

**INFORMATION PROCESSING IN MULTIPLE SCLEROSIS:
ACCURACY VERSUS SPEED**

by

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Abstract

Previous research has suggested that slowed speed of information processing is the primary cognitive impairment that occurs in multiple sclerosis (MS). The proposed study employed multiple cognitive measures to replicate these findings. Individuals with relapsing-remitting or secondary-progressive MS were compared to healthy controls in their performance on five cognitive measures. Three tests were covertly-timed and two were explicitly-timed to assess the impact of timing awareness on performance. It was hypothesized that MS patients would respond more slowly than controls and that accuracy of performance between the two groups would not differ. Results indicated that MS patients answered with significantly greater latency than controls. Accuracy of responding was similar between the groups on two of three measures. Overall, slowed information processing in MS patients was found across a range of cognitive measures. Combined with previous research, these findings suggest slowed information processing speed is a significant cognitive deficit in MS.

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Multiple Sclerosis (MS) is an autoimmune disease that impacts the central nervous system and derives from a progressive degeneration of the myelin sheath (Sheth, 2005). The disease is characterized by a variety of symptoms, including fatigue, bladder and bowel dysfunction, spasticity, gait disorders, visual problems, dizziness and vertigo, tremor, speech and swallowing disorders, numbness, pain, sexual dysfunction, seizures, emotional problems, and cognitive difficulties (Kesselring & Beer, 2005).

The diagnostic criteria for MS were recently revised by the International Panel on MS Diagnosis to reflect the current medical understanding of the disease. These requirements include the clinical presentation of an “attack,” a “lesion,” or “insidious neurological progression suggestive of MS,” usually followed by clinical testing in order to confirm accurate diagnosis through magnetic resonance imaging, cerebrospinal fluid analysis, or visual evoked potentials (McDonald, Compston, & Edan, et al, 2001). The four primary classifications of MS relate to the course of the disease and include the following: 1) relapsing-remitting, the most common form of MS, involving cyclical “flare-ups” followed by periods of partial or complete recovery, 2) primary-progressive, marked by a slow, continuous worsening of the disease and its symptoms over time, 3) secondary-progressive, characterized by an initial period of relapsing-remitting MS followed by a steady and continuous degeneration, and 4) progressive-relapsing, entailing a steadily worsening pattern interrupted by occasional acute relapses, which may or may not be followed by subsequent recovery (National Multiple Sclerosis Society, 2006).

Neuropsychological symptoms associated with MS are highly variable and may be attributed to the progressive demyelination and neurological degeneration that characterizes the disease. Not all individuals with MS experience cognitive dysfunctions (Rao, 1995). Estimates of the proportion of MS patients with cognitive impairment range from 30 to 72 percent (Rao, 1995; Amato & Zipoli, 2003; Birnboim & Miller, 2004). Cognitive difficulties often include deficiencies in recent memory, attention, executive functions, visuospatial perception, and speed of information-processing.

In recent years, researchers have begun to place greater emphasis on speed of information processing in MS patients, with several studies illustrating the deleterious impact of the disease on this particular domain of cognitive function. A generalized slowing in the speed of information processing in MS patients has been demonstrated with a variety of measures, including the Sternberg Task (Archibald & Fisk, 2000; Litvan, Grafman, Vendrell, & Martinez, 1988; Rao, St. Aubin-Faubert, & Leo, 1989), the Paced Auditory Serial Addition Test (DeLuca, Johnson, & Natelson, 1993; Demaree, DeLuca, Gaudino, & Diamond, 1999; Hohol et al., 1997; Kujala, Portin, Revonsuo, & Ruutiainen, 1994; Litvan, Grafman, Vendrell, & Martinez, 1988; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Snyder, Cappelleri, Archibald, & Fisk, 2001), symbol-digit tests (Beatty et al., 1988; Beatty & Monson, 1994; Ryan, Clark, Klonoff, Li, & Paty, 1996), alphanumeric sequencing (Grigsby, Kaye, & Busenbark, 1994; Heaton, Nelson, Thompson, Burks, & Franklin, 1985), and the Stroop Test (Pujol, Vendrell, Deus, et al., 2001; Rao, Leo, Bernardin, et al., 1991; Scarrabelotti & Carroll, 1999; Vitkovitch, Bishop, Dancey, & Richards, 2002). Rather than

reviewing all of these studies, this paper focused on those most relevant to the present study.

One of the most widely used tests in the MS literature is the Paced Auditory Serial Addition Test (PASAT). This test assesses auditory attention and calculation skill as well as information processing speed. DeLuca, Johnson, and Natelson (1993) compared the performance of samples of chronic fatigue patients and MS patients to matched healthy controls using the PASAT. MS patients scored significantly lower than controls on all four trials of the PASAT, indicating that speed of information processing may be significantly impaired in this population.

Demaree, DeLuca, Gaudino, and Diamond (1999) devised variations of the PASAT to demonstrate more clearly that the deficits in performance on this measure were attributable to information processing speed. The variations were administered to 81 patients with relapsing-remitting, primary progressive, or secondary progressive MS types and to 36 healthy control subjects. Between-group comparisons on the serial addition measures demonstrated that the MS group required significantly more time to complete the problems with at least 50 percent accuracy than did the controls. However, when the MS patients were allowed unlimited time to complete the problems, their rates of accuracy in problem solving did not differ from that of the controls. The investigators therefore concluded that the only significant difference between the groups was a deficiency in information processing speed in the MS sample.

More recently, Denney, Lynch, Parmenter, and Horne (2004) analyzed groups of relapsing-remitting and primary-progressive MS patients on a battery of

neuropsychological tests. The battery included the Wisconsin Card-Sorting Test and the Tower of London (TOL) to evaluate executive functions, a paired associates learning test to assess verbal learning and memory, and the Stroop Color Word Interference Test (Stroop) to assess complex attention and speed of information processing. The investigators showed that when differences between the MS patients and controls in gender, age, education level, depression, and fatigue were statistically controlled, the only significant differences that distinguished the two groups were those implicated in speed of information processing. Specifically, MS patients took significantly longer times to plan their solutions to each of the problems presented in the TOL, and the disparity between patients and controls in these planning times became greater as the problems progressed in difficulty level. Furthermore, patients completed fewer items than controls on all three trials of the Stroop Test, involving word reading, color naming, and color-word naming. The investigators demonstrated through factor analysis that speed of information processing was the common feature underlying the differences between patients and controls.

In a follow-up study, Denney, Sworowski, and Lynch (2005) administered the TOL and the Stroop to relapsing-remitting, primary-progressive, and secondary-progressive MS patients. Two comparison groups were also recruited, a healthy control group and a clinical control group consisting of patients with rheumatoid arthritis. Inclusion of the clinical control group allowed the researchers to compare the performance of the MS patients with that of a sample of patients whose disease is unrelated to the nervous system but results in similar levels of physical disability and who commonly experience fatigue and depression in conjunction with their illness.

Analysis of covariance models that statistically controlled for age, gender, education level, depression, and fatigue replicated the findings of the earlier study, again showing differences between the MS patients and the control groups in speed of information processing. Specifically, the MS patients scored more poorly on initial planning times on the TOL, and on word reading, color naming, and color-word naming on the Stroop. Also, secondary-progressive patients performed worse than primary progressive patients on planning time and color-word naming. The investigators concluded that a generalized slowing in the speed of information processing is a prominent feature of the cognitive impact of multiple sclerosis and appears to be the only cognitive factor that consistently reflects deficits when controlling for other potentially confounding variables.

This assertion has been challenged on the basis of the fact that the tests used to measure speed of information processing also have sensory and motor components that may disadvantage patients with MS. Denney and his colleagues have argued that the computerized version of the Stroop they designed for their research minimized these components and that the planning time measure derived from the TOL was assessed during a time that the patient was quietly contemplating his/her solution to a problem and was completely devoid of sensory and motor components. To further demonstrate the unlikelihood that sensory and motor factors were causing slower responding on speed of information measures, Bodling, Denney, and Lynch (2006) administered the Stroop Test, along with a specifically designed test called the Picture Naming Test (PNT) to 63 MS patients and 59 healthy controls. The PNT was designed to vary the degree of sensory-motor “challenge” incorporated within a

simple measure of information processing speed. On separate trials, subjects were presented with either the same four pictures shown repeatedly or novel pictures displayed on each presentation. Also, the pictures were displayed either repeatedly in the center of the computer screen or in one of nine different locations on the screen. The varying conditions in the PNT were intended to illustrate the extent to which ancillary problems, primarily nystagmus and dysarthria, impacted results on measures of speed of information processing. Relative to controls, MS patients scored significantly lower on all three Stroop trials and all four PNT trials. In addition, comparisons between MS patients with and without nystagmus and dysarthria demonstrated that these motor problems made negligible contributions to slowed performance revealed by these simple speeded information processing tasks.

The present study was designed to build on the results reported by Denney et al. (2004), Denney et al. (2005) and Bodling et al. (2006). Namely, our primary aim was to further demonstrate that speed of information processing is the most prominent feature of the cognitive impairment occurring in MS patients and that this deficit is not attributable to ancillary sensory and motor impairments. The present study assessed speed of information processing in groups of MS patients and healthy controls, using measures that employed both explicit and covert timing methods. This variation was employed to allow for examination of the influence of timing awareness on subjects' performance. The covert tests emphasized accuracy of responding and the assessment of time-to-solution was accomplished "behind the scenes," whereas the explicit tests represented the measures of rapid serial processing used in prior studies and were structured in such a way that speed was the obvious

feature of performance being evaluated. As in Demaree et al. (1999) and Denney et al. (2004), we proposed that MS patients and controls would achieve similar levels of accuracy on the covert measures, but that the patients would show slower speed of information processing on both the covert and explicit measures.

The five tests utilized in the present study included two explicit measures and three covert measures of information processing speed. Both of the explicit measures (the Stroop and the PNT) as well as one of the covert measures (the TOL) have been used in previous research by Denney and his colleagues. Two new covert measures were designed for the present study, the Rotated Figures Test (RFT) and the Remote Associates Test (RAT). The Stroop test (Stroop, 1935), originally designed in paper form, was formulated for computerized administration. The test is composed of three tasks in which subjects were timed while 1) reading one of four color words, 2) naming one of four colors displayed on the screen as “XXXX” that correspond to the four color words, and 3) naming the color of the letters used to print one of four color words displayed on the screen. All the stimuli used in the third trial were incongruent (i.e., the word “BLUE” printed in red letters). In each trial, subjects were told to complete as many stimuli as possible in the allotted time of 60 seconds.

The Picture Naming Test (Bodling et al., 2006) was also administered on a computer and required subjects to name pictures presented on the screen. As described earlier, the test presents four different pictures repeatedly in the first and third trials and many different pictures in the second and fourth trials. In addition, in the first and second trials, the pictures are presented in the same position in the center of the computer screen, while in the third and fourth trials the pictures are shown in

one of nine different locations on the screen. Like the Stroop test, the PNT is also an explicitly-timed test, in that subjects were challenged to name as many pictures as possible before time has expired.

The Tower of London (Krikorian, Bartok, & Gay, 1994) was designed to distinguish impairments in planning processes that tend to be associated with specific damage in the frontal lobe, a part of the brain often affected by MS lesions. The test involves a series of problems in which subjects must move three different colored discs on three pegs to match a pattern appearing on the computer screen. The problems become progressively more difficult with regard to the number of moves required for successful solution, thus requiring more protracted planning on the part of the subject. The TOL was one of the tests that utilized covert timing measures, allowing subjects to focus on accuracy rather than the speed with which they are arriving at solutions to the problems. Unbeknownst to the subject, the computer records the time between the initial presentation of each problem and the subject's first move toward solving the problem (i.e., initial planning time). Denney et al. (2004) has shown that initial planning times lengthen as the problems become more difficult and are more protracted for MS patients than for controls.

The Rotated Figures Test (Shepard & Metzler, 1971) makes use of a series of paired 3-dimensional geometric figures that are either identical to or slightly different from one another. One figure is rotated to a varying degree compared to the other figure; the degree of rotation ranges from 20 to 180 degrees. The amount of time required by subjects to determine whether the two figures are identical or different is recorded as a function of the degree of rotation between the figures. The RFT

measures these times covertly while emphasizing accuracy rather than speed of responding. The degree of difference in rotation between the two objects and the time required by the subjects to “mentally rotate” the objects have been shown to be positively correlated.

The Remote Associates Test (Mednick, 1962; Mednick & Mednick, 1967) entails the presentation of three words that are related in some qualitative manner (e.g., head, mouse, cottage) and requires subjects to provide a fourth word (“cheese”) which is associated with the previous three. This processing task also uses covert timing. The computer records the amount of time that elapses before the subject responds with an associate to link the three stimulus words.

The order of administration of the five tests in the present study was important. The covert tests preceded the explicit tests so that the central focus of the study upon speed of performance was not apparent to subjects until after the covert tests had been administered. Because of their novelty as covert measures of information processing speed that also permitted assessment of performance accuracy, we were particularly interested in patients’ performance on the RFT, RAT, and TOL. The Stroop and PNT, as well as the TOL, were included to demonstrate the primacy of deficits in information processing speed and to link the present study with our preceding investigations. The principal hypothesis was that the MS patients and healthy controls would differ from the controls in terms of the speed with which they performed the explicit and covert tests, though not necessarily in the accuracy of their performance on the covert tests.

Research Design and Methods

Subjects

Subjects included 40 patients with clinically-definite MS (as described by McDonald et al., 2001) and 40 healthy control subjects. The MS patients were recruited by Dr. Sharon Lynch of the Department of Neurology at the University of Kansas Medical Center and met the following inclusion criteria: 1) a clinically definite diagnosis of MS with a minimum of 6 months duration; 2) a disease pattern consistent with either relapsing-remitting or secondary progressive subtypes of MS; 3) between the ages of 18 and 60, and; 4) based on Dr. Lynch's clinical judgment, possessed the cognitive ability to understand what was involved in the study, provide informed consent, and complete the measures to the best of their abilities.

Furthermore, any of the following exclusionary criteria disqualified a prospective subject from participation in the study: 1) presence of any neurological disorder (controls) or any such disorder other than MS (patients), 2) past or present alcohol or substance abuse, 3) severe visual impairment exceeding 20/50 or color-blindness, 4) current use of narcotics or benzodiazepines, and 5) any severe worsening of MS symptoms in the previous 30 days (patients). These exclusionary criteria were implemented to reduce the possibility of extraneous variables influencing the results of the study.

Patients ranged in age from 20 to 60 with a mean age of 44.82 (SD=10.2), and 36 of 40 were female. Twenty five patients had diagnoses of relapsing-remitting MS and 15 had secondary-progressive type. Expanded Disability Status Score (EDSS; Kurtzke, 1983) ratings ranged from 0 to 7.5, with a mean rating of 3.3 (SD=2.0) and a

median of 2.5. Age at MS diagnosis ranged from 12 to 53 with an average age of 34.3 (SD=10.0), while the length of patients' MS diagnosis ranged between 2 and 32 years with a mean length of 10.6 years (SD=6.6).

The healthy control subjects were recruited from the general Lawrence community and the St. Louis, Missouri metropolitan area. They had no major or chronic medical problems and were following no continuous medication regimen. Like the MS group, 36 of the 40 healthy controls were female. These subjects ranged in age from 25 to 59 with an average age of 40.3 (SD=10.7).

Measures

The Rotated Figures Test (RFT; Shepard & Metzler, 1971). This test was formatted for computer administration, and consisted of twelve practice items and 54 actual test items. For each item, two images consisting of blocks arranged in geometric shapes were pictured on the screen. The images were either identical or mirror images of one another, and were rotated relative to each other between 20 and 180 degrees. The subject was asked to respond whether the two block figures were the same or different. The experimenter recorded the subject's response using one of two computer keys. The time required by the subject to respond to each item, as well as the accuracy of the subject's response, were recorded for each item.

The Remote Associates Test (RAT; Mednick & Mednick, 1967). The computerized version of this test consisted of 20 items. Each item presented a group of three words and the subject was asked to provide a fourth word that was related to the previous three (i.e., "DRIBBLE", "TAKE", "STUNT"; answer: "DOUBLE"). Subjects were instructed to take as long as necessary and as soon as they thought of a

word to say it aloud. The experimenter then pressed a button on the computer to stop a timer that had been covertly measuring the subject's latency of response. The experimenter entered the word given by the subject. If the subject was unable to think of a word, he or she had the option to "pass," and the item was recorded as skipped. The subject's score corresponded to the total number of correct responses as well as the length of time required to respond to each item.

The Tower of London (TOL; Krikorian, Bartok, & Gay, 1994). The computerized format of this measure assessing planning and problem-solving ability was composed of twelve problems. Subjects were asked to move three colored "disks" situated on three "pegs" to reproduce the arrangement in a model displayed at the bottom of the screen. Throughout the test, problems became more challenging by requiring an increasing number of moves for solution. The 12 problems ranged from 2-move problems to 5-move problems. The subject was allowed up to three attempts to solve each problem. Subjects dictated the moves they wished to make to the experimenter, who manually operated the computer. Total point score was derived from the number of problems correctly solved and the trial on which the correct solution occurred; this point score was recorded by the computer. The computer also recorded the "initial planning time," the amount of time between the initial presentation of the problem and the point at which the subject initiated his/her first move.

The Stroop Color-Word Interference test (Stroop; Golden, 1994). Though reformulated for computerized administration, the test was organized in similar fashion to the original Stroop task. Subjects completed three trials, before each of

which they were provided with eight practice items. In the first trial (word reading, WR), the subject was presented with a series of four color words (RED, BLUE, GREEN, YELLOW) and was asked to read each word as it appeared on the screen. In the second trial (color naming, CN), five colored X's appeared on the screen and subjects were asked to name the color of the X's. In the third trial (color-word naming, SW), subjects were presented with the same four color words used in the first trial, but the letters of the word were printed in a conflicting color. The subject was asked to name the color of the letters. Subjects were instructed to work as fast as possible while maintaining accuracy, and to avoid stopping to correct themselves if they happened to make a mistake. As soon as the subject responded to each item, the experimenter pressed a button on the keyboard and the next item in the series was displayed. Subjects' scores corresponded to the number of items completed during each 60-second trial. Relative interference was also assessed. This measure indicates the degree to which subjects' responses during the third trial were hampered by the incongruity between the words and the color of the printing. Interference is commonly measured by simply computing the difference between subjects' performance in the second (CN) and third (SW) trials. Relative interference is determined by dividing this simple difference score by the subject's score on the color naming (CN) trial. Recent work by Denney and Lynch (2008) has shown that the resultant relative interference measure is a superior measure of the color-word interference effect that was the original objective of Stroop's test.

The Picture Naming Test (PNT; Bodling et al. 2006). This computerized measure presented subjects with a series of achromatic pictures of readily

recognizable objects and animals. The test was composed of four trials, with a set of eight practice items presented before the beginning of each trial. Subjects were asked to respond by naming the picture as quickly as possible while maintaining accuracy, and the experimenter pressed a button on the keyboard to proceed to the next picture. In the first trial (PNC1), four different pictures were displayed in the center of the screen in random order. In the second trial (PNC2), a variety of different pictures were displayed in the center of the screen, with no repeated pictures. In the third trial (PND1), the same four pictures from trial one were repeated, but instead of being presented only in the center of the computer screen, they appeared in one of nine different locations on the screen. In the fourth and final trial (PND2), a variety of different pictures were displayed in the nine locations on the screen. The computer tallied the number of items completed during each of the four 60-second trials.

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). This is a self-report measure consisting of nine items intended to assess the degree of fatigue the subject had experienced over the previous week. The questions are answered on a scale from 1 (“strongly disagree”) to 7 (“strongly agree”), with a higher total score indicating greater levels of fatigue. Krupp et al. (1989) asserted the primacy of fatigue as a presenting symptom among individuals with MS.

Determination of fatigue levels among individuals in this population is important for valid assessment of cognitive functioning.

The Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977). The CES-D is a self-report measure of depressive symptoms designed for use in the general population, though it is acceptable for use in clinical samples. This test

includes 20 mood-related statements and subjects are asked to rate their level of agreement with each item on a scale ranging from 1 (“rarely or none of the time”) to 4 (“most or all of the time”). Recent findings have suggested a relationship between depression and slowed information processing speed (Arnett, Higginson, & Randolph, 2001), thus necessitating examination of this factor.

Procedure

Recruitment of the MS sample was largely undertaken by Dr. Sharon Lynch, who introduced and briefly explained the study to her patients during their regular appointments at the University of Kansas MS Clinic. If the patient agreed to participate, Dr. Lynch then examined the patient in terms of appropriateness and capability for participation. This examination included the administration of the EDSS (Kurtzke, 1983). The EDSS rating is assigned on the basis of the patient’s status with respect to eight functional systems typically affected by MS: pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, cerebral, and other. Possible scores on the EDSS range from 0 (normal, no impairment) to 10 (death due to MS). Special consideration was given to the rating assigned to the brain stem functional system due to its relevance to speed of information processing.

Subjects of both samples were then met by either the researcher or her assistant at the KU Medical Center, or were contacted by telephone in order to arrange an appropriate time to complete the study. Appointments were arranged to take place at the most convenient, appropriate location for subjects, whether in their homes or at the KU Medical Center. The subjects were given an informed consent document to read and sign. The experimenter reviewed this consent statement and

ensured subjects fully understood the requirements of the study. Subjects were also informed of their right to withdraw from participation at any time. During the testing appointment, subjects were asked to complete the fatigue and depression questionnaires, and the five tests were administered in the following order: RFT, RAT, TOL, Stroop, and PNT. Administration of fatigue and depression questionnaires was counterbalanced for presentation either before or after the cognitive battery. The full testing procedure took approximately 60 to 75 minutes.

Results

The demographic variables (gender, age, education) and the scores for depression and fatigue for the MS and control groups are summarized in Table 1. Differences between groups were examined using either a chi-square analysis (gender) or a t test for independent samples (other variables). The ratio of males to females did not differ between the groups (chi-square = .00, $df = 1$, $p = 1.000$; Fisher's exact test: $p = 1.00$). A near significant between-group difference was detected with regard to age ($t = 1.96$, $df = 78$, $p = .054$). Education was rated on a scale from 1 to 5, where 1 indicated "high school education", 2 indicated "some college", 3 indicated "completed four-year degree", 4 indicated "some graduate school", and 5 indicated "completed advanced graduate degree". The groups differed significantly in education ($t = -4.22$, $df = 78$, $p < .001$). Because of these differences, age and education were used as covariates in the principal analyses that were applied to the cognitive variables.

Level of depression was significantly greater in the MS group than in the control group ($t = 3.03$, $df = 78$, $p = .003$). The MS group also reported higher levels

of fatigue than the control group ($t = 6.64$, $df = 78$, $p < .001$). Both depression and fatigue could potentially influence speed and accuracy of responding on the cognitive items, and therefore these variables were also included as covariates in the analyses of the cognitive variables. It is important to note, however, that the between-group differences in age and education are different in nature from those involving depression and fatigue. Differences in age and education occurred simply as a result of sampling; the MS patients who agreed to participate in the study were somewhat older and had less education than the controls. On the other hand, the differences involving depression and fatigue are endemic to the two populations. MS patients typically have higher scores on questionnaires assessing these two variables than do healthy controls.

In order to preserve this distinction when analyzing the data from the cognitive tests, two covariance models were employed. In the first, age and education were entered as covariates. The first model was considered the primary model for determining whether patients differed from the controls on the cognitive measure in question, with age and education level statistically controlled. In the second model, all four variables (age, education, depression scores, and fatigue scores) were used as covariates. The importance of this second model lay in its being able to determine whether the difference between patients and controls on the cognitive measure in question persisted or might be more readily attributed to the substantially greater levels of depression and fatigue seen in MS patients.

Table 1: Comparison of MS Patients and Healthy Controls on Demographics and Covariate Measures

Measure		MS Patients	Controls	Chi square or t	p
Gender (M/F)		4/36	4/36	1.00	1.000
Age	M (S.D.)	44.82 (10.18)	40.25 (10.70)	1.96	.054
Education	M (S.D.)	2.55 (1.03)	3.63 (1.23)	-4.22	< .001
Depression	M (S.D.)	11.48 (8.99)	6.38 (5.64)	3.03	.003
Fatigue	M (S.D.)	32.74 (15.91)	15.70 (6.39)	6.64	< .001

Explicit measures of information processing speed were derived from the Stroop and the PNT. With respect to the Stroop, these measures included the scores on each of the three separate trials of the Stroop, the combined score for word reading and color naming (WR+CN). The relative interference score ($[(CN-SW/CN)*100]$) from the Stroop was also analyzed, although as Denney and Lynch (2008) have recently shown, this is not actually a measure of information processing speed. With respect to the PNT, the measures of information processing speed included the scores on each of the four trials and the average of these four scores. Finally the overall average across all seven trials (the three trials of the Stroop and the four trials of the PNT) was also included for examination.

Table 2 presents the unadjusted means and standard deviations for the patient and control groups on each of these measures and summarizes the results for (a) analyses of covariance applied to each measure with age and education serving as covariates (Model 1) and (b) analyses of covariance applied to each measure with age, education, depression, and fatigue serving as covariates (Model 2).

When I performed the analysis of covariance using Model 1, significant differences were evident between MS patients and controls on virtually every measure except for interference. Furthermore, the differences between patients and controls on every one of these other variables were significant at $p < .001$, and likewise, the effect sizes (partial eta-square) were large, ranging from .20 to .47. There was a significant covariate (age) for the SW scores ($p = .034$) and the interference measure ($p = .012$). When I performed the analyses of covariance using with Model 2, similar results were demonstrated with regard to differences in

processing speed between patients and controls. With the exception of the interference score on the Stroop Test, all measures were significant at $p \leq .001$. In this second model, age and depression were significant covariates for several of the measures. For age, these included: color-word naming ($p = .024$) and interference ($p = .020$), and for depression, these included color-naming ($p = .015$), word-reading plus color-naming ($p = .042$), and trial 3 on the PNT (PND1: repeated, distributed pictures) ($p = .029$).

Table 2: Comparisons between MS Patients and Control on Explicit Measures of Information Processing Speed

Cognitive Measure	Patients Mean ^a (SD)	Controls Mean ^a (SD)	Model 1 ^b			Model 2 ^c		
			F	p	η^2 ^d	F	p	η^2 ^d
Word Reading (WR)	73.05 (7.78)	88.28 (7.76)	53.55	< .001	.413	28.71	< .001	.280
Color Naming (CN)	60.68 (7.95)	74.35 (5.46)	58.21	< .001	.434	39.67	< .001	.349
Color-Word Naming (SW)	43.2 (8.41)	53.05 (6.95)	19.30	< .001	.203	10.89	.001	.128
WR & CN	133.73 (14.75)	162.63 (11.82)	66.42	< .001	.466	40.10	< .001	.351
Relative Interference (IntB)	28.83 (9.36)	28.63 (7.78)	.54	.464	.007	.76	.386	.010
Trial 1 (PNC1)	60.23 (7.01)	72.03 (5.64)	55.80	< .001	.423	28.83	< .001	.280
Trial 2 (PNC2)	42.95 (8.93)	52.95 (5.13)	34.01	< .001	.309	18.06	< .001	.196
Trial 3 (PND1)	56.10 (6.61)	67.75 (4.76)	59.83	< .001	.440	30.35	< .001	.291
Trial 4 (PND2)	41.18 (8.31)	52.58 (4.58)	52.24	< .001	.407	25.96	< .001	.260
PNT avg	50.11 (7.09)	61.40 (4.37)	59.68	< .001	.440	30.69	< .001	.293
RSP avg	53.91 (6.78)	65.90 (4.35)	66.05	< .001	.465	36.52	< .001	.330

^a Unadjusted means are reported for patients and controls

^b Model 1: analysis of covariance with age and education entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 76 degrees of freedom.

^c Model 2: analysis of covariance with age, education, depression, and fatigue entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 74 degrees of freedom.

^d η^2 = partial eta-square

The next set of analyses pertained to differences between MS patients and controls in response latencies on the covert measures of speeded information processing. Two of these cognitive tests, the TOL and RFT, involved items that varied systematically in their degree of difficulty. To examine the interaction between groups and problem difficulty on these tests, I performed mixed factorial analyses of covariance with age and education entered as covariates. For the TOL, the 2 (group) x 4 (moves) mixed factorial analysis indicated a significant main effect for group ($F = 7.76$, $df = 1\&76$, $p = .007$, $\eta^2 = .09$), resulting from the fact that MS patients responded more slowly than controls. This main effect will be discussed in greater detail in a later section. A significant main effect for moves was also demonstrated ($F = 58.82$, $df = 3\&74$, $p < .001$, $\eta^2 = .71$). The interaction, however, was not significant ($F = 1.51$, $df = 3\&74$, $p = .220$, $\eta^2 = .06$). This relationship is shown in Figure 1. For the RFT, a 2 (group) x 6 (rotation) mixed factorial analysis of covariance was performed on the mean response latencies for correct items at each of the six degrees of rotation with age and education included as covariates. This analysis showed there was a significant main effect for group ($F = 10.41$, $df = 1\&76$, $p = .002$, $\eta^2 = .120$). A significant main effect for rotation was also found ($F = 33.00$, $df = 5\&72$, $p < .001$, $\eta^2 = .696$). Results indicated that there were no significant interactions ($F = .70$, $df = 3\&74$, $p = .626$, $\eta^2 = .05$). This relationship is shown in Figure 2.

Figure 1: Initial Planning Times by Number of Moves per Problem (Tower of London)

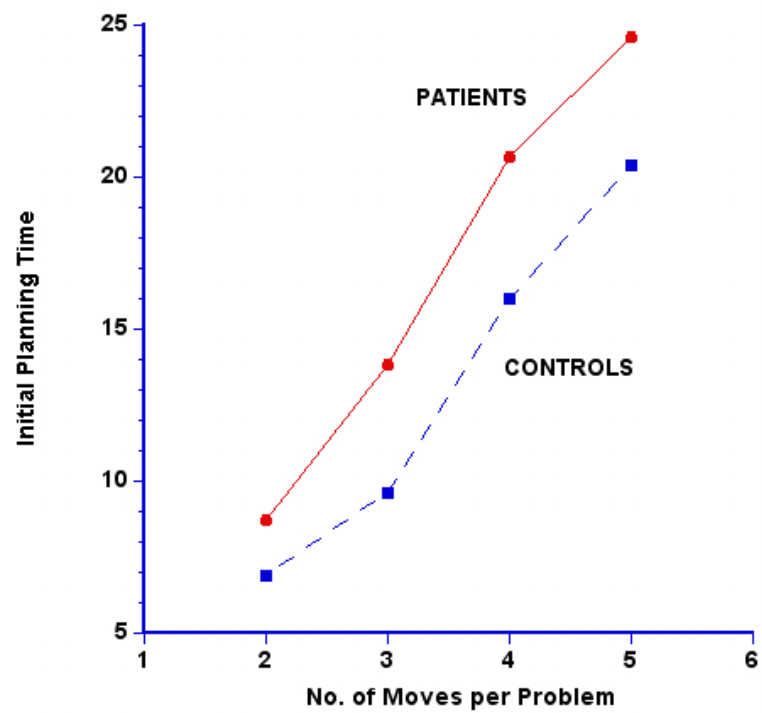
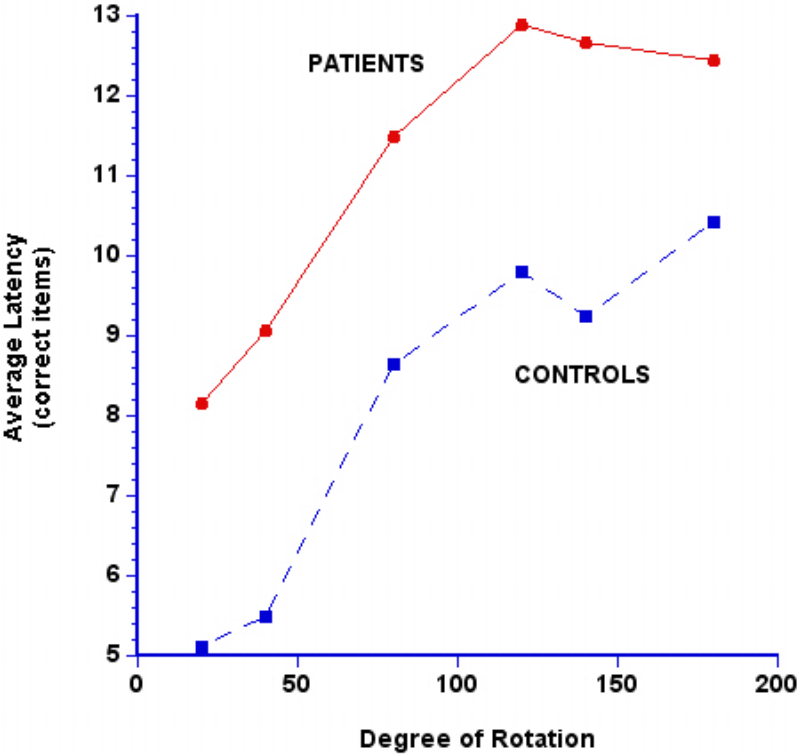


Figure 2: Latencies for Responses to Correct Items by Degree of Rotation (Rotated Figures Test)



Because the interaction between group and degree of problem difficulty was not significant in either of the preceding mixed factorial analyses, I focused on the overall differences between MS patients and controls on speeded information processing for these covertly-timed measures. Differences between MS patients and controls on the following three variables were examined using univariate analyses of covariance: (a) mean latencies for correct items on the RFT combined across all rotations, (b) mean planning times for first trials combined across all problems on the TOL, and (c) mean latencies for correct answers on the RAT. The first model included age and education as covariates, while the second model added fatigue and depression as additional covariates. Results from these univariate analyses are shown in Table 3. In the first model, patients responded with significantly longer latencies than controls on correct items on the RFT, initial planning times on the TOL, and correctly answered items on the RAT. In the second model, the difference in mean latencies for correctly-answered items on the RFT was nearly significant ($p = .059$), and the other two covert measures of processing speed were not significant.

Table 3: Comparisons between MS Patients and Control on Covert Measures of Information Processing Speed

Cognitive Measure	Patients Mean ^a (SD)	Controls Mean ^a (SD)	Model 1 ^b			Model 2 ^c		
			F	p	η^2 ^d	F	p	η^2 ^d
RFT Combined Mean Latencies (Correct)	10.88 (4.31)	8.07 (3.09)	11.66	.001	.133	3.68	.059	.047
TOL Combined Mean Planning Time (First Trials)	18.22 (7.51)	14.86 (5.35)	6.97	.010	.084	1.53	.220	.020
RAT Mean Latencies (Correct)	13.02 (4.81)	10.58 (4.18)	6.37	.014	.077	.79	.378	.01

^a Unadjusted means are reported for patients and controls

^b Model 1: analysis of covariance with age and education entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 76 degrees of freedom.

^c Model 2: analysis of covariance with age, education, depression, and fatigue entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 74 degrees of freedom.

^d η^2 = partial eta-square

I also performed univariate analyses of covariance to assess differences between groups with regard to accuracy of responding on the covert measures of information processing speed. MS patients and controls were compared in terms of (1) total items correct on the RFT, (2) total items correct on the RAT, and (3) total point score on the TOL. Similar to previous analyses, I included age and education as covariates in Model 1, and included fatigue and depression as additional covariates in Model 2. Results for these accuracy measures are presented in Table 4. In terms of the first model, MS patients displayed significantly less accuracy than controls on the RFT and the TOL. No significant between-group difference in accuracy was evident on the RAT. In the second model, a significant difference in accuracy was found only on the RFT, with MS patients showing lower accuracy than controls.

Table 4: Comparisons of Accuracy between MS Patients and Control on Covert Measures of Information Processing Speed

Cognitive Measure	Patients Mean ^a (SD)	Controls Mean ^a (SD)	Model 1 ^b			Model 2 ^c		
			F	p	η^2 ^d	F	p	η^2 ^d
RFT Total Score	40.95 (6.73)	46.43 (6.25)	10.20	.002	.118	6.18	.015	.077
TOL Total Score	31.65 (3.85)	33.00 (1.97)	4.75	.032	.059	1.40	.240	.019
RAT Total Score	9.38 (3.47)	10.45 (2.85)	.96	.327	.013	.06	.806	.001

^a Unadjusted means are reported for patients and controls

^b Model 1: analysis of covariance with age and education entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 76 degrees of freedom.

^c Model 2: analysis of covariance with age, education, depression, and fatigue entered as covariates. The values reported for F, p, and η^2 are for the main effect comparison between patients and controls and are based on 1 and 74 degrees of freedom.

^d η^2 = partial eta-square

I also performed a series of correlations to examine potential relationships between the cognitive measures and demographic or disease-related variables among MS patients. I was particularly interested in the extent to which age, education, age at first diagnosis of MS, duration of MS, EDSS score, depression, and fatigue were related to performance on the array of cognitive measures. A full presentation of these correlations may be found in Table 5. Neither age nor age at MS diagnosis was significantly correlated with any of the explicit or covert speeded information processing measures. EDSS scores were significantly correlated with only one explicit measure, the mean scores on the PNT. Education and fatigue were significantly correlated only with covertly-timed measures. Education and fatigue were both correlated with initial planning times on the TOL. Education was also correlated with total point score on the TOL. Fatigue was correlated with the mean latencies for correctly-answered items on the RFT. Length of MS diagnosis and depression scores were significantly correlated with several of the explicitly- and covertly-timed measures.

Table 5: Correlations between Demographic Variables and Cognitive Measure Performance for MS Patients

	Cognitive measure	Age	Education	Age at MS Diagnosis	Length of MS Diagnosis	EDSS score ^{1, 2}	Depression score	Fatigue score
Explicitly-timed measures	Word reading (WR)	-.079	-.064	.132	-.320(*)	-.268	-.324(*)	-.170
	Color naming (CN)	.067	-.146	.260	-.261	-.278	-.387(*)	-.101
	Color-word naming (SW)	-.164	-.113	.073	-.351(*)	-.230	-.245	-.115
	PNT mean scores	-.081	-.224	.230	-.457(**)	.359(*)	-.302	-.225
	Combined Stroop & PNT mean scores	-.079	-.189	.216	-.433(**)	-.318	-.342(*)	-.203
	Combined WR & CN	-.005	-.112	.207	-.308	-.291	-.379(*)	-.145
	Relative interference (Stroop)	.309	.013	.158	.237	-.070	-.035	.054
	TOL mean planning time (first trials)	.241	.322(*)	.104	.208	.271	.364(*)	.386(*)
	RFT combined mean latency (correct)	.198	.307	-.091	.435(**)	.074	-.096	.383(*)
	Covertly-timed measures	RAT mean latency (correct)	.161	-.025	-.002	.242	.312	.167
TOL total point score		.226	-.349(*)	.185	.067	-.287	-.126	-.140
RFT total score		.033	-.136	.212	-.263	-.211	-.038	-.109
RAT total score		.049	.012	.115	-.080	-.194	-.186	-.077

** Correlation is significant at the $p < .01$ level (2-sided).

* Correlation is significant at the $p < .05$ level (2-sided).

¹ Spearman correlation.

² EDSS scores were available for 32 of the 40 MS patients.

Finally, I performed a series of correlations across all subjects to examine relationships between explicit and covert measure performance. For the explicit measures, I examined scores for word-reading plus color-naming (WR & CN) and average number of responses across all seven trials for the Stroop Test and the PNT. For the covert measures, I included overall mean planning times for problems on the TOL, mean latencies for correct items on the RFT, and mean latencies for correct items on the RAT. These correlations are presented in Table 6. Mean latencies on the RFT were correlated ($p < .05$) with both of the explicit measures, and mean latencies on the RAT were correlated ($p < .01$) with the combined latencies for Stroop and PNT trials. A significant relationship ($p < .001$) was found between the two explicit measures. In addition, all three covert measures were inter-correlated ($p < .001$).

Table 6: Correlations between Explicit and Covert Measures of Information Processing Speed

	Combined WR & CN	Combined Stroop & PNT mean scores
TOL mean planning time (first trials)	-.163	-.173
RFT combined mean latency (correct)	-.224(*)	-.278(*)
RAT mean latency (correct)	-.219	-.300(**)

** Correlation is significant at the $p < .01$ level (2-sided).

* Correlation is significant at $p < .05$ level (2-sided).

Discussion

The present study examined information processing speed in patients with two subtypes of MS, and compared their performance with that of healthy control subjects. Due to consistent findings implicating information processing speed as the primary cognitive deficit in MS (Denney et al., 2004, 2005; Bodling et al., 2006), my aim was to replicate these findings using a wider variety of measures. The main hypothesis was that MS patients would exhibit significantly slower information processing speed on both explicitly- and covertly-timed measures. Both explicit and covert measures of information processing speed were examined in order to assess the influence of timing awareness on subjects' performance. I also hypothesized that accuracy of responding would not differ significantly between MS patients and controls. An interaction between subject type (MS patient or healthy control) and problem difficulty was expected, such that as problems increased in difficulty MS patients would respond with progressively greater latency than controls. The RFT and TOL allowed for concurrent examination of information processing speed across items of variable difficulty. I controlled for the effects of age, education, fatigue, and depression when performing the analyses due to the potential influence of these variables on the cognitive results.

The hypothesis that MS patients and healthy controls would differ with regard to information processing speed was supported. Robust differences between patients and controls were found on explicit measures of information processing speed with effect sizes (partial eta square) ranging between .233 and .466 after adjusting for differences in age and education. Differences in response latencies on all these

measures remained highly significant (partial eta square = .128 to .351) after additionally controlling for fatigue and depression scores, which are usually higher in MS patients as a consequence of their disease (Sheth, 2005). The absence of age and education effects on these measures suggests that performance differences are not an artifact of education levels or slowing due to normal aging. It has been suggested that depression may underlie information processing speed deficits among MS patients (e.g. Arnett et al., 2001), but our findings indicate increased latencies exhibited by MS patients are more likely a result of a primary cognitive effect. Fatigue, another prominent symptom associated with MS (Krupp et al., 1989), also failed to significantly influence deficits in information processing speed. These findings support previous research (Demaree et al, 1999; Denney et al, 2004, 2005; Bodling et al., 2006) which implicated speed of information processing as the primary cognitive deficit among individuals with MS. The present findings also suggest these delays are not a consequence of variables such as age and depression.

Significant differences between MS patients and healthy controls were also found on covert measures of information processing speed, although these differences were less robust than on the explicit measures. Significant differences in latencies of response were seen for all three tests after age and education were statistically controlled ($p < .05$, partial eta square = .077 to .133), indicating that the differences were not due to variation in education or aging. However, differences between MS patients and healthy controls were no longer significant when also controlling for the influence of depression and fatigue ($p = .059$ to .323, partial eta square = .010 to .047). These findings failed to replicate those of Denney et al. (2004), who used the TOL

and found significant differences in speed of information processing between MS patients and controls after statistically controlling for these variables. Our findings suggest that the covertly-timed measures used in this battery may be more sensitive to depression and fatigue status than the explicit measures of processing speed. Fatigue and depression may therefore be more influential when the tests of processing speed involve more complex mental operations. However, it is important to note that neither the RAT nor the RFT have been used in previous research with MS patients, so replication of these findings will be necessary before a conclusive statement can be made.

The hypothesis that MS patients and controls would not differ in terms of accuracy was partially supported. MS patients were significantly less accurate than controls on the RFT and the TOL but achieved similar levels of accuracy on the RAT when age and education were statistically controlled. When depression and fatigue scores were also controlled, only on the RFT were the MS patients significantly less accurate in their responses. In other words, controls displayed higher accuracy levels than MS patients when adjusting for age and education, but when the influence from all four variables was removed, the two groups exhibited similar accuracy on two of three measures. Denney et al. (2004, 2005) and Demaree et al. (1999) reported that when subjects were allowed unlimited time to complete measures of cognitive processing, response accuracy did not differ between MS patients and healthy controls. Denney et al. (2004, 2005) used the TOL and similar levels of accuracy were achieved between patients and controls when controlling for age, education, depression, and fatigue. The present study was the first to use a computer-adapted

version of the RFT with MS patients. Contrary to expectation, healthy controls had more correct answers than MS patients after controlling for age, education, depression, and fatigue ($p=.015$, partial eta square=.077). One explanation could be that the comparatively greater complexity and cognitive load of these measures, especially the RFT and TOL, which employed problems of variable difficulty, may have influenced accuracy of MS patients' responses. The RAT did not entail problems of increasing difficulty, and accuracy levels of the two groups did not differ significantly. Differences between patients and controls in age and education level may have contributed to divergent accuracy of responses on the RFT. Also, fatigue and depression are notable symptoms among MS patients (Sheth, 2005), and it is possible that the combination of variable problem difficulty and higher levels of fatigue and depression led to these differences in accuracy.

Relationships between disease and demographic variables for the MS patients and their performance on the cognitive measures were also examined. There were no significant correlations between cognitive measure performance and either age or age at MS diagnosis, indicating that latency and accuracy scores were likely not impacted by cognitive decline that accompanies normal aging. Education was significantly correlated with accuracy and latency measures on the TOL, but our analyses showed that latencies on the TOL were significantly different between groups even after controlling for education. Total point score on the TOL was different between groups after adjusting for age and education, but was no longer significant when controlling for all four variables (age, education, fatigue and depression). These results indicate that in this study education level may have influenced accuracy on the TOL.

Previous studies (Denney et al., 2004, 2005) have not reported accuracy differences between MS patients and controls, so the present results may be specific to this sample. Length of time since MS diagnosis, which may be indicative of increased impairment as a consequence of disease progression over time, was significantly correlated with several measures of processing speed. These relationships suggest increasing impairment from MS contributed to slower information processing speed across a variety of measures. Depression and fatigue were correlated with some of the processing speed measures, signaling that these patient variables could negatively influence cognitive processing speed. This finding was expected, as fatigue and depression are prevalent among individuals with MS and may negatively influence cognitive processing (e.g. Arnett et al., 2001), though the role of fatigue in processing speed is less clear (Denney et al., 2004). However, these variables did not significantly influence most measures, indicating that their influence on cognitive function is not the chief determinant of delayed information processing speed. Inter-correlations were also found between performances on covert ($p < .001$) and explicit ($p < .001$) measures of information processing speed. Furthermore, two of three covert measures were significantly correlated ($p \leq .05$) with explicit measures of processing speed. Relationships between performance on explicit and covert measures across subjects suggest these measures assessed similar cognitive properties.

A surprising finding from this study was that no significant interactions were found between group and problem difficulty. Namely, as degree of rotation (on the RFT) or number of moves per problem (on the TOL) increased, MS patients did not

require progressively more time to respond to items than controls. Due to the nature of cognitive deficit in MS, we expected processing speed to be increasingly delayed as greater levels of cognitive processing were needed to solve a problem. Using the TOL, Denney et al. (2004, 2005) demonstrated that as greater number of moves were required to correctly solve the problems, initial planning times for controls gradually increased while MS patients' planning times increased exponentially. In our study, MS patients exhibited greater deficits in information processing speed than controls, but delay of responding among the two groups increased in a parallel fashion. One explanation for this result could be that the difficult nature of these tests required an inherent baseline level of cognitive functioning. Higher functioning MS patients may have self-selected to participate and the tests used may have been less sensitive to subtle cognitive deficits. Such an explanation could also explain the less robust between-group differences found on covert measures compared to explicit measures of processing speed: differences between the MS patients and healthy controls who chose to participate may have been less apparent on the covert measures of speeded information processing. As previously stated, the RFT has not been used in a similar manner so a conclusive statement whether other cognitive variables may have influenced these results can not be made.

Overall, results from comparison of MS patients and healthy control subjects on a variety of cognitive tests supported previous findings which suggested that speed of information processing is among the primary cognitive deficits in MS. Strong effects were evident on explicit measures of speeded information processing, even after statistically adjusting for the influence of age, education, depression, and

fatigue. Significant differences were also apparent on the more complex covert indices of speeded information processing, though these results were less robust when accounting for differences in fatigue and depression. Previous studies (Demaree et al., 1999; Denney et al, 2004, 2005; Bodling et al., 2006) demonstrated the primacy of information processing speed after removing the influence of confounding variables, and indicated these findings were not a consequence of ancillary sensory or motor impairments (Bodling et al., 2006). Slowed processing speed is certainly not the only cognitive feature of MS which contributes to impairment, as locations of individual lesions will inevitably lead to variation in particular deficits and symptom presentation among individuals with this disease (Rao, 1995). However, recent findings reported that tests of information processing were especially strong predictors of long-term cognitive decline (Bergendal, Fredrikson, & Almkvist, 2007; Denney, Lynch, & Parmenter, 2007), which may offer support for the primacy of this cognitive deficit in MS. Combined with previous findings, the present study offers further evidence that information processing speed is a significant cognitive impairment in MS.

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Appendix A

SUBJECT NO. _____

DATE _____

MOOD SCALE

Directions: Below is a list of ways you might feel or behave at times. For each statement, please rate how often you have felt this way during the past week.

- 1: Rarely or none of the time (less than 1 day)
- 2: Some or a little of the time (1-2 days)
- 3: Occasionally or a moderate amount of the time (3-4 days)
- 4: Most or all of the time (5-7 days)

During the past week:

- _____ 1. I was bothered by things that usually don't bother me.
- _____ 2. I did not feel like eating; my appetite was poor.
- _____ 3. I felt that I could not shake off the blues even with the help of my family and friends.
- _____ 4. I felt that I was just as good as other people.
- _____ 5. I had trouble keeping my mind on what I was doing.
- _____ 6. I felt depressed.
- _____ 7. I felt that every thing I did was an effort.
- _____ 8. I felt hopeful about the future.
- _____ 9. I thought my life had been a failure.
- _____ 10. I felt fearful.
- _____ 11. My sleep was restless.
- _____ 12. I was happy.
- _____ 13. I talked less than usual.
- _____ 14. I felt lonely.
- _____ 15. People were unfriendly.
- _____ 16. I enjoyed life.
- _____ 17. I had crying spells.
- _____ 18. I felt sad.
- _____ 19. I felt that people disliked me.
- _____ 20. I could not "get going."

Appendix B

SUBJECT NO. _____

DATE _____

FATIGUE SCALE

Directions: The following statements pertain to your experience of fatigue **during the past week, including today.**

Choose a number from 1 to 7 to indicate how much you agree with each of these statements -- where

1 indicates that you STRONGLY DISAGREE and

7 indicates that you STRONGLY AGREE.

[STRONGLY DISAGREE] 1 2 3 4 5 6 7 [STRONGLY AGREE]

During the past week:

_____ 1. My motivation was lower because I was fatigued.

_____ 2. Exercise brought on my fatigue.

_____ 3. I was easily fatigued.

_____ 4. Fatigue interfered with my physical functioning.

_____ 5. Fatigue caused frequent problems for me.

_____ 6. My fatigue prevented sustained physical functioning.

_____ 7. Fatigue interfered with carrying out certain duties and responsibilities.

_____ 8. Fatigue was among my three most disabling symptoms.

_____ 9. Fatigue interfered with my work, family, or social life.