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BRIEF COMMUNICATION

Rapid serial processing in patients with multiple sclerosis: The role of peripheral deficits

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Abstract

This study compared speed of information processing in patients with relapsing–remitting or secondary progressive multiple sclerosis (MS) and healthy controls using the Stroop Test and a Picture Naming Test (PNT). While both tests evaluated processing speed within a format calling for rapid serial processing of stimulus information, the PNT included trials designed to impose greater verbal–motor and ocular–motor challenges by using novel rather than repeated pictures and by presenting the pictures in distributed locations rather than always centered on the screen. The results confirmed that a decrease in the speed of information processing is a key feature of the cognitive impairment occurring in conjunction with MS. When this feature is evaluated with tests requiring rapid serial processing of stimulus information, the contribution of peripheral motor deficits appears to be modest. (*JINS*, 2008, *14*, 646–650.)

Keywords: Cognition, Neuropsychology, Nystagmus, Dysarthria, Disability, Human information processing

INTRODUCTION

Deficits in processing speed have been demonstrated in MS patients using a variety of measures, including the Paced Auditory Serial Addition Test (PASAT: Demaree et al., 1999), the Symbol Digits Modality Test (SDMT: Beatty et al., 1989), and the Stroop Test (Rao et al., 1989). Differences occurring on individual measures have occasionally prompted alternative interpretations. For example, investigators focusing exclusively upon performance involving Stroop stimuli by themselves (Scarrabelotti & Carroll, 1999) or on interference scores (Rao et al., 1989, 1991) have concluded that MS patients exhibit deficits in selective attention. However, numerous studies (Denney et al., 2004, 2005; Jennekens-Schinkel et al., 1990; Kujala et al., 1995; Pujol et al., 2001; Van den Burg et al., 1987; van Dijk et al., 1992, Vitkovitch et al., 2002) report differences between patients and controls on the preliminary word reading and color naming trials of the Stroop, and not just on the Stroop stimuli alone. In these studies, differences on interference measures are often nonsignificant (Denney et al., 2005; Jennekens-Schinkel et al., 1990; Pujol et al., 2001; Van den Burg et al., 1987; van Dijk et al., 1992) or have notably smaller effect sizes (Denney et al., 2004). Moreover, when research findings are examined across the full array of measures such as the PASAT, SDMT, and Stroop, a compelling case emerges for processing speed as the common factor distinguishing the neuropsychological performance of MS patients from that of controls.

Many of these tests share a common format calling for the rapid serial processing of information. Items appear sequentially with little or no variation in the operation to be performed on each item. The operation itself is typically not very demanding, but must be executed quickly, the goal usually being to complete as many items as possible in some allotted period of time.

The Stroop test performs especially well in this capacity. Using a battery of tests, we found the greatest differences between MS patients and controls occurring on the individual trials of the Stroop (Denney et al., 2004) and also that performance on these separate trials was the most sensitive measure of decline in patients' cognitive performance over the course of a 3-year longitudinal study (Denney et al., 2008). However, as in any rapid serial processing task, the Stroop

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engages the subject in a time-delimited activity laden with sensory and motor features. Our conclusion that patients' performance on the Stroop is indicative of a generalized slowing in central processing speed have been questioned by others who have raised concerns regarding the extent to which deficits in ocular–motor or verbal–motor functioning confound patients' performance on such tasks. Lending support to these concerns is the finding that patients' disability status correlates with performance on each trial of the Stroop (Denney et al., 2004) and that the particular functional system most highly related to this performance appears to be the brainstem. Brainstem ratings are indeed influenced by problems involving eye movements (e.g., nystagmus) and oral–motor function (e.g., dysarthria, dysphagia).

Previous studies have generally attempted to minimize such peripheral problems through procedural modifications (e.g., the use of auditory rather than visual stimuli on the PASAT). However, studies offering direct examination of the potential contribution of ocular–motor and verbal–motor problems to performance on RSP tasks are virtually absent from the MS literature. To conduct such an examination, we devised a picture naming task that allowed us to alter the levels of verbal and ocular–motor "burden" by varying the number of different pictures and their location during the course of four 1-min trials. We hypothesized that MS patients would name fewer pictures than controls on each trial. Furthermore, we expected the additional verbal and ocular–motor burden posed by the greater variety of pictures and locations to result in lower scores for both patients and controls on those trials compared with the first. However, if ocular–motor problems are an important factor affecting patients' performance, the decrement in their scores on trials with varying picture locations should be greater than that of the controls. Likewise, if verbal–motor problems are an important factor, the decrement in patients' performance on trials using a wider variety of pictures should be greater than that of the controls.

METHODS

Seventy-two patients with clinically definite MS were recruited. Patients were excluded if they had neurological disorders other than MS, a history of alcohol or drug abuse, current use of narcotics or benzodiazepines, visual impairment exceeding 20/50, impaired color vision, or were currently undergoing a relapse. Nine patients were excluded from analyses due to their inability to complete the tasks or to computer problems during test administration. The 63 remaining patients (50 females, 13 males) ranged between 22 and 70 years of age (M = 45.4) and between 12 and 20 years of education (M = 15.0). There were 43 patients with relapsing-remitting and 20 with secondary progressive MS. Duration of disease ranged from 1 to 36 years (M = 10.6), and Expanded Disability Status Scale (EDSS) scores ranged from 1.0 to 8.0 (Mdn = 3.0).

Fifty-nine healthy controls were recruited from university staff personnel. Individuals were excluded if they had any chronic health problems, history of alcohol or drug abuse, an ongoing medication regimen; visual impairment exceeding 20/50, or impaired color vision. Two controls were excluded from analysis because of difficulty understanding testing instructions or problems with test administration. The final sample of 57 individuals (40 females and 17 males) ranged between 24 and 70 years of age (M = 44.8) and between 12 and 24 years of education (M = 15.6).

Measures

Stroop Color-Word Interference Test (Stroop)

A computerized version of the Stroop was used consisting of three 1-min trials during which the subject first read color words (word reading; WR), then named the color of a row of four X's (color naming; CN), and finally, named the color of the letters for a set of Stroop stimuli (color-word naming; CWN). In each trial, the stimulus appeared in the center of the computer screen, the subject gave a verbal response, and the examiner pressed the spacebar to display the next stimulus. Each trial was preceded by an eight-item practice session. The computer timed the trial and recorded the number of stimuli completed. Errors occurred very infrequently and were not analyzed in this study.

Picture Naming Test (PNT)

The PNT was also computerized and consisted of four 1-min trials. In each trial, the subject named objects depicted as achromatic line drawings on the screen, the experimenter pressed the space bar, and the next picture appeared. Each trial was preceded by an eight-item practice session. The computer timed the trial and recorded the number of stimuli completed. In Trial 1 (PNT1), each stimulus was presented in the center of the computer screen and was one of only four different pictures (bell, dog, fan, pencil), so each picture was repeated several times over the course of the trial. In PNT2, a set of 50 different pictures was used and no picture was repeated during the trial. PNT3 used the same four pictures as PNT1, but each stimulus now appeared in one of nine random locations on the screen. In PNT4, the random locations used in PNT3 were combined with another set of 50 pictures. Two sets of 50 pictures were developed for use in the second and fourth trials; their order was determined randomly and counterbalanced across subjects. Scores consisted of the number of pictures named during each trial. Subjects could say "pass" if they did not recognize a particular drawing. Naming errors and passes occurred very rarely for both groups and were not analyzed.

Expanded Disability Status Scale (EDSS)

Functional status in each of the eight areas comprising the EDSS was rated, and these ratings were combined according to Kurtzke's (1983) guidelines to yield the EDSS score.

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Questionnaires

Levels of fatigue and depression during the preceding week were assessed using the Fatigue Severity Scale (Krupp et al., 1989) and the CES-Depression Scale (Radloff, 1977)

Procedure

This study was approved by the Human Subjects Committee of the University of Kansas Medical Center. All subjects provided informed consent. All patients were under the care of the same neurologist (S.G.L.) and were tested during the course of their regularly scheduled appointment at the MS clinic. The order of administration for the Stroop and PNT was randomized and counterbalanced across subjects.

RESULTS

The two groups did not differ in age, education, or gender. Depression and fatigue levels were significantly higher in the MS group (both p's $< .001$). Analyses of the cognitive measures were first conducted with depression and fatigue scores entered as covariates; however, because neither was a significant covariate, the analyses reported below exclude these covariates.

Comparisons on Rapid Serial Processing Measures

A multivariate analysis comparing patients and controls on the full array of Stroop and PNT scores was significant ($p < .001$; $\eta^2 = .23$). Univariate analyses revealed that patients achieved significantly lower scores on each trial of the Stroop and PNT, but did not differ from controls on the Stroop interference score (Table 1).

Figure 1 shows the Brinley plot for the seven trial scores (Kail, 1998; Myerson et al., 2003). The close proximity of all seven points to the regression line indicates the presence of a single factor common to this set of measures. The slope

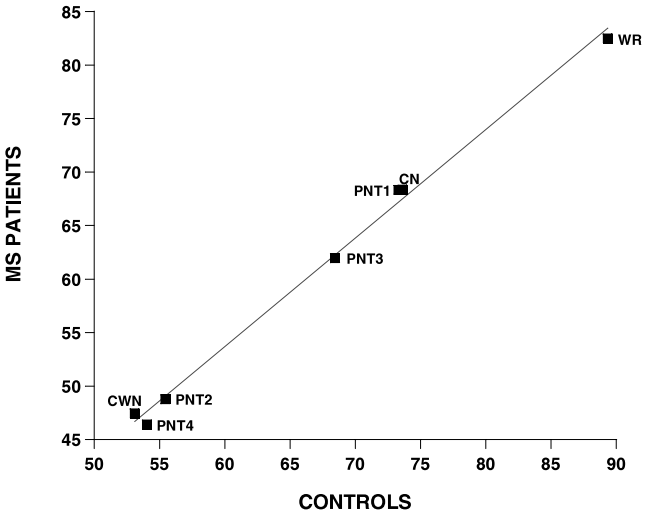

Fig. 1. Brinley plot showing mean performance on each rapid serial processing trial for multiple sclerosis (MS) patients (y-axis) *versus* controls (x-axis). WR = Word Naming; CN = Color Naming; PNT = picture naming test; CWN = Color–Word naming.

reflects the difference between patients and controls on this common factor and is significant ($t = 3.4$; $p = .02$). A principal components factor analysis provides further confirmation of a single factor underlying these measures. Only one factor (eigenvalue = 5.7) emerged, with factor loadings for the seven measures ranging from .82 (CWN) to .96 (PNT3).

Scores on the PNT trials were also subjected to a 2 (Group) × 2 (Novelty) × 2 (Location) factorial analysis of variance, with Novelty and Location serving as within-groups factors. Main effects were significant for Group ($F = 20.5$; $df = 1\&118$; $p < .001$; $\eta^2 = .15$), Novelty ($F = 1649.6$; $df = 1\&118$; $p < .001$; $\eta^2 = .93$), and Location ($F = 218.4$; $df = 1\&118$; $p < .001$; $\eta^2 = .65$). Patients completed fewer items overall than controls (M = 56.4 *vs.* 62.8), and all subjects completed fewer items on trials with novel *versus* repeated pictures (M = 51.2 *vs.* 68.0) and on trials with dis-

Table 1. Comparisons between MS patients and controls on rapid serial processing measures

Cognitive Measure	Patients Mean (SD)	Controls Mean (SD)	F (1&118)	p	η^2
Stroop					
Word Reading (WR)	82.5 (12.7)	89.4 (8.9)	11.6	.001	.090
Color Naming (CN)	68.4 (11.1)	73.6 (7.9)	8.8	.004	.069
Color-Word Naming (CWN)	47.5 (10.3)	53.1 (8.4)	10.6	.001	.083
Interference (CWN-CN)	20.9 (6.6)	20.5 (5.8)	.10	.751	.001
PNT					
Trial 1 (PNT1): (centered; repeated)	68.3 (8.9)	73.3 (7.7)	10.8	<.001	.084
Trial 2 (PNT2): (centered; novel)	48.8 (9.2)	55.4 (7.4)	18.9	<.001	.138
Trial 3 (PNT3): (distributed; repeated)	61.9 (10.0)	68.4 (6.7)	17.2	<.001	.127
Trial 4 (PNT4): (distributed; novel)	46.4 (9.5)	54.1 (6.4)	26.4	<.001	.183

Note. η^2 = partial eta-squared.

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tributed *versus* centered pictures (M = 57.7 *vs*. 61.5). These main effects were qualified by two-way interactions between Group and Location ($F = 5.9$; $df = 1\&118$; $p = .02$; $\eta^2 = .05$) and between Location and Novelty ($F = 50.2$, $df = 1\&118$; $p < .001$; $\eta^2 = .30$). The first of these interactions occurred because patients' scores were diminished to a greater extent than those of controls when the pictures were presented in different locations, suggesting a possible role for ocular–motor deficits in the patients' performance. The Group × Novelty interaction was not significant; patients' scores were not diminished to a significantly greater extent than controls when novel rather than repeated pictures were displayed. The significant Location × Novelty interaction shows that the two stimulus variations combined synergistically to increase the difficulty of the Picture Naming Task. However, the three-way interaction was not significant ($p = .61$), indicating that this combined effect impacted patients and controls to the same degree.

Correlations

Significant correlations were found between EDSS ratings and each of the seven trial scores, ranging from −.40 (PNT1) to −.56 (PNT4; all p's $< .01$) Likewise, the rating for the brainstem functional system was significantly related to each of these trials, with the exception of color naming and color–word naming; the other trials ranged from −.28 (PNT1 & 3) to −.32 (PNT4; all p's $< .05$). Although age was negatively related to performance on several of the measures, education level was not.

DISCUSSION

MS patients achieved significantly lower scores on all seven trials comprising the Stroop and PNT, with effect sizes ranging from .07 (CN) to .18 (PNT4). The overall decrease in patients' performance across all trials of the Stroop and PNT is indicative of a deficit in processing speed and consistent with the kind of diffuse white matter pathology characterizing MS (Rao, 1996).

The effect sizes for the three trials of the Stroop ranged from .07 to .09 and were comparable to those of previous studies (e.g., Denney et al., 2004). A similar effect size (.08) occurred for PNT1, as might be expected because the stimuli consisted of only four frequently repeated pictures always displayed in the center of the screen. Notably larger effect sizes (.14, .13, and .18) occurred on the last three trials of the PNT when stimulus parameters were varied. Effect sizes increased by approximately .05 when either the novelty or location parameter was altered and by .10 when both were.

Factorial analysis of the PNT scores revealed a significant Group × Location interaction. Patient's performance was diminished to a greater extent than that of controls by the presentation of pictures in random locations on the screen. This variation may have heightened the impact of ocular–motor problems associated with MS, thereby confounding the assessment of processing speed. It is worth noting that, in the typical administration of the Stroop, the stimuli for each trial are presented together, arranged in rows and columns on a card. This presentation mode requires greater visual tracking and is therefore conducive to the type of ocular–motor confounding evident on the "distributed" trials of the PNT. An advantage of the computerized version of the Stroop used in all our studies (Denney et al., 2004, 2005, 2008) is that stimuli appear individually in the center of the screen, thereby minimizing this potential confound. The corresponding Group × Novelty interaction on the PNT was not significant, indicating that problems with verbal–motor functioning may have posed less of a potential confound than those involving the ocular–motor system.

We readily acknowledge that some patients may have such profound dysarthria or nystagmus that their performance on rapid serial processing tasks will be severely affected. However, among the patients who have participated in our research past and present, such individuals are rare. A review of the EDSS recording forms completed on the 63 patients in the current study revealed only 4 with dysarthria (all rated as mild) and 14 with nystagmus (12 mild). For patients such as these, the overall impact of peripheral motor problems appears to be trivial. This is especially true under the usual conditions surrounding computerized measures of rapid serial processing such as the Stroop, where a very limited set of stimuli are presented repeatedly in the center of the screen. Attempts to enhance the impact of these peripheral deficits by manipulating stimulus novelty and location resulted in substantially more difficult trials on the PNT, but were only modestly successful in *differentially* affecting patients' performance relative to controls. Performance declined significantly for both patients and controls when the stimulus condition changed from centered to distributed or from repeated to novel pictures. The former manipulation reduced patients' and controls' performance by an average of 4.4 and 3.1 pictures, respectively; the latter by an average of 17.5 and 16.1 pictures, respectively. Furthermore, when trial means for patients and controls were arrayed on a Brinley plot, all seven trials were closely aligned with the regression line, and factor analysis further confirmed a single common component underlying performance on these trials. It seems clear that this factor is information processing speed and that MS patients are substantially impaired on this factor relative to controls.

Stronger associations between ratings of the brainstem functional system and specific trials posing greater peripheral motor challenge were anticipated, but in general, these did not occur. With the exception of color naming and color-word naming, performance on all rapid serial processing trials correlated about equally well with patients' brainstem functional ratings. Performance on these trials also correlated with overall disability status, with correlations ranging from −.40 to −.56. The strength of these latter relationships indicates the usefulness of brief rapid serial processing measures within performance-based screening batteries to assess MS disability. The measure

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commonly used in such batteries is the PASAT. However, the measures used in the present study are less frustrating and more readily accepted by patients, as well as being arguably more ecologically relevant to their everyday functioning.

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