After each presentation of the list, the participant was asked to repeat, in any order, as many words as he/she could recall. After the fifth trial, the examiner read a 15-item "distracter" word list, and participants repeated as many words as possible from this second list. A short-delay free recall trial directly followed, in which participants recalled as many words as possible from the first list. A recognition trial was completed after approximately 25 minutes in which participants viewed a total of 50 words (15 target words, 35 distracter words) presented singly and centrally on the computer screen. Participants indicated whether each word was included on the first list by pressing one of two buttons on the keyboard corresponding to yes or no; response times for recognition trials were recorded covertly, and participants were not given any instruction about the rate with which they should respond. A number of scores can be generated from this test. Those of primary interest in the present study were (a) the total number of words recalled on the five learning trials, (b) the number of words recalled after short-delay,

(c) the number of correct responses on recognition and (d) the latency of responses on each recognition trial.

The Expanded Disability Status Scale (EDSS; Kurtzke, 1983): The EDSS was administered only to MS patients, and provided a measure of each patient's current level of disability. Specifically, this measure was used to rate cerebral, brainstem, visual, sensory, pyramidal, cerebellar, bowel and bladder and ambulatory functioning. Functional status in each area was rated separately, and then scores were combined to give an overall EDSS score. Total scores range from zero to ten with zero defined as "normal neurological exam" and ten as "death due to MS." The EDSS is the most widely used measure of disability in individuals with MS, although it has some psychometric limitations (Sharrack, Hughes, Soudain, & Dunn, 1999). Inter-rater and intra-rater reliabilities on the overall EDSS score are sufficient (kappa coefficients = 0.65 and 0.70, respectively), but the EDSS has been shown to be relatively unresponsive to clinical change (Sharrack et al., 1999). Validity has been demonstrated via high correlations with similar measures of disability (e.g., Scripps Neurological Rating Scale: r = -0.92; the Functional Independence Measure: r = -0.87; and patient's self-ratings of perceived disability: r = 0.89; Sharrack et al., 1999).

The Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977): This self-report measure assessed depression. Participants were asked to rate how often each of twenty statements applied to their life during the past week. Ratings were given on a scale from one to four, indicating that the experience or feeling occurred "rarely or none of the time" or "most or all of the time," respectively. The CES-D has been shown to be a reliable and valid instrument for the assessment of recent experience of depressive symptoms in healthy individuals as well as those with psychiatric and medical illnesses. Internal-consistency

estimates for this measure are equally high in studies of healthy individuals and studies with MS patients (alpha = 0.85-0.93; Radloff, 1977; Verdier-Taillefer, Gourlet, Fuhrer, & Alperovitch, 2001). Test-retest reliability estimates are moderate (r = 0.45-0.70), and acceptable given this assessment is designed to measure current experience of depression (Radloff, 1977). The CES-D has been shown to discriminate between psychiatric and general population samples, and correlates strongly with other measures of depression including the Hamilton Clinician's Rating Scale and SCL-90 (r = 0.44-0.75; Radloff, 1977).

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989): This 9-item, self-report measure evaluated participants' levels of fatigue and its impact on daily functioning during the past week. Subjects were asked to rate each statement using a seven point Likert scale, with the total score computed as the sum of the nine ratings. The FSS has high internal consistency (alpha = 0.81-0.88) and good test-retest reliability (r = 0.84). It has been shown to correlate strongly with other measures of fatigue (e.g., VAS scale: r = 0.68) and has been shown to discriminate between MS patients and healthy individuals in terms of experience of fatigue (Krupp et al., 1989).

Visual Analogue Scale Rating Form (VAS): This self-report, 5-item rating form was adapted from previously published measures (e.g., Global Vigor and Affect; Monk, 1989) and was administered immediately prior to and immediately following cognitive testing. Individuals were asked to indicate their current levels of fatigue, sadness, alertness, anxiety and happiness by placing an "X" on the corresponding 10 cm line at the point which most accurately described their experience "in the present moment." Lines for each of the five items were anchored with descriptions: "Not [*fatigued, sad, alert, anxious, or happy*] at all" and "Very [*fatigued, sad, alert, anxious, or happy*]." A sample item preceded the first administration of this instrument to

facilitate comprehension of the instructions. Scores were recorded separately for each item as the distance in millimeters from the left end point of the line to the center of the "X". Reliability and validity estimates are not available for this measure, as it was developed for the current study. However, similar VAS measures have been shown to have high internal consistency reliabilities (e.g., VAS-Fatigue: alpha = 0.91-0.96; Lee et al., 1991). Similar measures have also demonstrated concurrent validity with ratings of alertness and sleepiness (e.g., Global Vigor and Affect; Monk, 1989), and have been shown to differentiate between depressed and non-depressed individuals (Global Vigor and Affect; Monk, 1989) as well as fatigued individuals with sleep disorders and healthy individuals (VAS-Fatigue; Lee, Hicks, & Nino-Murcia, 1991).

Procedure

Eligible MS patients were approached regarding participation in the study during the course of their regularly scheduled appointment at the MS Clinic. Control participants were recruited through staff at the University of Kansas Medical Center and through personal contacts of research personnel. All interested participants met with a research assistant who thoroughly explained the purpose, procedures, and risks/benefits of participation and obtained informed consent. After providing consent, Dr. Lynch completed the EDSS (MS patients only), and the testing session was scheduled to be completed either at the University of Kansas Medical Center or at the participant's home.

During the testing session, individuals were first asked to provide demographic information and elaborate on medical history directly applicable to inclusion/exclusion criteria. Participants then completed the CES-D, FSS, and the VAS Rating Form. Computerized tasks were administered in the following order: RAVLT (Trials 1-6 and short delay), SRT, CRT-2, CRT-4, 1-BRT, Stroop, and RAVLT (recognition). At the end of the session, the VAS Rating

Form was administered a second time. Time required to complete the entire procedure was approximately 45 minutes.

Results

Analysis of Demographic and Disease Variables

Means and standard deviations for MS and control groups on demographic and disease-related variables are given in Table 1. The majority of participants in this study were female. For both groups, participants ranged in age from 30 to 60 and had completed between 12 and 20 years of education. Analyses of between-group differences on demographic variables revealed no significant differences in gender ($X^2 = 0.09$, df = 1, p = 0.77), age (t = 1.26, df = 69, p = .214), or level of education (t = 1.00, df = 69, p = 0.32).

With respect to disease-related characteristics, the majority of MS patients carried diagnoses of relapsing-remitting MS (RRMS = 72%), with length of diagnosis ranging from 1 to 29 years. Extent of disability as assessed by the EDSS ranged from one to seven.

Table 1: Summary of Demographic and Disease-Related Variables for MS and Control Groups

	MS Group N = 39	Control Group N = 32
Gender (M/F)	4/35	4/28
Age	47.36 (7.72)	44.59 (10.31)
Education	15.46 (1.99)	15.95 (2.16)
MS Type (RR/SP)	28/11	N/A
Length of Diagnosis (years)	12.45 (7.76)	N/A
EDSS Total	3.66 (2.00)	N/A

Analysis of Self-Report Measures

Group differences on self-report measures (CES-D, FSS, and VAS Rating Forms) were analyzed via separate independent groups t-tests to identify any variable(s) that might require inclusion as covariates in the principal analyses. Results are given in Table 2. Analyses revealed significant differences on depression as measured by the CES-D, with MS patients having more elevated scores for depression compared to control participants. Group differences in fatigue ratings from the FSS were also significant, with MS patients again reporting more severe symptoms of fatigue. Patients and control participants did not differ significantly on any items from the VAS Rating Forms, suggesting relative equivalency in current experience of fatigue and emotional status for the groups immediately before and after testing. Change in pre- and post-ratings for each VAS item was also assessed via separate 2 (Group) X 2 (Time) repeated measures analyses of variance. None of these analyses resulted in significant main effects for Group or Time, and none of the Group X Time interactions were significant.

Group differences in depression and fatigue from the CES-D and FSS could have potentially impacted cognitive performance. Therefore, these variables were initially entered as covariates in all analyses pertaining to the cognitive scores. None of the variables emerged as significant covariates in any of the analyses. Thus, analyses were repeated without covarying depression and fatigue, and the results presented here are those obtained without covariates.

Table 2: MS and Control Group Responses on Self-Report Measures

	Means (SD)		t (df = 69)	p
	MS Group	Control Group		
CES-D Total	31.21 (6.57)	24.78 (5.22)	4.49	<0.001
FSS Total	37.69 (14.22)	16.03 (7.84)	8.13	<0.001
VAS—Initial Ratings				
Fatigue	34.92 (25.90)	31.02 (20.92)	0.69	0.49
Sadness	10.95 (12.83)	11.56 (13.42)	0.20	0.85
Alertness	69.28 (25.65)	69.84 (20.82)	0.10	0.92
Anxiety	18.41 (20.08)	16.80 (15.92)	0.37	0.71
Happiness	74.18 (17.88)	74.39 (18.64)	0.05	0.96
VAS—Final Ratings				
Fatigue	38.68 (33.71)	32.83 (22.21)	0.88	0.38
Sadness	8.90 (12.02)	11.31 (12.47)	0.83	0.41
Alertness	62.99 (28.42)	65.52 (21.49)	0.43	0.67
Anxiety	20.47 (22.00)	22.94 (19.10)	0.50	0.62
Happiness	81.55 (16.10)	72.91 (21.76)	1.92	0.06

Analysis of RT Tests

Data Preparation. Prior to any analyses of the RT tests, data for three subjects (2 MS patients, 1 control) on the CRT-4 and two MS patients on the 1-BRT were eliminated. In four of these cases, technical difficulties interfered with test administration and data for the test were incomplete. In the remaining case, the participant committed an excessive number of errors (total correct = 12/50) which far surpassed that of any other participant. In each of these cases, data were only eliminated for the cited test, and data from all other cognitive measures were retained.

Individual item reaction times for each RT test (SRT, CRT-2, CRT-4, and 1-BRT) were then examined for outliers. Procedures for defining, eliminating, and replacing outlying scores were based on those reported in prior studies of individual variability (e.g., Bunce et al., 2004; Burton et al., 2006; de Frias et al., 2007; Hultsch et al., 2000, 2002). Extremely fast responses, defined as any reaction time less than 150 ms on any RT test, were removed from the data since they likely reflected participant error (e.g., accidental button press). Extremely slow responses were also identified and eliminated. Slow responses were defined as any reaction time exceeding the corresponding group mean for that test by at least three standard deviations.

Percentages of eliminated responses are given in Table 3. Numbers of outliers were small relative to the total number of reaction times in the data set and were comparable to percentages reported in prior studies (i.e., 1 to 3 percent per group; de Frias et al., 2007; Hultsch et al., 2000; Lovden et al., 2007).

Resultant missing values were subsequently replaced using linear regression procedures which identified the response trend at the missing data point. It is noteworthy that this procedure of eliminating extremely fast and slow responses and replacing values by way of regression

actually reduces variability in the data set and thus constitutes a conservative approach to analysis of variability.

Table 3: Percentages of Extreme Responses Eliminated for each RT Test

Reaction Time Test	MS Group	Control Group	Total
SRT	1.08%	0.69%	1.77%
CRT-2	1.95%	1.06%	3.01%
CRT-4	0.92%	0.97%	1.89%
1-BRT	1.41%	1.69%	3.10%

Accuracy of Performance. Total number of correct responses was recorded for each RT test. Individual response times associated with an incorrect button press were labeled in the data set as errors, but not eliminated (unless the response time qualified it as an outlier). Retaining erroneous response times in the data set is consistent with prior studies of individual variability (e.g., Bunce et al., 2006; Dixon et al., 2007) and was adopted here to prevent additional missing data requiring statistical reconstitution that would have further reduced variability.

However, because group differences in accuracy could potentially impact analyses of mean reaction time and/or variability in speed, accuracy variables were statistically evaluated to determine whether they warranted inclusion as covariates in the remaining analyses. Independent groups t-tests were used to assess accuracy on the CRT-2, CRT-4, and 1-BRT. Results are given in Table 4. On average, incorrect responses were rare, with the highest percentage for either group being 3.5% (recorded for the MS group on the 1-BRT test). Tests of group differences revealed that MS patients performed significantly less accurately than control participants on each RT test.

To control for these group differences, accuracy scores for the CRT-2, CRT-4, and 1-BRT were initially entered as covariates in the analyses performed on mean reaction times and variability on each of these tests. None of these variables emerged as significant covariates in the analyses. Therefore analyses were repeated without covariates, and the findings without covariates are presented here.

Table 4: Accuracy of performance for MS and Control Groups on RT Tests

	Mean Accuracy* (SD)				
Measure	MS Group	Control Group	t (df)	p	Cohen's d
CRT-2	49.15 (2.28)	49.94 (0.25)	2.13 (df = 69)	0.04	0.49
CRT-4	48.41 (1.77)	49.52 (0.63)	3.56 (df = 66)	0.001	0.84
1-BRT	48.27 (2.10)	49.34 (2.32)	2.01 (df = 67)	0.05	0.48

*Accuracy defined as total correct out of 50 trials.

Mean Reaction Time. Differences between MS patients and control participants on mean reaction times for the SRT, CRT-2, CRT-4, and 1-BRT were evaluated with separate independent group t-tests. Results, given in Table 5, reveal significant differences on each test, with MS patients responding more slowly than control participants.

Table 5: Analyses of Mean Reaction Times for MS and Control Groups on RT Tests

	Mean Reaction Time (SD)				
Measure	MS Group	Control Group	t (df)	p	Cohen's d
SRT	0.56 (0.14)	0.43 (0.06)	5.19 (df = 69)	<0.001	1.21
CRT-2	0.45 (0.06)	0.37 (0.04)	5.63 (df = 69)	<0.001	1.57
CRT-4	0.64 (0.11)	0.50 (0.05)	7.07 (df = 66)	<0.001	1.64
1-BRT	0.78 (0.25)	0.58 (0.17)	3.86 (df = 67)	<0.001	0.94

Inconsistency. Variability scores were computed for each participant on each RT test (SRT, CRT-2, CRT-4, 1-BRT). Several measures of intra-individual variability have been described in the literature (see Hultsch et al., 2008, for review). Each of these measures incorporates a statistical transformation of individual standard deviation scores to minimize systematic sources of variation, namely group differences in mean reaction time. Group differences in mean reaction time are known to confound analyses of individual variability since greater means are associated with greater standard deviations (Hultsch et al., 2000). Therefore, to eliminate this confound from measures of variability, individual standard deviations must be corrected for mean differences. The coefficient of variation (CoV) is one measure of inconsistency used in prior studies (e.g., Duchek et al., 2009) that corrects for mean differences by dividing each individual's standard deviation by their mean (CoV = Standard Deviation/Mean RT * 100). The CoV was selected here for analyses of inconsistency and calculated for each participant on each RT test.

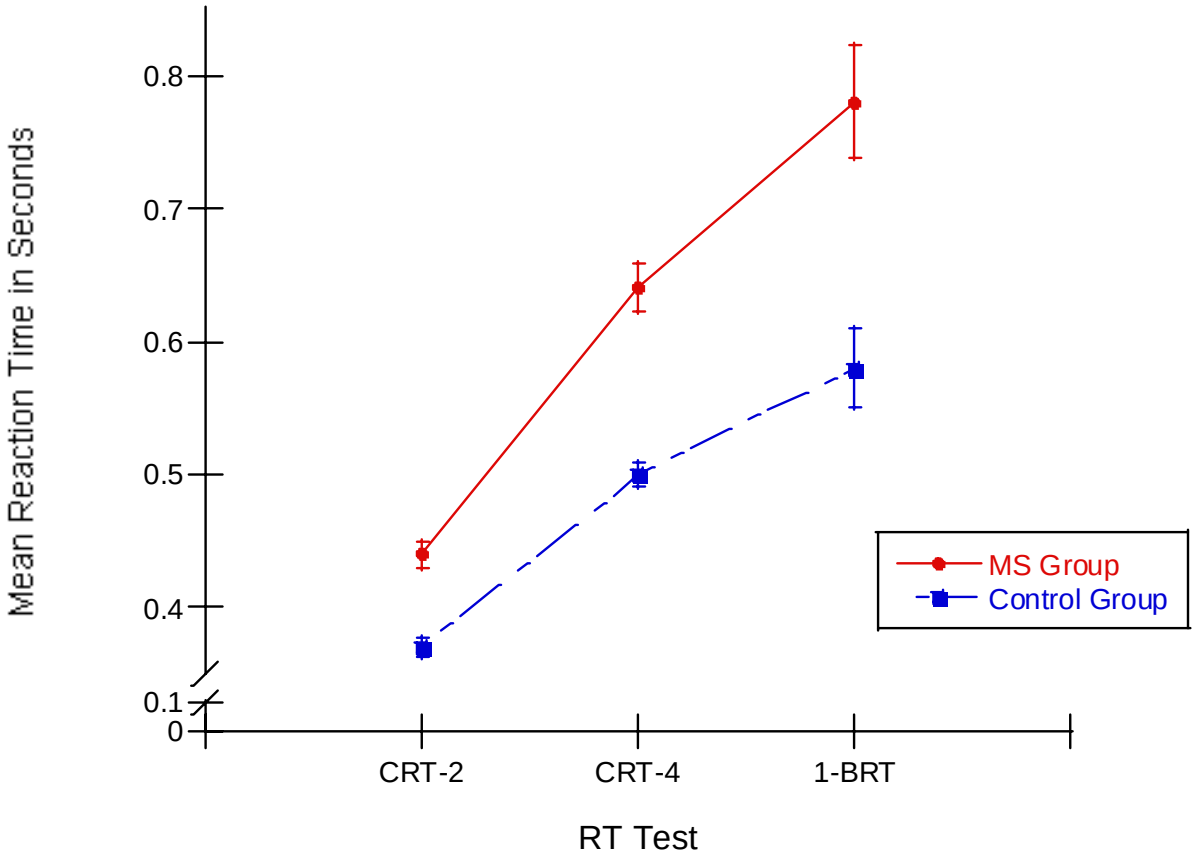
Group differences in CoVs for the SRT, CRT-2, CRT-4, and 1-BRT were then assessed via independent groups t-tests. Table 6 presents results which reveal statistically significant differences in CoV's for MS patients and control participants on each RT test. For each test, MS patients showed great variability in their reaction times from trial-to-trial than did control participants.

Table 6: Analyses of Coefficients of Variation for MS and Control Groups on RT Tests

	Mean CoV (SD)				
Measure	MS Group	Control Group	t (df)	p	Cohen's d
SRT	18.56 (6.05)	15.66 (3.79)	2.52 (df = 69)	0.01	0.57
CRT-2	18.86 (4.71)	15.22 (3.59)	3.94 (df = 69)	<0.001	0.87
CRT-4	21.45 (3.84)	18.63 (2.53)	3.56 (df = 66)	0.001	0.87
1-BRT	38.97 (8.48)	27.72 (8.83)	5.22 (df = 67)	<0.001	1.30

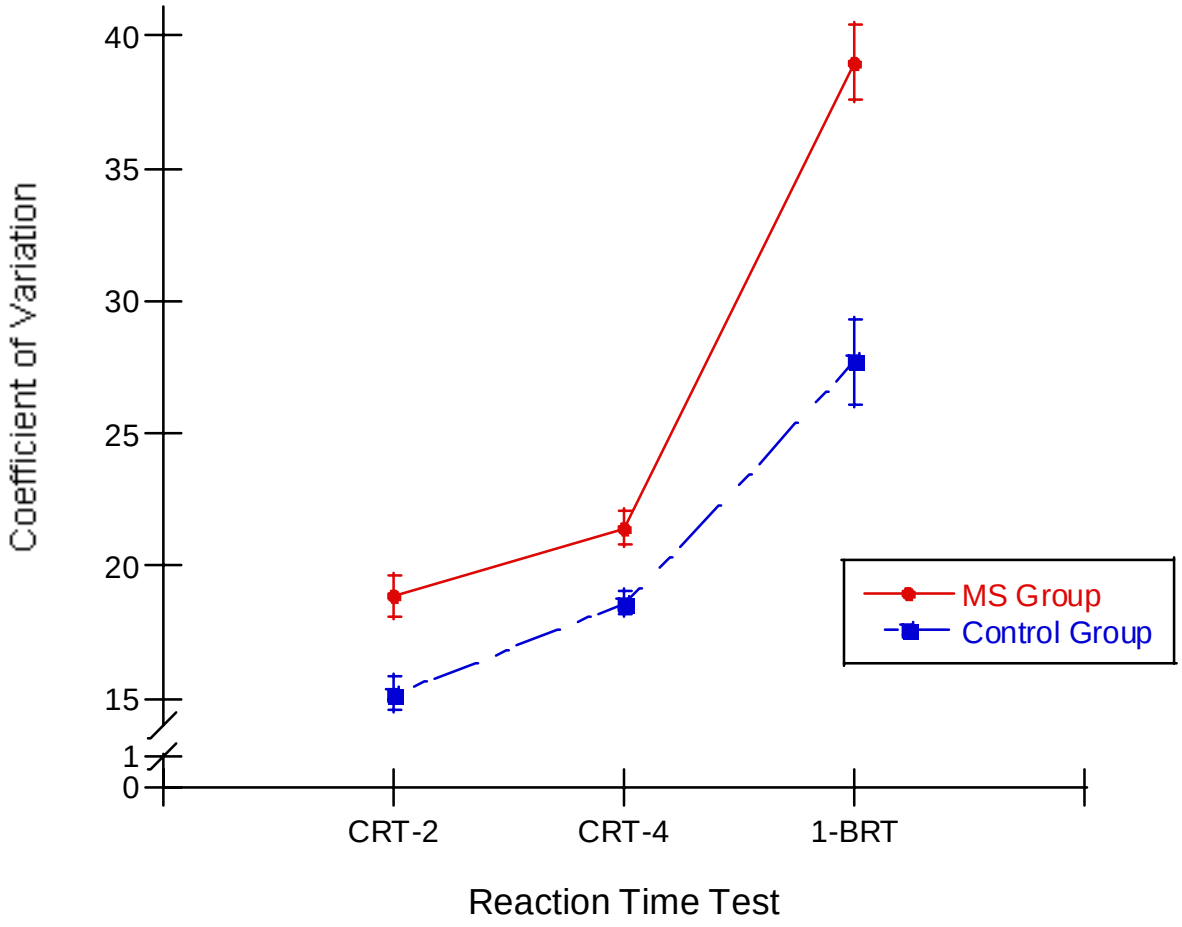
Cognitive Load. The graded complexity of the set of RT tests permitted analyses of the impact of "cognitive load" on average response time and CoV. Mean reaction times and CoVs for the CRT-2, CRT-4, and 1-BRT were evaluated via separate 2 (Group) X 3 (Load) mixed factorial analyses of variance with Group as the between-group factor and Load as the within-group factor. In the analysis of mean reaction times, main effects were significant for Group ($F = 27.37$, $df = 1 \& 65$, $p < 0.001$, partial $\eta^2 = 0.30$), and Load ($F = 259.92$, $df = 2 \& 64$, $p < 0.001$, partial $\eta^2 = 0.89$). The Group X Load interaction was also significant ($F = 11.47$, $df = 2 \& 64$, $p < 0.001$, partial $\eta^2 = 0.26$). Figure 1 illustrates that MS patients responded more slowly than control participants on each test, and also both groups responded more slowly as cognitive load increased. However, increasing cognitive load resulted in more a pronounce slowing of processing speed for MS patients than for healthy controls. Follow-up pairwise comparisons revealed significant differences in mean reaction times between each of the RT tests for the MS patients. For the control participants, mean reaction time on the CRT-2 was significantly different from that of the CRT-4 and 1-BRT, but reaction times on the CRT-4 and 1-BRT did not differ significantly.

Figure 1: Mean Reaction Times for MS and Control Groups on RT Tests of Increasing Complexity



A second 2 (Group) X 3 (Load) mixed factorial analysis of variance was applied to the CoVs for each RT test, and this analysis generated a similar overall pattern of results. Main effects were significant for Group ($F = 41.72$, $df = 1$ & 65, $p < 0.001$, partial $\eta^2 = 0.39$) and Load ($F = 94.82$, $df = 2$ & 64, $p < 0.001$, partial $\eta^2 = 0.75$), and were qualified by a significant Group X Load interaction ($F = 8.98$, $df = 2$ & 64, $p < 0.001$, partial $\eta^2 = 0.22$). As illustrated in Figure 2, trial-to-trial variability was greater for MS patients versus control participants and for tasks posing greater cognitive demand. The significant interaction resulted from a more prominent increase in variability for MS patients as cognitive load increased. Follow-up pairwise comparisons revealed that, for both MS patients and control participants, performances were significantly more variable on the 1-BRT relative to the CRT-2 and CRT-4, but that variability on the CRT-2 and CRT-4 was not statistically different.

Figure 2: Coefficients of Variation for MS and Control Groups on RT Tests of Increasing Complexity



Analyses of Additional Neuropsychological Measures

Stroop Test. Performances on the three trials of Stroop test were evaluated via independent groups t-tests. Statistically significant differences for MS patients and control participants were observed on each trial of the Stroop (Table 7), with MS patients giving fewer responses than healthy individuals across all trials.

Table 7: MS and Control Group Performances on the Stroop Test

	Mean (SD)				
Trial	MS Group	Control Group	t (df = 69)	p	Cohen's d
Word Reading	81.62 (10.41)	92.94 (6.11)	5.70	<0.001	1.33
Color Naming	68.08 (8.72)	77.19 (5.87)	5.24	<0.001	1.23
Color-Word Naming	47.18 (8.61)	52.37 (6.54)	2.81	0.006	0.68

Rey Auditory Verbal Learning Test. Performances on the memory measures of the RAVLT were analyzed via independent group t-tests. MS patients and control participants did not differ significantly on the total number of words recalled for trials 1-5, the total number of words recalled after a short-delay, or the total number of correctly recognized words following a longer delay (Table 8).

Latencies of yes/no responses on the delayed recognition trial were also analyzed for potential group differences in mean reaction time and variability. Prior to formal analyses, data were examined for outliers. Consistent with the procedure used for the RT tests, extremely fast responses (i.e., reaction times less than 150 ms) and extremely slow responses (i.e., reaction times exceeding the corresponding group mean by three standard deviations) were eliminated from the data set and replaced using linear regression procedures. Percentages of eliminated reaction times on this test for the MS and control groups were 1.28% and 2.13%, respectively. Coefficients of variation were then computed for each participant.

Independent group t-tests revealed that MS patients responded more slowly relative to control participants on this covertly-timed measure of speeded processing, but that group differences in the variability with which patients and healthy individuals responded from item to item were not statistically significant (Table 8).

Table 8: MS and Control Group Performances on the RAVLT

	Mean (SD)				
Measure	MS Group	Control Group	t (df = 69)	p	Cohen's d
Trials 1-5 Total	48.87 (10.57)	51.16 (8.12)	1.00	0.319	0.24
Short-Delay Total	9.56 (3.52)	10.22 (2.32)	0.90	0.352	0.22
Recognition Total	45.13 (4.13)	46.09 (2.99)	1.11	0.273	0.27
Recognition RT	1.29 (0.29)	1.10 (0.23)	3.65	0.001	0.73
Recognition CoV	45.75 (12.27)	44.07 (7.61)	0.70	0.484	0.16

Relative Predictive Value of Mean Reaction Time and Inconsistency Variables

To determine whether inconsistency variables offered additional predictive value for group performance beyond that attributable to mean reaction time measures, mean reaction times and CoVs for the SRT, CRT-2, CRT-4, and 1-BRT were assessed with two binary logistic regression analyses; the delayed recognition trial of the RAVLT was not included in this analysis due to the lack of significant group differences for the CoV from this test. In both analyses, group membership served as the dichotomous criterion variable with control participants coded as the reference group. In the first analysis, the four mean reaction time variables were entered as the first block of predictors, and the four CoV's were entered as the second block. Chi-square analysis of each block was significant (Block 1: $X^2 = 43.36$, df = 4, $p < 0.001$; Block 2: $X^2 = 25.25$, df = 4, $p < 0.001$). In the second analysis the order of variable entry was reversed, with the four CoV's entered as Block 1, and the four mean reaction times entered as Block 2. Again, chi-square analysis of each block was significant (Block 1: $X^2 = 31.96$, df = 4, $p < 0.001$; Block 2: $X^2 = 36.66$, df = 4, $p < 0.001$). Thus, the set of CoV's served as a significant predictor of group performance, providing additional predictive utility beyond that attributable to mean reaction time measures. For both analyses, the combined model accurately classified 33 of 36 MS patients and 28 of 31 control participants, for an overall percentage of 91.0% correct (Cox & Snell $R^2 = 0.64$; Nagelkerke $R^2 = 0.86$).

Correlational Analyses

Correlations between cognitive tests and select demographic variables, disease-related characteristics, and self-report measures are presented in Table 9. In general, CoVs for the RT tests were not strongly associated with any of the MS disease-related characteristics, although CoVs for the CRT-2 and 1-BRT were modestly related to depression scores on the CES-D. However, mean values on the speed of processing measures were highly correlated with the type of MS (i.e., relapsing-remitting or secondary progressive) and the extent of disability. The word reading and color naming trials of the Stroop showed the strongest relationships with these disease-related variables, and additionally were significantly related to the length of diagnosis. The mean values on speed of processing measures were also highly correlated with self-reported depression and fatigue on the CES-D and FSS. Each of the memory variables from the RAVLT was associated with length of diagnosis ($p < 0.05$), although these variables were not statistically related to other disease-related characteristics or to the self-report measures.

Table 10 presents correlations between measures of variability and the Stroop Test. Some of the CoVs were significantly associated with the word reading and color naming trials of the Stroop test, but not with the color-word naming trial.

Table 9: Correlations between Cognitive Tests and Select Demographic, Disease, and Self-Report Variables

Cognitive Measure	Age	MS Type† (RR vs SP)	Length of Diagnosis	Overall EDSS†	Depression (CES-D)	Fatigue (FSS)
RT Tests – Mean RT						
SRT	0.24*	0.47**	0.14	0.35*	0.35**	0.37**
CRT-2	0.34**	0.47**	0.16	0.43*	0.36**	0.46***
CRT-4	0.34**	0.36*	0.15	0.36*	0.38**	0.51***
1-BRT	0.34**	0.45**	0.24	0.38*	0.15	0.35**
RT Tests – CoV's						
SRT	0.13	0.37*	0.18	0.30	0.19	0.21
CRT-2	-0.06	0.08	-0.01	0.15	0.24*	0.34**
CRT-4	0.16	0.17	0.23	0.12	0.21	0.24*
1-BRT	0.13	-0.06	0.13	-0.03	0.26*	0.36**
Stroop Test						
Word Reading	-0.29*	-0.47**	-0.32*	-0.53**	-0.42***	-0.48***
Color-Naming	-0.27*	-0.61**	-0.50***	-0.57**	-0.37**	-0.46***
Color-Word Naming	-0.29*	-0.27	-0.27	-0.33	-0.27*	-0.36**
RAVLT						
Trials 1-5 Total	-0.26*	-0.31	-0.38*	-0.25	0.07	-0.08
Short Delay Total	-0.20	-0.25	-0.33*	-0.25	0.18	-0.05
Recognition Total	-0.18	-0.23	-0.33*	-0.26	0.00	-0.02
Recognition RT	0.39***	0.40*	0.31	0.27	0.25*	0.23
Recognition CoV	-0.12	-0.10	-0.12	-0.06	0.12	0.15

†Spearman Rank-Order Correlations.

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 10: Correlations between Coefficients of Variation and the Stroop Test

	Coefficient of Variation				
Cognitive Measure	SRT	CRT-2	CRT-4	1-BRT	RAVLT Recognition
Stroop Trials					
Word Reading	-0.28*	-0.22	-0.07	-0.24*	0.05
Color Naming	-0.33**	-0.24*	-0.19	-0.30*	0.06
Color-Word Naming	-0.18	-0.01	0.00	-0.15	0.10

* $p < 0.05$
** $p < 0.01$

Discussion

Slowing in speed of information processing has been extensively documented as one of the fundamental cognitive deficits associated with MS; however, this study was the first to broaden analyses of speeded processing in MS patients to include trial-to-trial variability as well as average speed. As expected, MS patients performed more slowly on traditional "mean level" speed of processing measures including each of the RT tests and all trials of the Stroop. Additionally, MS patients' response times were more variable across trials of each of the explicitly-timed RT tests (i.e., SRT, CRT-2, CRT-4, 1-BRT), and these variability measures accounted for unique variance in group performance beyond that attributable to mean reaction times.

Large effect sizes were observed for the vast majority of speeded processing tests in this study, including both mean reaction time and variability measures. The largest of these were obtained on measures of mean reaction time for the RT tests, which is likely due, at least in part, to the fact that these measures were uniquely impacted by ancillary slowing in motor function among the MS patients. The slightly smaller effect sizes for the CoV's may have occurred because these measures of variability controlled for differences in mean reaction time and thereby minimized this motor confound. The version of the Stroop test used here also avoids the potential confounding influence of motor slowing by requiring verbal as opposed to manual responses. Even so, effect sizes for this test, and particularly those on the preliminary Stroop trials, were sizable.

Group differences in mean reaction time were observed on both explicitly- and covertly-timed measures of processing speed, although the explicitly-timed tests were more sensitive to differences between the patients and control participants. This finding is consistent with that of

another recent study (Steiger et al., 2008) that employed both types of measures with MS patients and healthy control participants and found larger effect sizes on the explicitly-timed measures. In terms of variability, however, only the explicitly-timed tasks resulted in significant differences between patients and control participants; the CoV for the delayed recognition trial on the RAVLT was the only measure of variability that failed to distinguish between groups. Several differences between this task and the RT tests might account for the lack of group differences. Because no instructions were given dictating the rate of response, participants were free to adopt their own pace on the delayed recognition test. This likely resulted in greater *inter*-individual variation for participants in both groups which, in turn, may have masked differences in *intra*-individual variability. Additionally, this was the only semantic reaction time test in the battery. It is possible that increased variability for MS patients does not generalize to semantic tasks. Future studies including additional semantic tests would confirm whether increased variability for MS patients exists on verbal as well as nonverbal RT tests.

The more detailed analyses of the impact of cognitive load on speeded processing revealed that the most pronounced differences between patients and control participants occurred on the most cognitively demanding tasks. Of the RT tests, the 1-BRT carried the highest cognitive load by not only requiring rapid processing of the maximum number of stimuli but also by posing an additional demand on working memory. This increased cognitive demand forced greater slowing in mean reaction time as well as increased trial-to-trial variability in speed for the MS group. A number of studies have described impaired working memory in MS patients, in addition to deficits in speeded processing (Parmenter et al., 2006, 2007; Paul et al., 1998). Indeed, the present data revealed a small, albeit statistically significant, difference between patients and control participants in terms of accuracy of performance on the 1-BRT. However,

similar differences in accuracy existed on the other RT tests which did not include working memory components. Thus, while MS patients may experience slight deficits in working memory, the most obvious impairments are those in the speed of processing domain, and speeded working memory tasks afford greater sensitivity to cognitive impairment in MS patients by eliciting more substantial deficits in processing speed.

While considerable group differences in reaction time and variability were found for the majority of speeded processing tests, none of the memory variables derived from the RAVLT yielded significant findings. Preserved memory functioning in MS patients has been similarly documented in prior studies (e.g., DeLuca et al., 1994; Denney et al., 2004), although others have reported memory dysfunction as a more common consequence of MS (e.g., Benedict et al., 2006; Rao et al., 1991). This lack of consistency across studies argues that memory impairment is not a fundamental deficit associated with the disease, but instead a secondary consequence experienced by a subset of patients. In the present study, each memory variable was significantly correlated with length of MS diagnosis, suggesting that memory may be impacted later in the course of the disease.

More generally, the existence of greater individual variability in MS patients offers an additional dimension relating cognitive functioning in MS to that associated with healthy aging. Not only are the two populations similar in terms of exhibiting increased variability, but the pattern of performance for MS patients and healthy older adults across speeded tests is strikingly similar. Healthy older adults have been found to respond more variably in terms of trial-to-trial reaction time across a range of speeded tests, but responses are most inconsistent on complex as opposed to simple reaction time measures (e.g., Dixon et al., 2007; Hultsch et al., 2008). Additionally, differences between older and younger adults are less robust on verbal RT tests as

opposed to nonverbal tasks (Hultsch et al., 2002, 2008). These similarities validate comparisons between MS- and age-related cognitive dysfunction, and imply that measures of variability may serve an important role in the assessment of cognitive status and prediction of cognitive outcome in both populations.

Finally, relevance of the present findings extends beyond the MS literature and bears more generally on the study of variability. Individual variability has been linked to neurological dysfunction, and the present findings add to the evidence bearing on this connection by documenting increased inconsistency in individuals with MS. It is surprising that studies of individual variability have not been previously extended to the MS population, especially given that one of the proposed mechanisms contributing to individual variability is demyelination of central nervous system axons. Studying the relationship between inconsistency and integrity of white matter in individuals with MS would certainly provide an important test of this hypothesis. Data from the present study are limited in terms of informing theories of the underlying mechanism for inconsistency, although the absence of significant correlations between inconsistency and disease-related variables (e.g., extent of disability and MS type) may call into question the connection between variability and demyelination. One could certainly maintain that, if inconsistency were closely aligned with demyelination, the correlations with disability, duration of disease, and MS subtype would be stronger. That said, none of these disease-related variables are particularly good estimates of underlying pathology. The MS population is incredibly heterogeneous in terms of clinical manifestations of the disease, age of onset, and rate of progression. Additionally, the disease process itself is characterized not only by demyelinating lesions, but also more general processes such as neurodegeneration. The nature and extent of neuropathology is far more complex than one limited merely to demyelination, and

thus the absence of significant correlations between behavioral inconsistency and disease variables is not particularly revealing. The true test of the relationship between individual variability and neurological dysfunction as well as that of the clinical utility of inconsistency measures in individuals with MS will require further examination, particularly with studies incorporating neuroimaging methods to provide more direct measures of neuropathology.

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