Cognitive Aging in Patients with Multiple Sclerosis: A Cross-Sectional Analysis of Speeded Processing

Angela M. Bodlinga, Douglas R. Denneya,*, Sharon G. Lyncha

Department of Psychology, University of Kansas, Lawrence, KS, USA
Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

Accepted 11 September 2009

Abstract

Studies have identified generalized slowing in information processing speed as the primary cognitive deficit in multiple sclerosis (MS). Similar changes are also commonly observed in healthy cognitive aging. The present study is the first to examine the combined impact of aging and disease on the course of cognitive slowing. MS patients (N = 245) and healthy controls (N = 188) were assessed using two measures of processing speed (the preliminary word reading and color naming trials of the Stroop). Participants ranging in age from 18 to 74 were grouped into five age cohorts. Slowing in processing speed was evident for patients vs. controls and for older vs. younger cohorts. The age-related declines in performance were parallel for patients and controls, indicating that the disease process in MS does not interact with general cognitive aging to effect a more rapid decline in functioning.

Keywords: Cognitive aging; Multiple sclerosis; Processing speed; Neuropsychology; Stroop test; Neurodegenerative disease

Introduction

Cognitive impairment in individuals with multiple sclerosis (MS) have been reported across a range of cognitive domains (see reviews by Bobholz & Rao, 2003; Brassington & Marsh, 1998; Rao, 1986). A host of studies have indicated that slowing in the speed of information processing may be the fundamental cognitive deficit associated with this disease (Archibald & Fisk, 2000; Bergendal, Fredriksson, & Almkvist, 2007; Bodling, Denney, & Lynch, 2008; de Sonneville et al., 2002; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Demaree, DeLuca, Gaudino, & Diamond, 1999; Denney, Lynch, & Parmenter, 2008; Denney, Lynch, Parmenter, & Horne, 2004; Denney, Sworowski, & Lynch, 2005; Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Kail, 1998; Kalmar, Bryant, Tulsky, & DeLuca, 2004; Lengenfelder et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991; Reicker, Tombaugh, Walker, & Freedman, 2007). Arguments in favor of the “primacy” of processing speed are bolstered by the consistency of reports of cognitive slowing in MS patients across studies involving a variety of neuropsychological tasks (Kujala, Portin, Revonsuo, & Ruutiainen, 1994; Kail, 1997, 1998; Steiger, Denney, & Lynch, 2008), by the emergence of cognitive slowing early in the course of the disease (Archibald & Fisk, 2000; Bergendal et al., 2007; DeLuca et al., 2004; Grigsby et al., 1994), and by the relevance of cognitive slowing as a predictor of future cognitive decline (Bergendal et al., 2007).

This emphasis upon the primacy of processing speed in MS closely parallels that found in research on healthy cognitive aging. In fact, MS researchers have frequently commented on the similarities between the profile of deficits in MS and that observed in healthy aging, particularly in the context of slowed processing (DeLuca et al., 2004; Denney et al., 2004; Kail, 1997, 1998; Kalmar et al., 2004; Reicker et al., 2007). However, there has been virtually no attention given to the intersection...
of these two processes; that is, the inevitable combination of aging and disease in older MS patients and its impact on cognitive performance. A search of the literature did not locate any cross-sectional studies directly addressing this combination.

The most relevant work, reported by Kail (1997), featured direct comparisons of processing speed in MS patients and older adults using Brinley plots. Results supported the contention that cognitive slowing in patients is largely equivalent to that occurring in older adults. However, these data afforded no comparison of processing speed in younger versus older MS patients and therefore do not address the combined impact of disease and aging.

Longitudinal studies are admittedly best suited to address the issue of age-related changes in cognitive functioning regardless of the population of interest. Several such studies are available in the MS literature (see review by Amato, Zipoli, & Portaccio, 2006), but their applicability here is limited because most of these studies employ follow-up periods of 4 years or less, far too constrained to portray the broader picture of cognitive aging. Furthermore, these studies typically fail to address the influence of age on the cognitive changes occurring in the subjects followed, other than citing the correlations between the cognitive data and subjects’ ages or using covariance analysis to statistically control for these age differences. And finally, not all the longitudinal studies have included analyses of processing speed, which are arguably most relevant for reflecting the combined impact of aging and disease.

The longitudinal study that best addresses this issue is a recent study by Bergendal and colleagues (2007) reporting on an 8-year follow-up of a small sample of MS patients. Speed of information processing was the only cognitive domain classified as impaired at initial assessment, and a specific analysis by age revealed that older patients showed a more prominent decline in processing speed at follow-up than younger patients. These results are consistent with those of several other studies identifying processing speed as the primary cognitive deficit in MS patients and also showing age to be a significant covariate in the analyses of processing speed (e.g., Amato, Ponziani, Siracusa, & Sorbi, 2001; Denney et al., 2004, 2005). These results also agree with another recent longitudinal study (Denney et al., 2008) indicating that measures of processing speed provide the most sensitive index of decline in MS patients’ cognitive performance over time. However, Bergendal’s study lacked a control group and therefore cannot fully answer the question of age-related slowing in MS. It remains unclear whether the steeper decline for older versus younger patients paralleled the result one might expect to find in their healthy peers.

The present study was therefore aimed at correcting what we consider to be a surprising omission in the literature by providing the first cross-sectional analysis of age-related cognitive slowing in samples of MS patients and healthy controls. Data from two basic measures of information processing speed were combined from previous investigations yielding a large sample spanning a broad age range. Previous research strongly suggested that these data would reveal (a) cognitive slowing for patients compared with controls (a result documented by all prior analyses from the original studies) and (b) cognitive slowing for older compared with younger healthy individuals. The unique contribution and central focus of this investigation centered on the interaction between these two factors. The lack of a group by age interaction would indicate comparable trajectories of cognitive slowing for patients and controls across the lifespan. In contrast, a significant interaction would suggest a divergent pattern of decline between the patients and the controls. The specific nature of this interaction could potentially take several forms, the most likely being a more precipitous decline in processing speed for patients relative to controls.

Materials and Methods

The following analyses are based on data compiled primarily from five previous studies (Bodling et al., 2008; Denney et al., 2004; Lynch, Dickerson, & Denney, 2007; Parmenter, Denney, & Lynch, 2003; Steiger et al., 2008). All studies were approved by the Human Subjects Committee at the University of Kansas Medical Center and were designed to examine the cognitive performance of patients with MS using various combinations of neuropsychological tests. The present analyses focus on data from one of the tests of processing speed common across the study batteries, a computerized version of the Stroop. Because of the limited number of older aged controls in the previous studies, 11 healthy control participants aged 60 or older were recruited explicitly for the present study.

Participants

A total of 245 patients (195 women, 50 men) with clinically definite MS were included in this combined sample. All patients had been under the care of the same neurologist (S.G.L.) for at least 1 year. 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, or impaired vision (including color vision). Patients were also excluded if they were deemed too intellectually impaired to comprehend testing instructions; this judgment was made on the basis of the neurologist’s clinical experience with her patient. Patients ranged in age from 18 to 74 years (M = 45.1, SD = 9.7) and had between 12 and 20 years of education.
(\(M = 15.5, SD = 2.3\)). All patients had been diagnosed with MS for at least 1 year, and duration of disease ranged from 1 to 37 years (\(M = 9.0, SD = 7.1\)). This sample included patients with relapsing–remitting (RR; \(n = 179\)), primary progressive (PP; \(n = 32\)), and secondary progressive (SP; \(n = 34\)) disease. Disability scores on the Expanded Disability Status Scale (EDSS: Kurtzke, 1983) ranged from 1 to 8 (\(Mdn = 3.5\)).

Healthy controls were recruited for each of the previously listed studies, yielding a combined total of 188 healthy controls (141 women, 47 men) for analysis. The control group consisted of personnel from the University of Kansas and its medical center as well as community volunteers. In addition to meeting the criteria outlined for patients, eligible controls were free of chronic medical conditions and individuals taking any continuous medications other than vitamin and mineral supplements, birth control, and low-dose aspirin were excluded. Controls ranged in age from 23 to 73 (\(M = 45.2, SD = 11.2\)) and had from 12 to 20 years of education (\(M = 16.6, SD = 2.4\)).

**Measures**

A computerized version of the original Stroop Test (Stroop, 1935) was administered consisting of three 60 s trials. Participants first read a series of color words (red, yellow, blue, and green) appearing in black letters on the computer screen (word reading), then named the color of a series of X’s printed in the same four colors (color naming), and finally named the color of print for a series of color words printed in these colors (i.e., the original Stroop stimuli). Stimuli for each trial were presented individually in the center of the computer screen. Participants gave a verbal response to each stimulus, and the experimenter immediately pressed the spacebar to display the next stimulus. Each trial began with an 8-item practice session followed by the full 60 s trial.

Prior to each trial, the participant was given the following instruction: “Work quickly but try not to make any mistakes. If you do make an error, try not to correct it. Just go on to the next item.” Consistent with these instructions, the examiner was trained to act like a voice-activated relay, pressing the spacebar regardless of the participant’s response. The computer timed the trial and recorded the total number of stimuli completed during the trial. Errors occur rarely in this task and were not recorded in any of the compiled studies.

**Procedure**

The procedure followed for each of the previous studies was the same. Informed consent was obtained from all participants. Patients were provided with information about the study during a regular clinic appointment, and if they consented to participate, disability assessment was completed with the EDSS during the course of this appointment. The remaining assessments were administered directly following their clinic appointment or scheduled for a future date. All participants completed the Stroop Test as part of each study’s neuropsychological battery. The order of administration of this test and the number of other assessments included in the battery varied among the five studies, and the total assessment time ranged from 25 to 90 min. All data constitute independent observations; each individual participated in only one of the studies from which the present data were compiled.

**Results**

**Analysis of Demographic Variables**

Patient and control groups did not differ with respect to gender or age. However, controls had significantly higher education than patients, \(t(431) = 4.5, p < .001\). Differences in education could potentially impact cognitive performance, and therefore education was initially entered as a covariate in the analyses. Because education did not emerge as a significant covariate, the analyses were repeated without the covariate, and the results reported here are those conducted without this covariate.

Participants were divided into five age cohorts for analysis (18–29, 30–39, 40–49, 50–58, 59 years and above). The last cohort was initially defined as 60 and above, but was adjusted to include 59-year olds due to the limited number of control participants in this oldest age group. Even with this adjustment, 11 additional controls were recruited explicitly for the present study so the size of this oldest cohort would be similar to that of the patients. Means and standard deviations for age and education are presented in Table 1 for patients and controls in each cohort. Table 1 also includes additional data pertaining to disease-related characteristics for the patients in each of the age cohorts.
Comparison of Stroop Performance by Age Cohort

Table 2 presents the results for the Stroop Test, including the scores for each trial and the relative interference score (Denney & Lynch, 2009). Separate 2 (group) × 5 (age) analyses of variance were performed on each of these scores, although the main focus was on the scores from the two preliminary trials since these provide the most unambiguous measures of processing speed. Analysis of word reading (W) and color naming (C) scores revealed significant main effects for group—W: \(F(1, 423) = 82.8, p < .001, \eta^2 = .16\); C: \(F(1, 423) = 99.6, p < .001, \eta^2 = .19\)—and age—W: \(F(4, 423) = 4.5, p = .001, \eta^2 = .04\); C: \(F(4, 423) = 6.2, p < .001, \eta^2 = .06\)—with patients performing more slowly than controls and older adults performing more slowly than younger adults. The group × age interactions for W and C scores are illustrated in Fig. 1. Neither interaction was significant (both F-values <1) suggesting that the decline in performance across ages was equivalent for patients and controls.

Scores for the third trial of the Stroop (CW) are affected by both processing speed and interference due to the incongruity between words and colors. Nevertheless, the analysis of these scores yielded the same outcome: Main effects for group, \(F(1, 423) = 77.7, p < .001, \eta^2 = .16\), and age, \(F(1, 423) = 10.9, p < .001, \eta^2 = .09\), but no significant interaction \((F < 1)\). Analysis of the relative interference scores revealed only a significant main effect for age, \(F(1, 423) = 4.8, p = .001, \eta^2 = .04\), with interference scores increasing for older adults. Patients and controls did not differ in interference on the Stroop \((F < 1)\).

Table 2. Means (SD) on the Stroop Test for MS patients and controls by age cohorts

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>18–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–58</th>
<th>59–74</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Word reading (W)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>79.4 (8.4)</td>
<td>79.5 (9.5)</td>
<td>77.3 (11.0)</td>
<td>75.6 (9.4)</td>
<td>73.7 (9.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>91.4 (10.3)</td>
<td>90.0 (8.6)</td>
<td>87.6 (11.9)</td>
<td>84.6 (8.9)</td>
<td>84.5 (8.8)</td>
</tr>
<tr>
<td><strong>Color naming (C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>65.8 (7.9)</td>
<td>66.2 (8.3)</td>
<td>63.8 (10.1)</td>
<td>62.8 (7.8)</td>
<td>58.7 (8.2)</td>
</tr>
<tr>
<td>Controls</td>
<td>77.6 (9.1)</td>
<td>74.9 (6.0)</td>
<td>72.8 (8.4)</td>
<td>70.9 (7.4)</td>
<td>69.4 (7.0)</td>
</tr>
<tr>
<td><strong>Color-word naming (CW)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>48.7 (9.4)</td>
<td>48.2 (8.3)</td>
<td>45.4 (7.8)</td>
<td>43.6 (8.6)</td>
<td>40.7 (7.5)</td>
</tr>
<tr>
<td>Controls</td>
<td>57.6 (8.3)</td>
<td>56.7 (7.5)</td>
<td>51.6 (6.6)</td>
<td>51.2 (6.7)</td>
<td>48.9 (6.8)</td>
</tr>
<tr>
<td><strong>Relative interference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>26.0 (9.8)</td>
<td>27.4 (6.2)</td>
<td>28.7 (7.8)</td>
<td>30.6 (10.2)</td>
<td>30.9 (7.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>25.9 (6.1)</td>
<td>24.4 (7.3)</td>
<td>28.9 (6.9)</td>
<td>27.6 (7.3)</td>
<td>32.2 (7.5)</td>
</tr>
</tbody>
</table>

*Relative interference: \((|C - CW|)/C) \times 100.$
Alternatively, the separation of participants into age cohorts could be ignored and the scores on the Stroop analyzed using stepwise multiple regression with education, age, group, and the age × group interaction serving as predictors. When this alternative analysis was performed on each of the trial scores, the outcome was the same: group emerged as a significant predictor in the first step; age emerged as a significant predictor in the second step; and neither the age × group interaction nor education was significant. The adjusted \( R^2 \) for this two-variable solution ranged from .23 to .26 (all \( p \)-values < .001) across the trials. The standardized coefficients (\( \beta \)) for group ranged from .41 to .45, and those for age ranged from -.19 to -.29 (all \( p \)-values < .001). The \( p \)-values for the interaction term were .53 for \( W \), .88 for \( C \), and .15 for \( CW \).

**Discussion**

On the basis of previous research, we hypothesized cognitive slowing for patients compared with controls and older compared with younger participants. But the focus of this investigation was the interaction between group and age. We expected to find a significant interaction indicating a steeper decline in patients’ processing speed across the lifespan. The absence of any significant group by age interactions suggests that patients undergo the same process of cognitive aging as healthy adults and that the disease process does not appear to interact with aging to alter the trajectory of cognitive slowing. It is important to emphasize, however, that this conclusion is based on only a single test of processing speed, one which is less commonly featured in MS research. This is a clear limitation of the present study. An unqualified assertion that MS does not interact with aging in effecting the course of cognitive slowing must await confirmation using several of the more common tests of processing speed such as the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test.

While readily admitting the limitation stemming from this reliance on a single test, we nevertheless believe the preliminary trials of the Stroop do provide excellent measures of processing speed. Previous studies from which most of the present data were compiled offer consistent evidence that patients perform more slowly than controls on these preliminary trials and that the difference is readily attributable to a decrease in the speed of information processing (Bodling et al., 2008; Denney et al., 2004; Lynch et al., 2007; Steiger et al., 2008). One paper (Lynch et al., 2007) features a comparison between our computerized version of the Stroop and the PASAT and shows that the \( C \) and \( W \) scores from the Stroop were actually more sensitive to differences between patients and controls than the scores from the PASAT.

Researchers implicitly acknowledge the existence of age-related cognitive change in MS patients whenever they use methodological (e.g., matching) or statistical procedures (e.g., including age as a covariate) to equate patients and controls with respect to age. The use of covariance procedures is predicated upon a “homogeneity of slopes” assumption, namely that the interaction between the principal variable of interest and the covariate is nonsignificant. In the present context, the assumption would be that advancing age impacts MS patients and controls in an equivalent fashion. Prior to this study, there has been no empirical test of this assumption. However, the present findings indicate that cognitive aging operates similarly in both patients and controls, at least in terms of its impacting processing speed, and thereby provide justification for the use of covariance procedures to segregate the effects of age from those of MS itself on cognitive performance.

Further commentary upon the absence of a significant group by age interaction is warranted. First, it should be noted that this result was obtained for patients with established disease who had been diagnosed with MS for at least 1 year. At this stage, the
disease process had already impacted cognitive functioning such that patients exhibited slower processing than their healthy peers. Even for the youngest age cohort involving patients with the shortest duration of disease, significant differences in processing speed were observed between patients and controls ($p < .001$). This suggests that the impact of MS on the speed of information processing occurs very early in the course of the disease, perhaps within the first year or even prior to formal diagnosis. In essence, we are proposing that disease status almost certainly must interact with age at some point during the course of this disease, but to detect it one would have to study patients at an even earlier (and quite possibly preclinical) point in time. Indeed, an intriguing question concerns the point early in the course of the disease when MS patients diverge from their peers in terms of processing speed. Subsequent to this point, their rate of decline in processing speed appears to be remarkably similar to that seen in conjunction with healthy aging.

Second, the paucity of patients and controls over age 60 may have further constrained the group by age interaction in the present study. Had larger numbers of participants been available in the oldest age cohort, a significant interaction may have emerged. Indeed, Fig. 1 shows a slight trend toward greater separation between patients and controls in this last age cohort. Thus, in addition to our contention that a group by age interaction “must” occur at some point early in the course of MS, we also acknowledge that the present study can not rule out the possibility that an interaction “might” occur at the other end of the age spectrum as well.

Other characteristics of the patients enrolled in the present study might have mitigated the possibility of finding a significant interaction. The sample was comprised of individuals with mild to moderate levels of disability. It is possible that more severe disease could accelerate the decline in processing speed stemming from aging and might therefore have led to a significant group by age interaction. Furthermore, although they differed from controls in terms of years of education, the patients were nevertheless well educated, thereby raising the possibility that cognitive reserve might have diminished the group by age interaction. Future studies targeting older and less highly educated patients and those with greater disease burden are certainly warranted.

Using a cross-sectional design to examine MS patients in different age cohorts poses some inherent complications because the composition of these cohorts is likely to vary with respect to the type of MS. Most cases of MS begin with the RR form of the disease. However, with time, approximately half of these patients come to experience a progression of their symptoms without discernable remissions and are reclassified as SPMS. Patients with PPMS have a relatively steady progression of symptoms from the onset of disease, and the age of onset for this form of MS is generally older than that for RRMS. Therefore, older age cohorts are likely to be composed of proportionately larger numbers of patients with progressive symptoms and smaller numbers with RR symptoms.

One solution might be to limit investigation to RR patients. In the present study, sufficient numbers of RR patients were available within each age cohort to perform this limited analysis. The findings were entirely consistent with those reported for the full sample; the rate of cognitive decline for patients with RRMS again closely approximated that of the healthy control group. However, RR patients generally have less severe symptoms than those with chronic progressive MS. Limiting the sample to RR patients who adhere to this pattern throughout the course of their disease may inadvertently select for patients with more benign disease in the older age cohorts, and under the present circumstances, this selection bias reduces the likelihood of finding a significant group by age interaction. The inclusion of all types of MS in the present study permits a more general conclusion concerning the similarity between patients and controls in age-related declines in processing speed. Nevertheless, further studies should be conducted to determine whether this similarity is upheld when the patient sample is composed of individuals with more severe forms of MS.

**Conflict of Interest**

None declared.

**Acknowledgements**

A paper based on this research was presented in September 2008 at the World Congress for Treatment and Research in Multiple Sclerosis, Montreal, Canada. One of the studies (Denney et al., 2004) from which some of the present data were obtained was funded by a grant from Teva Neuroscience.

**References**
