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# Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS

S.C.J. Huijbregts, PhD; N.F. Kalkers, MD, PhD; L.M.J. de Sonneville, PhD; V. de Groot, MD, PhD; I.E.W. Reuling, MSc; and C.H. Polman, MD, PhD

**Abstract—***Objective:* To investigate the cognitive skills of patients with relapsing remitting multiple sclerosis (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) relative to healthy control subjects and to assess whether there is heterogeneity in the type of cognitive disabilities demonstrated by patients with different MS phenotypes. *Methods:* RRMS patients (n = 108), SPMS patients (n = 71), PPMS patients (n = 55), and healthy control subjects (n = 67) underwent neuropsychological assessment with the Brief Repeatable Battery of Neuropsychological Tests. *Results:* Relative to controls, cognitive performance of RRMS patients was deficient when tasks required higher-order working memory (WM) processes (Word List Generation, 10/36 Spatial Recall Test, Symbol Digit Modalities Test). PPMS and SPMS patients performed poorer than control subjects on all tasks. SPMS patients performed more poorly than PPMS patients when tasks required higher-order WM processes, except when speed of information processing played a relatively important role (Symbol Digit Modalities Test, Paced Auditory Serial Addition Test). Whereas RRMS patients generally performed better than the progressive subtypes, they showed relatively poor verbal fluency. *Conclusion:* MS patients with different disease courses have different cognitive profiles.

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Cognitive impairment is present in 40 to 60% of patients with multiple sclerosis (MS)[1,2] and occurs in all MS subtypes.[3-6] Previously, secondary progressive (SP) MS and primary progressive (PP) MS were often both classified as chronic progressive MS, but following the increase of reports on differences in pathology,[7-10] this classification was eliminated.[11] In a meta-analysis of effect sizes utilizing the older classification of MS patients, it was shown that chronic progressive MS patients were more likely than relapsing remitting (RR) MS patients to present with verbal IQ, fluency, and comprehension deficits, information-processing speed deficits, and cognitive flexibility and abstraction impairments.[12] In comparison with healthy control subjects, RRMS patients were most likely to present with memory problems.

In studies distinguishing SPMS, PPMS, and RRMS, a higher prevalence and greater severity of cognitive deficits have been reported for SPMS compared with RRMS and PPMS.[3,4,7] Only one study showed qualitative differences between all three MS subtypes: PPMS and SPMS patients had more difficulties with verbal new learning than RRMS patients, and SPMS and RRMS patients had more difficulties with visuospatial new learning (while controlling for visuospatial perceptual skills) than PPMS patients.[13] Two studies comparing SPMS and PPMS patients confirmed impaired visuospatial working memory (WM) in SPMS patients relative to PPMS patients.[3,7] Studies focusing on the type of cognitive problems observed in RRMS patients showed impairments when WM load was high or WM content had to be manipulated[5,6] and when verbal fluency was required.[14] Unfortunately, MS patients with progressive phenotypes were not included in the studies reporting higher-order cognitive processing deficits in RRMS,[5,6,14] whereas other studies included only the progressive subtypes.[3,7] The current study re-evaluates differences in cognitive profile between all three MS subtypes using relatively large samples for each subtype and compares performance with that of healthy control subjects.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the July 27 issue to find the title link for this article.

**Methods.** *Subjects.* Two hundred thirty-four patients with clinically definite MS[15] were recruited from all patients receiving regular follow-up care at the Vrije Universiteit Medical Center (VUMC). In addition, 67 control subjects were recruited through advertisements in hospital and other newspapers. All subjects gave (written) informed consent to participate in this study, which was approved by the Ethics Committee of the VUMC. Patients were classified as RRMS (n = 108), SPMS (n = 71), or PPMS (n = 55).[11]

Patients had not undergone relapse within 4 weeks of testing. A full medical history and detailed neurologic examination were

From the Department of Clinical Neuropsychology, Vrije Universiteit, (Dr. Huijbregts), and Departments of Neurology (Drs. Kalkers, de Groot, and Polman), Pediatrics (Dr. de Sonneville), and Medical Psychology (I.E.W. Reuling), Vrije Universiteit Medical Centre, Amsterdam, the Netherlands.

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Address correspondence and reprint requests to Dr. S.C.J. Huijbregts, School of Psychology, University of Southampton, Highfield, Southampton, SO17 1BJ, UK; e-mail: S.Huijbregts@soton.ac.uk

 

***Table 1*** *Demographic and clinical characteristics*

| Characteristic | Controls | RRMS | SPMS | PPMS | Significant differences* |
|---|---|---|---|---|---|
| n | 67 | 108 | 71 | 55 | |
| Age (SD), y | 44.1 (13.8) | 35.5 (8.8) | 45.1 (8.2) | 53.9 (11.6) | 1, 3, 4, 5, 6 |
| Education (SD) | 2.16 (0.75) | 2.25 (0.59) | 2.17 (0.66) | 2.27 (0.83) | |
| Gender, F/M, % | 63/37 | 70/30 | 42/58 | 60/40 | 2,† 4, 6‡ |
| EDSS (SD) | | 2.4 (1.1) | 5.0 (1.1) | 5.8 (1.6) | 4, 5, 6§ |
| Dur (SD) | | 3.4 (4.1) | 12.3 (6.8) | 13.0 (8.2) | 4, 5 |

* Student $t$-test for age and disease duration, Mann–Whitney $U$ test for EDSS and education, Pearson $\chi^2$ test for gender; $p < 0.001$, except where noted.
† $p = 0.016$.
‡ $p = 0.048$.
§ $p = 0.004$.

RR = relapsing - remitting; MS = multiple sclerosis; SP = secondary progressive; PP = primary progressive; Education: 1 = low, 2 = intermediate, 3 = high; EDSS = Expanded Disability Status Scale; Dur = disease duration. Significant differences: 1 = controls–RRMS, 2 = controls–SPMS, 3 = controls–PPMS, 4 = RRMS–SPMS, 5 = RRMS–PPMS, 6 = SPMS–PPMS.

obtained for all patients before assessment. For control subjects, medical history was obtained by means of a questionnaire followed by an interview preceding assessment. In case these evaluations showed current depression or (a history of) drug or alcohol abuse, psychiatric disorders other than depression, traumatic brain injury, metabolic or other CNS disorders with known effects on memory and concentration, diabetes, cardiovascular illness, insufficient command of the Dutch language, visual acuity of <6/12, or learning disabilities, subjects did not participate in the neuropsychological assessment.

Physical disability of the patients was scored using the Expanded Disability Status Scale (EDSS).[16] Level of education was coded as 1) when the participant did not finish secondary education or graduated at lower levels, 2) when the participant graduated from secondary education at intermediate levels or started postsecondary education but did not finish, or 3) when the participant graduated from secondary education at higher levels or finished postsecondary education. Table 1 shows age, education level, and gender distribution for all groups as well as EDSS scores and disease duration for the MS patients.

*Neuropsychological tasks.* Neuropsychological assessment was performed with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).[17] The Bushke Verbal Selective Reminding Test (SRT) is a measure of verbal learning and delayed recall of a 12-word list. The Long-Term Storage (LTS) score represents the sum of words recalled on two consecutive trials without reminding. The Consistent Long-Term Retrieval (CLTR) score is the sum of words recalled on all the subsequent trials without reminding. The Total Delay score is the number of words recalled after a delay of 10 minutes.

The 10/36 Spatial Recall Test measures visuospatial learning and memory. It requires subjects to recall the placement of 10 checkers that are randomly placed on a 6 × 6 checkerboard. One score is the sum of correct responses in the three immediate recall trials (10/36 SRT). The other score is delayed recall after 15 minutes (10/36 SRT Delay).

The Symbol Digit Modalities Test (SDMT) examines speed of information processing and complex visual scanning. The subject examines a series of nine geometric symbols that are labeled 1 to 9. During 90 seconds, the subject substitutes as many symbols as possible by the corresponding number and responds verbally. The score is the number of correct substitutions.

The Paced Auditory Serial Addition Test (PASAT) requires cognitive abilities such as mental calculation, interference suppression, and information-processing speed. Subjects must be able to rapidly refresh WM content and resist interference from a previous response. The subject is instructed to add 60 pairs of digits such that each number is added to the one that immediately precedes it and report the outcome verbally. The digits are presented by tape, first at a rate of every 3 seconds per digit, the second trial with every 2 seconds per digit. The score is the number of correct responses per trial (PASAT_3, PASAT_2).

The Word List Generation (WLG) is a semantic verbal fluency test evaluating the spontaneous production of names of a given category (animals) within 90 seconds. The score is the number of correct names. This version of the WLG is a modified version of the phonemic naming task (e.g., words beginning with F, A, or S) in the original BRB-N. Cognitive abilities required by WLG include associative thinking (clustering), mental imagery, and switching.[18]

*Statistical analysis.* Differences between groups on clinical and demographic characteristics were analyzed by means of independent-samples Student $t$-tests (two tailed; age and disease duration), independent-samples Mann–Whitney $U$ test for ordinal or rank data (EDSS and level of education), and Pearson $\chi^2$ tests (gender distribution).

Pearson correlations (for age and disease duration) and Spearman rank order correlations (for EDSS and level of education; bivariate, two tailed) were calculated to examine the relations between clinical and demographic characteristics and task performance. The relation between task performance and gender was investigated by means of independent-samples Student $t$-tests (two tailed).

Two multivariate procedures (SPSS 11.0; Chicago, IL) with all BRB-N scores as dependent variables were performed to examine differences between control subjects and MS patients and differences between MS subtypes. Age and gender were included as covariates in both procedures. Contrast analyses were performed to examine the direction of group differences on different tasks. As a measure of the effect sizes, the Cohen $d$ was calculated, which indicates the magnitude of mean differences (using the estimated marginal means) in SD units. Following Cohen,[19] effect sizes can be interpreted as being small ($d = 0.2$), medium ($d = 0.5$), or large ($d \geq 0.8$). Considering the strong correlations of EDSS and disease duration with each other ($r = 0.62$, $p < 0.001$) and with age (EDSS: $r = 0.59$, $p < 0.001$; disease duration: $r = 0.58$, $p < 0.001$), these were not included simultaneously as covariates in the multivariate procedure comparing performance of the MS groups to prevent overcorrection. Disease duration and EDSS were entered separately (in addition to gender) in two multivariate post-hoc procedures to investigate possible differences as compared with when age was included.

**Results.** Control subjects, RRMS patients, and SPMS patients were younger than PPMS patients. RRMS patients were also younger than control subjects and SPMS patients. Gender distribution differed between SPMS patients, which was the only group with a majority of men, and the other groups. RRMS patients had lower EDSS scores and shorter disease duration than PPMS and SPMS patients, and SPMS patients were less disabled than

***Table 2*** *Adjusted group means (SE) and 95% CIs after controlling for age and gender*

| Test | Ctrl, n = 67 | 95% CI | | RR, n = 108 | 95% CI | | SP, n = 71 | 95% CI | | PP, n = 55 | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SRT | | | | | | | | | | | | |
| LTS | 50.4 (1.5) | 47.7 | 53.3 | 48.5 (1.3) | 46.0 | 51.1 | 45.1 (1.5) | 42.1 | 48.0 | 44.0 (1.8) | 40.5 | 47.6 |
| CLTR | 39.8 (1.7) | 36.4 | 43.2 | 39.8 (1.5) | 36.9 | 42.8 | 32.8 (1.7) | 29.4 | 36.2 | 35.0 (2.1) | 30.9 | 39.2 |
| Total Delay | 9.6 (0.2) | 9.1 | 10.1 | 9.6 (0.2) | 9.2 | 10.0 | 8.5 (0.2) | 8.0 | 9.0 | 9.0 (0.3) | 8.4 | 9.5 |
| PASAT | | | | | | | | | | | | |
| PASAT_2 | 36.5 (1.7) | 33.1 | 39.8 | 33.6 (1.5) | 30.7 | 36.4 | 29.5 (1.7) | 26.2 | 32.8 | 29.7 (2.0) | 25.7 | 33.7 |
| PASAT_3 | 46.1 (1.8) | 42.5 | 49.7 | 44.9 (1.6) | 41.8 | 48.0 | 40.2 (1.8) | 36.6 | 43.7 | 38.5 (2.2) | 34.1 | 42.8 |
| SDMT | 60.2 (1.6) | 57.1 | 63.3 | 54.3 (1.3) | 51.7 | 57.0 | 45.1 (1.6) | 42.1 | 48.2 | 47.8 (1.9) | 44.0 | 51.6 |
| 10/36 Spatial Recall | | | | | | | | | | | | |
| 10/36 SRT | 24.0 (0.6) | 22.9 | 25.2 | 21.4 (0.5) | 20.4 | 22.3 | 17.7 (0.6) | 16.5 | 18.8 | 20.5 (0.7) | 19.1 | 21.9 |
| 10/36 SRT Delay | 8.5 (0.3) | 8.0 | 9.0 | 7.7 (0.2) | 7.2 | 8.1 | 6.5 (0.3) | 6.0 | 7.1 | 7.7 (0.3) | 7.0 | 8.3 |
| WLG | 34.6 (0.8) | 33.0 | 36.2 | 25.7 (0.7) | 24.3 | 27.1 | 25.1 (0.8) | 23.5 | 26.7 | 29.3 (1.0) | 27.4 | 31.3 |

Ctrl = control; RR = relapsing - remitting; SP = secondary progressive; PP = primary progressive; SRT = Selective Reminding Test; LTS = Long-Term Storage; CLTR = Consistent Long-Term Retrieval; PASAT = Paced Auditory Serial Addition Task (PASAT_2 = 2 s/digit; PASAT_3 = 3 s/digit); SDMT = Symbol Digit Modalities Test; 10/36 Spatial Recall (10/36 SRT = Immediate Recall; 10/36 SRT Delay = Delayed Recall); WLG = Word List Generation.

PPMS patients. Groups did not differ with respect to mean level of education (see table 1).

Women performed better than men on the SRT (LTS: $T[299] = 5.0$, $p < 0.001$; CLTR: $T = 4.7$, $p < 0.001$; Total Delay: $T = 4.9$, $p < 0.001$), SDMT ($T = 3.8$, $p < 0.001$), and WLG ($T = 3.5$, $p < 0.001$). Age, disability level, and disease duration generally correlated negatively and significantly with task performance, whereas a higher level of education was associated with better task performance (see table E-1 in the supplementary material on the *Neurology* Web site; go to www.neurology.org). The only exception was WLG performance, which did not show a significant association with any of these factors. A more detailed analysis of the (lack of) an association with age showed that for control subjects and PPMS patients, a curvilinear estimation of the relationship (controls: $R^2 = 0.0322$; PPMS: $R^2 = 0.0921$) fitted the data better than a linear estimation (controls: $R^2 = 0.0012$; PPMS: $R^2 = 0.0237$). To control for a quadratic relation between age and task performance for WLG, a univariate analysis was performed in which age * age was introduced as an additional covariate. For RRMS and SPMS patients, the quadratic and linear fits differed much less (RRMS: $R^2 = 0.1008$ vs $R^2 = 0.0936$; SPMS: $R^2 = 0.0065$ vs $R^2 = 0.0049$). In addition, for RRMS patients, there was a stronger correlation with age ($r = -0.31$, $p = 0.001$). Considering the apparent differences between groups in the relation between age and WLG performance, this task was also analyzed by means of pairwise comparisons (independent-samples Student *t*-tests) for different age categories.

*Neuropsychological task performance.* Table 2 shows the adjusted group means for each dependent variable after controlling for gender and age (unadjusted means [SD]

***Table 3*** *Contrast estimates (CEs) for differences between controls and multiple sclerosis subtypes after controlling for age and gender*

| Test | Ctrl vs RR | 95% CI | | *p* | *d* | Ctrl vs SP | 95% CI | | *p* | *d* | Ctrl vs PP | 95% CI | | *p* | *d* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SRT | | | | | | | | | | | | | | | |
| LTS | CE = −1.8 | −5.8 | 2.1 | 0.358 | 0.16 | CE = −5.3 | −9.5 | −1.2 | 0.012 | 0.41 | CE = −6.3 | −10.9 | −1.7 | 0.007 | 0.45 |
| CLTR | CE = 0.3 | −4.5 | 4.6 | 0.989 | 0.002 | CE = −7.0 | −11.9 | −2.2 | 0.005 | 0.46 | CE = −4.8 | −10.1 | 0.56 | 0.079 | 0.29 |
| Total Delay | CE = −0.002 | −0.65 | 0.64 | 0.996 | <0.001 | CE = −1.1 | −1.8 | −0.42 | 0.002 | 0.53 | CE = −0.6 | −1.4 | 0.14 | 0.111 | 0.26 |
| PASAT | | | | | | | | | | | | | | | |
| PASAT_2 | CE = −2.9 | −7.3 | 1.5 | 0.200 | 0.22 | CE = −6.9 | −11.6 | −2.2 | 0.004 | 0.47 | CE = −6.7 | −11.9 | 1.6 | 0.011 | 0.40 |
| PASAT_3 | CE = −1.2 | −6.0 | 3.6 | 0.621 | 0.09 | CE = −5.9 | −11.0 | −0.89 | 0.021 | 0.37 | CE = −7.6 | −13.2 | −2.1 | 0.007 | 0.42 |
| SDMT | CE = −5.9 | −10.0 | −1.7 | 0.006 | 0.46 | CE = −15.1 | −19.5 | −10.7 | <0.001 | 1.08 | CE = −12.4 | −17.3 | −7.6 | <0.001 | 0.88 |
| 10/36 Spatial Recall | | | | | | | | | | | | | | | |
| 10/36 SRT | CE = −2.7 | −4.2 | −1.2 | 0.001 | 0.57 | CE = −6.4 | −8.0 | −4.7 | <0.001 | 1.35 | CE = −3.5 | −5.3 | −1.7 | <0.001 | 0.76 |
| 10/36 SRT Delay | CE = −0.831 | −1.5 | −0.13 | 0.021 | 0.41 | CE = −2.0 | −2.7 | −1.2 | <0.001 | 0.89 | CE = −0.8 | −1.7 | −0.02 | 0.045 | 0.42 |
| WLG | CE = −8.9 | −11.0 | −6.7 | <0.001 | 1.37 | CE = −9.5 | −11.7 | −7.2 | <0.001 | 1.34 | CE = −5.2 | −7.7 | −2.7 | <0.001 | 0.72 |

Ctrl = control; RR = relapsing - remitting; SP = secondary progressive; PP = primary progressive; SRT = Selective Reminding Test; LTS = Long-Term Storage; CLTR = Consistent Long-Term Retrieval; PASAT = Paced Auditory Serial Addition Task (PASAT_2 = 2 s/digit; PASAT_3 = 3 s/digit); SDMT = Symbol Digit Modalities Test; 10/36 Spatial Recall (10/36 SRT = Immediate Recall; 10/36 SRT Delay = Delayed Recall); WLG = Word List Generation.

***Table 4*** *Contrast estimates (CEs) for differences between multiple sclerosis subtypes after controlling for age and gender*

| Test | RR vs SP | 95% CI | | *p* | *d* | RR vs PP | 95% CI | | *p* | *d* | PP vs SP | 95% CI | | *p* | *d* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SRT | | | | | | | | | | | | | | | |
| LTS | CE = −3.6 | −7.8 | 0.68 | 0.099 | 0.28 | CE = −4.6 | −9.9 | 0.63 | 0.084 | 0.33 | CE = 1.1 | −3.8 | 5.8 | 0.667 | 0.07 |
| CLTR | CE = −7.4 | −12.3 | −2.6 | 0.003 | 0.51 | CE = −5.7 | −11.7 | 0.33 | 0.064 | 0.36 | CE = −1.7 | −7.2 | 3.8 | 0.535 | 0.11 |
| Total Delay | CE = −1.1 | −1.8 | −0.40 | 0.002 | 0.54 | CE = −0.5 | −1.4 | 0.30 | 0.427 | 0.24 | CE = −0.54 | −1.3 | 0.23 | 0.166 | 0.23 |
| PASAT | | | | | | | | | | | | | | | |
| PASAT_2 | CE = −4.7 | −9.3 | −0.03 | 0.049 | 0.37 | CE = −5.5 | −11.2 | 0.28 | 0.062 | 0.36 | CE = 0.8 | −4.5 | 6.0 | 0.767 | 0.05 |
| PASAT_3 | CE = −5.5 | −10.5 | −0.58 | 0.029 | 0.42 | CE = −8.0 | −14.2 | −1.9 | 0.010 | 0.50 | CE = 2.5 | −3.1 | 8.1 | 0.379 | 0.14 |
| SDMT | CE = −10.0 | −14.5 | −5.4 | <0.001 | 0.71 | CE = −8.1 | −13.7 | −2.4 | 0.005 | 0.57 | CE = −1.9 | −7.1 | 3.3 | 0.476 | 0.12 |
| 10/36 Spatial Recall | | | | | | | | | | | | | | | |
| 10/36 SRT | CE = −3.8 | −5.5 | −2.1 | <0.001 | 0.73 | CE = −1.1 | −3.2 | 1.0 | 0.293 | 0.22 | CE = −2.7 | −4.6 | −0.75 | 0.006 | 0.53 |
| 10/36 SRT Delay | CE = −1.2 | −2.0 | −0.4 | 0.003 | 0.49 | CE = −0.08 | −1.1 | 0.89 | 0.864 | 0.04 | CE = −1.1 | −2.0 | −0.21 | 0.015 | 0.46 |
| WLG | CE = −0.2 | −2.4 | 2.0 | 0.830 | 0.04 | CE = 4.4 | 1.7 | 7.2 | 0.002 | 0.65 | CE = −4.7 | −7.2 | −2.2 | <0.001 | 0.63 |

RR = relapsing - remitting; SP = secondary progressive; PP = primary progressive; SRT = Selective Reminding Test; LTS = Long-Term Storage; CLTR = Consistent Long-Term Retrieval; PASAT = Paced Auditory Serial Addition Task (PASAT_2 = 2 s/digit; PASAT_3 = 3 s/digit); SDMT = Symbol Digit Modalities Test; 10/36 Spatial Recall (10/36 SRT = Immediate Recall; 10/36 SRT Delay = Delayed Recall); WLG = Word List Generation.

for each group are provided in table E-2 on the *Neurology* Web site). The first multivariate analysis showed large between-group differences ($F$[27,867] = 5.9, $p < 0.001$, $\eta^2 = 0.16$). The largest effect sizes were found for SDMT, 10/36 Spatial Recall, and WLG (table 3). RRMS patients performed poorer than control subjects on these three tasks. SPMS and PPMS patients performed poorer than control subjects on all tasks, but the greatest differences were observed for SDMT, 10/36 Spatial Recall, and WLG (see Cohen $d$ in table 3). The second multivariate analysis including only MS patients also showed large between-group differences ($F$[18,444] = 4.2, $p < 0.001$, $\eta^2 = 0.15$). Effect sizes were smaller but still in the moderate range (table 4). RRMS patients scored higher than SPMS patients on all measures except WLG and SRT-LTS. RRMS performed better than PPMS patients on the PASAT and SDMT but performed poorer on the WLG. SPMS patients performed poorer than PPMS patients on two of the five tasks: 10/36 Spatial Recall and WLG. The largest difference was observed for WLG (see Cohen $d$ in table 4).

A number of differences between control subjects and RRMS patients (SDMT, 10/36 SRT Delay), control subjects and PPMS patients (SRT-CLTR and Total Delay), SPMS and RRMS patients (SRT-LTS and WLG), and PPMS and RRMS patients (SRT-LTS, CLTR, and Total Delay, 10/36 SRT and 10/36 SRT Delay) depended on whether age differences were taken into account. The difference between RRMS and PPMS patients on the WLG was smaller when age differences were not controlled for (contrast estimate = 2.1, $p = 0.066$). Previous analyses had revealed that linear adjustment for age might not be ideal for this task. In separate univariate analyses for WLG, RRMS and PPMS patients and SPMS and PPMS patients still differed after the introduction of a quadratic term for age ($F$[2,228] = 7.6, $p = 0.001$; PP vs RR: 4.5, $p = 0.001$; PP vs SP: 4.9, $p < 0.001$). In pairwise comparisons by age category, RRMS patients in their forties or fifties performed poorer than PPMS patients of the same age (forties: $T$[30] = 2.7, $p = 0.011$; fifties: $T$[23] = 4.5, $p < 0.001$) (see table E-3 on the *Neurology* Web site). SPMS patients in their fifties performed more poorly than PPMS patients of the same age ($T$[36] = 5.3, $p < 0.001$).

When EDSS or disease duration replaced age as a covariate in the overall analyses, the results remained largely unchanged. After controlling for EDSS, however, RRMS and PPMS patients no longer differed on PASAT ($p = 0.066$ for PASAT_3; $p = 0.269$ for PASAT_2) and SDMT ($p = 0.320$). The differences between RRMS and SPMS patients on the PASAT and SDMT also decreased ($p = 0.550$ for PASAT_3; $p = 0.725$ for PASAT_2; $p = 0.044$ for SDMT).

**Discussion.** We found that all MS groups have cognitive deficits. Deficits were generally most severe in SPMS patients, followed by PPMS patients and then RRMS patients who differed from control subjects in three of the five tasks of the BRB-N. We also found that there is heterogeneity in the type of cognitive disabilities demonstrated by patients with different MS phenotypes. RRMS patients performed significantly better on the SDMT and the PASAT than PPMS and SPMS patients. Like all other tasks of the BRB-N, SDMT and PASAT require specific WM operations, which in turn require central processing speed.[20] PASAT and SDMT, however, appear to depend more strongly on processing speed than the other tasks, considering that PASAT is externally paced, whereas in the instruction of SDMT, the emphasis is on performing as many substitutions as possible within a given time span. The observed group differences possibly reflect that progressive MS subtypes have more widespread white matter disease (either lesions or diffuse pathology), resulting in loss of information-processing speed. Differences with RRMS patients were observed after controlling for age but largely disappeared after controlling for EDSS, which suggests that disease

severity accounts for more variation in information-processing speed than age.

On the tasks requiring higher-order WM processes with less evident processing speed demands, that is, the 10/36 SRT and WLG, the SPMS patients had more problems than the PPMS patients. Patients with RRMS also performed more poorly on WLG than PPMS patients. Relatively poor spatial WM in SPMS and RRMS compared with PPMS is in agreement with findings from other studies.[3,7,13] Despite the fact that poor verbal fluency and poor higher-order WM memory operations have been shown in RRMS before,[5,6,14] poor verbal fluency in RRMS relative to PPMS contrasts earlier findings.[12] Our result does appear to be robust, considering the fact that it remained significant after controlling for a curvilinear relationship with age. Still, introducing factors such as age, EDSS, and disease duration as covariates might not be ideal as these are essentially inherent to the disease subtype. For the same reason, matching groups on age would be problematic for the population of this study. However, when we did take this approach for verbal fluency, poorer performance by RRMS compared with PPMS was confirmed for patients in their forties and fifties.

Biochemical changes in response to inflammation might help explaining cognitive differences between MS subtypes.[21,22] For instance, enhancing inflammatory lesion events on MRI are more frequent in SPMS and RRMS relative to PPMS[8-10] and have been associated with blood–brain barrier disruption.[9,23] It might be hypothesized that blood–brain barrier disruption interferes with normal transport ratios of neurotransmitter precursors across the blood–brain barrier, leading to specific neurotransmitter imbalances, or that the blood–brain barrier becomes more permeable, resulting in an increase of toxins in the brain. Such mechanisms may be associated specifically with poor performance on the WLG and the 10/36 SRT, considering the fact that the WM operations required by these tasks were shown to be very sensitive to catecholaminergic modulation[24-26] and proinflammatory cytokines.[27,28]

Future studies aiming at elucidating the pathophysiology of cognition in different forms of MS should employ sensitive cognitive tests that strongly demand (central or peripheral) processing speed and few other cognitive operations and tasks that require high-order WM operations without an explicit demand for information-processing speed.


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## References


1. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685–691; comment in Neurology 1991;41:2014–2015.
2. Camp SJ, Stevenson VL, Thompson AJ, et al. Cognitive function in primary progressive and transitional progressive multiple sclerosis: a controlled study with MRI correlates. Brain 1999;122:1341–1348.
3. Foong J, Rozewicz L, Chong WK, Thompson AJ, Miller DH, Ron MA. A comparison of neuropsychological deficits in primary and secondary progressive multiple sclerosis. J Neurol 2000;247:97–101.
4. de Sonneville LMJ, Boringa JB, Reuling IEW, Lazeron RHC, Adèr HJ, Polman CH. Information processing characteristics in subtypes of multiple sclerosis. Neuropsychologia 2002;40:1751–1765.
5. Rovaris M, Iannucci G, Falautano M, et al. Cognitive dysfunction in patients with mildly disabling relapsing–remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. J Neurol Sci 2002;195:103–109.
6. Pelosi L, Geesken JM, Holly M, Hayward M, Blumhardt LD. Working memory impairment in early multiple sclerosis: evidence from an event-related potential study of patients with clinically isolated myelopathy. Brain 1997;120:2039–2058.
7. Comi G, Filippi M, Martinelli V, et al. Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. J Neurol Sci 1995;132:222–227.
8. Thompson AJ, Kermode AG, Wicks D, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. Ann Neurol 1991;29:53–62.
9. Revesz T, Kidd D, Thompson AJ, Barnard RO, McDonald WI. A comparison of the pathology of primary and secondary multiple sclerosis. Brain 1994;117:756–765.
10. Olerup O, Hillert J, Frederikson S, et al. Primarily chronic progressive and relapsing/remitting multiple sclerosis: two immunogenetically distinct disease entities. Proc Natl Acad Sci USA 1989;86:7113–7117.
11. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907–911.
12. Zakzanis KK. Distinct neurocognitive profiles in multiple sclerosis subtypes. Arch Clin Neuropsychol 2000;2:115–136.
13. Gaudino EA, Chiaravalloti ND, DeLuca JD, Diamond BJ. A comparison of memory performance in relapsing–remitting, primary progressive and secondary progressive, multiple sclerosis. Neuropsychiatr Neuropsychol Behav Neurol 2001;14:32–44.
14. Weinstein A, Schwid SR, Schiffer RB, McDermott MP, Giang DW, Goodman AD. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. Arch Neurol 1999;56:319–324.
15. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13:227–231.
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444–1452.
17. Rao SM. Cognitive Function Study Group, NMSS. A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. New York: National Multiple Sclerosis Society, 1990.
18. Troyer AK, Moscovitch M, Winocur G. Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. Neuropsychology 1997;11:138–146.
19. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Earlbaum Associates,1988.
20. Kail R. Speed of information processing in patients with multiple sclerosis. J Clin Exp Neuropsychol 1998;20:98–106.
21. Huitinga I, Erkut ZA, Van Beurden D, Swaab DF. The hypothalamo-pituitary-adrenal axis in multiple sclerosis. Ann NY Acad Sci 2003;992: 118–128.
22. Maeda A, Sobel RA. Matrix metalloproteinases in the normal human central nervous system, microglial nodules, and multiple sclerosis lesions. J Neuropathol Exp Neurol 1996;55:300–309.
23. Sobel RA. The pathology of multiple sclerosis. Neurol Clin 1995;13:1–21.
24. McDowell S, Whyte J, D'Esposito M. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain 1998;121:1155–1164.
25. Robbins TW. Chemical neuromodulation of frontal–executive functions in humans and other animals. Exp Brain Res 2000;133:130–138.
26. Sharma T, Hughes C, Soni W, Kumari V. Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. Psychopharmacology 2003;169:398–403.
27. Heyser CJ, Masliah E, Samimi A, Campbell IL, Gold LH. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proc Natl Acad Sci USA 1997;94:1500–1505.
28. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001;58:445–452.