Variables Affecting Memory Deficits in Relapsing-Remitting Multiple Sclerosis

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Abstract

Memory impairment features prominently among the cognitive problems caused by Multiple Sclerosis (MS). In the present study 33 patients diagnosed with the relapsing-remitting form of MS and 30 controls matched on age, education, gender, and IQ were tested on measures of verbal learning (immediate and delayed recall of word lists and short stories), and lexical retrieval from long term memory (verbal fluency tests). MS patients demonstrated significant deficits in both immediate and delayed recall ability as well as in verbal fluency. Group differences in delayed verbal recall depended upon initial encoding ability of the same material, with the exception of delayed recall of the Wechsler Memory Scale Logical Memory story B. This finding may have been due to greater susceptibility of MS patients to the effects of proactive interference. Verbal fluency deficits appeared to depend upon a general impairment in the speed of information processing.

INTRODUCTION

Multiple sclerosis is a common idiopathic inflammatory disorder of undetermined etiology that involves the white matter of the cerebral hemispheres, brainstem, optic nerves, cerebellum and spinal cord (Kurtzke, 1988). Cognitive impairment can be one of the various manifestations of MS (Bobholz, & Rao, 2003). Cognitive dysfunction typically consists of different intermingled domain-specific deficits rather than a uniform overall cognitive decline. Memory, attention, speed of information processing (auditory, visual, and visuomotor), executive functions and visuospatial abilities are most commonly affected by MS.

Memory impairment is typically observed, although not all forms of memory function are uniformly affected by the disease (Rao, Leo, Bernadin, & Unversagt, 1991). While the retrieval and use of lexical/semantic information stored in long-term memory, as measured by tests of vocabulary knowledge, appears to be intact (Zakzanis, 2000), significant deficits have often been reported in the ability to retrieve lexical information on cue and in the ability to learn and subsequently recall new verbal information. The former ability is typically assessed through verbal fluency tasks requiring active search of the contents of secondary memory, retrieval and verbal production of words based on either semantic (conceptual category) or phonemic/orthographic criteria. Performance on both subtests is affected by speed of information processing as well as speech (motor) automaticity, although the extent to which they involve executive functions is debatable (De Sonneville, et al., 2002). Generating words based on phonemic/orthographic criteria may tap into executive abilities more than verbal search and retrieval based on semantic categories, as the former task requires the implementation of an unusual cognitive strategy (Perret, 1974). Both tasks require participants to switch search and retrieval criteria, as well as to monitor continuously their responses in order to avoid repetition and to inhibit inappropriate response alternatives. Performance of the semantic task, however, is believed to reflect, additionally, the integrity of semantic memory (Rosser & Hodges, 1994).

Studies on patients with the RR form of MS have found greater impairment on semantic than phonemic fluency tasks (Caine, Bamford, Schiffer, Shoulson, & Levy, 1986). Given the strong correlation between general verbal ability measures and performance on verbal fluency tasks (Crawford, Obonsawin, & Bremner, 1993; Miller, 1984), it is important to control for individual differences on the former when assessing group differences on the latter measures. Moreover, in view of the incontrovertible evidence regarding reduced processing speed in MS (e.g., Denney, Sworowski, & Lynch, 2005; Rao, Aubin-Faubert, & Leo, 1989; Ryan, Clark, Klonoff, Li, & Paty, 1993), it is important to assess the effects of the disease on verbal

fluency, independent of the effects of processing speed, especially in tasks that have a motor component.

With respect to verbal learning abilities, the impairment is often found affecting episodic and working memory, while implicit memory functions involving skill learning, word stem (lexical) and semantic priming, as well as primary short-term memory appear to be intact (Rao, 2004). Evidence of failed long-term memory recall caused by a retrieval deficit has often been reported as the primary cause of the episodic memory impairment with relative preservation of the encoding and storage processes (Rolania, Olmos, Urdiain, 2006; Ruggieri et al., 2003; Coolidge, Middleton, & Griego, 1996; Armstrong et al., 1996). This conclusion is supported by findings of preserved recognition ability. Other investigators have provided evidence that verbal long-term memory impairment among MS patients results from inadequate encoding and initial learning (De Luca, Barbieri-Berger, & Johnson, 1994; Drake, Carra, Allegri, & Luetic, 2006), and ability to bind contextual information during the encoding phase (Thornton, Raz, & Tucke, 2002). As in the case of verbal fluency, verbal learning ability is affected by general verbal ability, as indexed by vocabulary knowledge, among other measures (Steinberg, Bieliauskas, Smith, & Ivnik, 2005; West, Crook, & Barron, 1992). It is therefore important to evaluate performance on verbal learning measures in relation to general verbal ability.

Individual variability seems to be the crucial factor in establishing the neurocognitive status in MS. Clinical variables such as disease course, disease duration, lesion load, brain region(s) involved and level of physical disability can influence specific patterns of acquisition and retrieval impairments in MS (Calabrese, 2006; Deloire et al., 2005). Several studies have shown that patients with the relapsing-remitting form of MS (RR-MS) have less severe cognitive and functional difficulties than patients with the progressive form of the disease (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001; Huijbregts et al., 2004), although other investigations have failed to find any association between memory impairment, on the one hand, and physical disability, illness duration or course, on the other (Rao, 2004; Amato et al., 2006; Bagert, Camplair, & Bourdette, 2002).

The present study had four specific aims. First, to confirm the severity of memory dysfunction in a group of patients affected by RR-MS. Two types of memory function were assessed: (a) the ability to learn new verbal information in either list or story form and subsequently retrieve this information following various time delays and (b) the ability to retrieve lexical entities from secondary memory storage according to pre-specified criteria (verbal fluency). The clinical significance of presumed deficits in verbal fluency and verbal learning abilities was assessed concurrently, by comparing patient's performance with population norms and in relation to measures of crystallized verbal ability. In parallel, patient performance was compared to that of a group of healthy controls who were individually matched to the patients on demographic, educational, and socioeconomic-cultural characteristics.

Second, to evaluate the role of initial encoding-learning ability of the word list and story material on group differences in delayed verbal recall ability.

Third, to examine the contribution of processing speed and executive abilities to verbal fluency deficits. Processing speed was indexed by performance on two visuomotor tasks, the Grooved Pegboard (Heaton, Grant, & Matthews, 1992) and Trail Making-A (Reitan, 1955). Executive ability was assessed using two indices: performance on a visual problem-solving test (WASI Matrices) and differential performance on Trails-A and Trails-B (Lezak, 1995; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991).

Fourth, to assess the potential relation between patient clinical characteristics (disease duration and physical disability) to verbal learning and fluency deficits (Huijbregts et al., 2004).

MATERIALS AND METHODS

PARTICIPANTS

Thirty-three patients, who met the criteria for clinically definite MS, with a relapsing-remitting course and mild to moderate physical disability, were recruited from the University Hospital Neurology Department. Healthy controls (n = 30) were individually pair-matched with the patients for age, gender, level of education, and geographic area of origin (rural/urban). Written informed consent was obtained from all patients and confidentiality was assured. Diagnosis of MS was confirmed by a Board Certified Neurologist according to Poser et al.'s (1983) criteria.

Exclusion criteria for patients and controls included: (a) history of alcohol or drug abuse, head injury with loss of consciousness, schizophrenia or bipolar disorder, learning disability or any neurological disorder other than MS, (b) significant visual or motor impairment that would interfere

with cognitive testing, (c) current exacerbation in the patient's illness (testing was performed at least 4 weeks after the full remission of motor/sensory deficits).

Physical disability of the patients was assessed by the Expanded Disability Status Scale (EDSS), which examines functional integrity in seven core areas (motor, sensory, cerebellar, brain stem, visual, mental, and sphincter function). The patients averaged 8.2±5.4 years since initial diagnosis and scored between 0 and 6 points on EDSS (Mean = 2.5±1.86). Clinical information on the patients is presented in Table 1.

Figure 1

Table 1: Individual clinical information for the RR-MS patients.

S	Gen.	Age (yrs)	DD (yrs)	First symptom	EDSS	CES-D
1	m	39	26	True binocular diplopia	6	3
2	m	34	16	Transient weakness/paraesthesiae of left hand	1	3
3	m	41	18	Unilateral (left) optic/ retrobular neuritis	6	15
4	f	35	8	L optic neuritis	1	7
5	f	29	9	Transient weekness/paraesthesiae of entire right limb	5.5	16
6	m	31	10	R optic/retrobular neuritis	1.5	14
7	m	31	6	Transient weakness/paraesthesiae of left hand	1.5	18
8	m	44	9	Transverse myelitis	4.5	18
9	m	21	4	Optic/ retrobular neuritis and transient weakness/paraesthesiae	1	14
10	m	27	3	True binocular diplopia	1	20
11	f	35	11	Unilateral optic/ retrobular neuritis	2	22
12	f	45	9	L optic/ retrobular neuritis	6	36
13	f	32	10	Transient weakness/paraesthesiae	1	9
14	f	34	8	True binocular diplopia	1	3
15	m	30	3	Transient weakness/paraisthesiae of hands and legs	1	19
16	f	29	12	R optic/retrobular neuritis & transient weakness/paraisthesiae	1	21
17	f	35	9	Gait ataxia	5.5	14
18	m	35	7	L transient weakness/paraisthesiae	1.5	28
19	f	51	15	L optic/ retrobular neuritis	1	33
20	f	36	13	True binocular diplopia	1.5	31
21	m	51	8	True binocular diplopia	4.5	22
22	f	33	4	L transient weakness/ hemiparaesis	3	11
23	m	33	7	Transverse myelitis	3.5	17
24	m	47	16	True binocular diplopia and gait ataxia	4	38
25	m	34	7	Transient weekness/paraesthesiae of entire right limb	1.5	34
26	f	40	10	L optic/retrobular neuritis	1.5	29
27	m	41	3	Transient acute non-positional vertigo and transient weakness/paraesthesiae of entire left limb	1	36
28	f	38	14	Transient weakness/paraesthesiae of entire left limb	2.5	23
29	f	35	4	L true binocular diplopia & unilateral tremor/incoordination	3.5	19
30	f	45	20	R optic neuritis and gait ataxia	2	33
31	m	32	12	True binocular diplopia	1	32
32	f	51	9	Transient weekness/paraesthesiae of entire right limb	4.5	21
33	m	39	17	Transient weekness/paraesthesiae of entire left limb	2	11

MEASURES

Participants received a battery of neuropsychological tests administered by the same clinical neuropsychologist over the course of one session. Two subscales from the Wechsler Abbreviated Scales of Intelligence (WASI) were used as indices of crystallized (Vocabulary) or fluid intelligence (Matrices). Episodic memory was assessed with the Logical Memory subscale from the Wechsler Memory Scale (WMS-LM) and the California Verbal Learning Test (CVLT). The following indices were computed from WMS-LM: (a) Number of elements correctly recalled from Story A in the immediate recall condition (LM-Immediate Recall-A), (b) Number of elements correctly recalled from Story B-immediate recall (LM-Immediate Recall-B), (c) Number of elements correctly recalled from Story A after a 25 minute delay without reminding (LM-Delayed Recall-A), (d) Number of elements correctly recalled from Story B after a 25 minute delay without reminding (LM-Delayed Recall-B), (e) LM Immediate Recall index minus number of elements recalled without retelling after a 25 minute delay (LM Retention Index).

The CVLT consisted of: a) word-list learning (auditory verbal learning of a list of 16 words along 5 trials), b) delayed free recall (free recall of the list after a 20 minute delay), c) Immediate Cued Recall (free recall aided by semantic category cueing), d) Delayed Cued Recall (free recall aided by semantic category cueing after the 20 minute delay), e) recognition. The following indices were derived from CVLT: (i) number of correct responses on each of the first and fifth learning trials (CVLT-1, CVLT-5), (ii) total words recalled after a delay without reminding (CVLT Delayed Recall Index), (iii) difference in the number of words correctly recalled on Trial-5 minus the number of words recalled on Trial-1 (CVLT Learning Index), (iv) number of words recalled on Trial-5 minus the Delayed Recall Index (CVLT Retention Index). Perseveration errors (unintentional repetition of items during the same trial) as well as intrusion errors (production of items not present on the list) were also recorded.

Cued retrieval from long term memory was assessed using the Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976; Kosmidis, Vlahou, Panagiotaki, Kiosseoglou, 2004). The test consists of six trials, three of which are preceded by a different semantic (category) cue (animals, fruits, objects) and three preceded by a phonological (or letter) cue (A, X, □). The total score on each condition is considered to be an index of the ability to use external strategies to aid verbal retrieval as well as an index of strategy-switching ability. Accordingly, in addition to the total score for each condition, we examined the score for the first trial in each condition, as an index of retrieval from long-term memory that is independent of strategy-switching

ability.

Visuomotor speed and executive ability was assessed using the Trail Making Test –Form A (TMT-A) and the Grooved Pegboard Test (which also requires fine motor coordination). The Trail-Making Test-Form B (TMT-B) provided a measure of set shifting ability indexed by the difference in execution time between TMT- and TMT-. This measure is much less dependent upon individual differences in visuomotor speed than TMT-A or TMT-B scores alone.

The Center for Epidemiology Studies-Depression Scale (CES-D; Radloff, 1977) was completed by all participants and used as a covariate in the analyses in order to control for differential effects of mood disturbances between groups on cognitive ability.

Normative data from the Greek population were available for two tests, the COWAT (Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004) and Logical Memory Story recall (Simos & Kasselimis, unpublished data). Analyses were performed on both standard and raw scores, the latter in order to take advantage of the careful matching of the patient and control group on geographic and cultural characteristics.

RESULTS

Preliminary analyses established the equivalence of the two study groups on demographic and general cognitive measures. The two groups did not significantly differ with respect to demographic variables (age, gender and years of education), verbal or non-verbal IQ, CES-D score or age, although, as evident in Table 2, patients as a group scored slightly higher than controls on measures of verbal and non-verbal intelligence. A non-significant tendency for higher scores on CES-D was also noted for MS patients ($p > .06$).

Figure 2

Table 2: Demographics and performance of controls (n = 30) and RR-MS patients (n = 33) on measures of verbal and non-verbal intelligence, and depression.

		Mean	SD	p
WASI- Vocabulary	Control	50,70	11,84	.62
	Patient	52,00	8,86	
WASI-Matrices	Control	35,87	20,34	.24
	Patient	41,64	17,84	
CES-D	Control	15,40	9,76	.06
	Patient	20,21	10,30	
Age	Control	34,27	9,45	.41
	Patient	36,06	7,48	
Education (years)	Control	14,17	2,12	,18
	Patient	13,30	2,80	
M/F	Control	13/17		
	Patient	17/16		

Aims 1 & 2: Memory impairment in RR-MS. The first specific aim of the study was to assess the pattern and severity of verbal memory deficits in patients with RR-MS. As shown in Table 3, group differences were significant on all immediate recall measures with similar effect sizes, and persisted after controlling for CES-D scores. Perseveration (mean = 1.7±1.7 and 2.0±1.9 for controls and patients, respectively) and intrusion errors (mean = 1.0±1.5 and 1.0±1.2 for controls and patients, respectively) were too few to meaningfully assess group differences.

Figure 3

Table 3: Group effects on immediate recall measures

				Controlling for CES-D score	
		(1,61)		1,59)	
LM A-Immediate Recall	48	02	3	2	)
LM B-Immediate Recall	68	02	)	3	3
CVLT-1	20	009	1	1	1
CVLT-5	61	005	2	2	)
CVLT Immediate Cued Recall	57	008	1	2	)

Regarding delayed recall of the stories and word list, significant group differences persisting after controlling for CES-D score were restricted to three indices (LM Delayed Recall of Story B and CVLT Delayed recall, with and without category cues; see Table 4). Differences in the ability to perform delayed recall of the CVLT word list (cued or uncued) were abolished when controlling for immediate recall ability (CVLT Immediate Recall on Trial 5; $p > .94$, $^2 = .00$). Controlling for variance in immediate recall of Story B, however, did not affect group differences in the ability to recall the story following a delay ($F[1,57] = 14.21$, $p < .0001$, $^2 = .20$). Therefore, initial learning ability accounted for group differences in delayed recall, with the

exception of LM Story B (Specific Aim 2).

On the COWAT controls produced significantly more words on both the phonological and semantic subtests (see Table 5). The results (effect size indices) indicated greater group differences on the semantic task which were independent of CES-D scores. In view of the fact that total scores on each of the COWAT subtests may reflect set-shifting ability (participants had to change search and retrieval rules every minute), we compared the two groups on performance on each part of each subtest (animal names, fruits, objects and words beginning with "X", "S", or "A"). The largest effect sizes were found for the first trial of each subtest, making it unlikely that patient difficulties in set-shifting ability contributed to group differences in total subtest scores.

Figure 4

Table 4: Group effects on delayed recall, learning, and retention measures.

				Controlling for CES-D score	
	F	p (1,61)	η^2	p (1,59)	η^2
LM Delayed Recall-A	3.96	.05	*.06*	.05	*.06*
LM Delayed Recall-B	18.20	.0001	*.23*	.0001	*.25*
CVLT-Delayed Recall	5.75	.02	*.09*	.04	*.07*
CVLT Learning Index	.03	.86	*<.01*	.9	*<.01*
CVLT-Cued Delayed Recall	7.91	.007	*.12*	.02	*.09*
LM Retention Index	.09	.74	*<.01*	.7	*<.01*
CVLT Retention Index	.001	.99	*<.01*	.8	*<.01*

Figure 5

Table 5: Group differences and corresponding effect sizes (η^2) on the Logical Memory-Delayed recall of story B and COWAT controlling for cognitive variables.

Covariates	LM Delayed Recall-B			COWAT Phonological			COWAT Semantic		
	F	p	η^2	F	p	η^2	F	p	η^2
(1,61)	18.20	.0001	.23	5.36	.02	*.08*	9.27	.003	*.13*
(1) WASI-Vocabulary (df: 1,60)	26.65	.0001	.31	4,99	.03	*.08*	8.94	.004	*.13*
(2) TMT B-A, WASI-Matrices (df: 1,59)	11.36	.001	.17	2.95	.09	*.05*	11.64	.001	*.17*
(3) Pegboard, TMT-A				.89	.35	*.02*	3.38	.07	*.05*

Ability indices which were entered as covariates in three separate tests of group differences: (1) Crystallized verbal ability, (2) Executive abilities, and (3) Visuomotor processing speed. Given that LM is not a timed task, it was not deemed necessary to control for individual differences on visuomotor speed when assessing group differences on this variable.

Age- and education-adjusted standard scores based on Greek norms were available for LM and COWAT scores. Significantly impaired performance was defined by a score lower than 1.3 SDs below the population mean (corresponding to the 10th percentile). Significant impairment was defined as performance lower than 1 SD below the population mean. The distribution of scores meeting this criterion did not differ significantly between groups in any but two measures, LM Delayed Recall of Story B and COWAT Semantic, where the rate of significant deficit was significantly higher in patients than controls, X^2 = 8.39, $p < .004$ and X^2 = 3.96, $p < .05$, respectively. Impaired performance was found in 14 patients and 3 controls in the former, and 10 patients and 3 controls in the latter task.

Determinants of group differences in verbal learning and fluency. In view of the central role of visuomotor processing speed and executive ability in addressing specific aim 3, group differences on these measures were assessed first. As expected, patients' performance was significantly slower than controls' on the Grooved Pegboard, $F(1,59) = 8,47$, $p < .005$, as well as on both Trails A and B, $F(1,59) = 13,93$, $p < .0001$ and $F(1,59) = 9,06$, $p < .004$, respectively. The group difference on the Trails B minus A index was also significant, $F(1,59) = 4,67$, $p < .04$. These differences persisted after controlling for variance due to CES-D score. Group differences were stronger on Trails A (η^2 = .19) compared to Trails B (η^2 = .13), and Trails B-A (η^2 = .07). Taken together these findings suggest that the primary deficit of the present group of patients concerned motor and visuo-motor speed rather than executive function (elaboration and alternation of cognitive strategies). Moreover, as previously noted, if anything, patients as a group slightly outperformed controls on the measure of non-verbal problem solving ability (WASI Matrices).

The potential contribution of cognitive measures to group differences on the COWAT and Delayed Recall of story B was assessed. In separate ANCOVAs with Group as the between subjects variable, the following variables were included as covariates: (a) WASI Vocabulary (a measure of crystallized verbal ability), (b) WASI Matrices and Trails B minus Trails A score (complementary measures of fluid intelligence and executive function), and (c) Trails A and Grooved Pegboard mean performance (indices of visuomotor processing speed). As shown in Table 5, covariates representing general verbal and executive ability did not affect the significance or the magnitude of the group

effect on the Delayed Recall of Story B and the Semantic COWAT subtest. Group differences on both measures, however, were all but eliminated when measures of processing speed were entered as covariates.

Specific Aim 4: Relation between clinical indices and cognitive measures. As shown in Table 6, cognitive measures did not appear to be related to clinical variables, namely level of physical disability and disease duration, with the exception of Delayed Recall of Story B. Score on the EDSS scale was a significant predictor of recall performance independent of disease duration (partial r = -.46, p < .006). Disease duration, on the other hand, did not make an independent significant contribution to recall performance (partial r = -.12, p > .42).

Figure 6

Table 6: Partial correlation coefficients with EDSS controlling for age and education level

LM-A1	LM-B1	LM-A2	LM-B2	CVLT	Sem	Phon	Matrices	TrailsA	TrailsA-B	Pegs
-,29	-,21	-,46	-,58	-,27	-,39	-,03	-.09	,33	,48	,61
*	*	,01	,001	*	,04	*	*	*	,01	,001

LM-A1, LM-A2: Logical Memory Immediate and delayed recall of story A, respectively. LM-B1, LM-B2: Corresponding values for LM Story B. CVLT: Delayed recall of CVLT List. Sem., Phon.: Semantic and Phonetic COWAT subtests. TrailsA-B: Difference in performance (time to complete) between Trails A and Trails B. Pegs: Performance on the Grooved Pegboard. *: p > .1.

Disease duration did not correlate significantly with measures of executive function, verbal learning, fluency, or physical disability (partial correlation coefficients controlling for age and education level < .2 in all cases). Disease duration was, however, a significant predictor of indices of visuo-motor processing speed, as suggested by partial correlation coefficients r = .44 (p < .02) and r = .43 (p < .02) with Pegboard and Trails-A.

DISCUSSION

Our findings confirm previous reports on the deleterious effect that RR-MS exerts on memory functioning. Reduced memory performance was found relative to a group of healthy participants who were individually matched to the patients on demographic variables (age, gender, education, geographical origin, and socioeconomic background), and verbal and non-verbal IQ. The ability to learn new, supraspan, verbal information, in a story or list form, and to retrieve this information shortly after it had left consciousness, even when semantic (category) cues were provided, was impaired. On average, patients scored significantly lower on delayed recall measures than controls (Logical Memory Stories A and B, CVLT, cued and uncued delayed recall). Nevertheless, group differences on all but one such measure (Logical Memory Delayed recall of Story B) were statistically eliminated when performance on immediate recall performance on respective tests was controlled for. This result is not consistent with an impairment in learning rate or consolidation (which would result in significantly more impaired delayed than immediate recall). It is therefore likely that group differences in subsequent recall ability can be accounted for by systematic group variance in the initial encoding of the information. This is in general agreement with findings that when testing conditions ensure comparable levels of initial verbal learning MS patients perform at similar levels on delayed recall tasks compared to healthy controls (Demaree, Gaudino, DeLuca, & Ricker, 2000).

In contrast, delayed recall deficits were pronounced and apparently not mediated by group differences in immediate recall ability in the case of LM Story B. One interpretation of this finding relates to the placement of Story B within the Logical Memory subtest administration, which renders it susceptible to proactive interference from information contained in Story A. One may hypothesize that individual variance in immediate recall of Story B reflects the application of strategic encoding and/or retrieval processes to a greater extent than immediate recall of Story A (which is not affected by proactive interference). The added cognitive demands presented by Story B may also account for the prominent role of Story B delayed recall performance as a predictor of functional impairment, as revealed in the present study.

Presumably then, conscious processing and cognitive control abilities (Scarrabelotti & Carroll, 1999) which were not tapped by the two indices of executive function used in the present study may account for the asymmetric impairment in delayed recall of story B. Difficulties in these cognitive domains may have adversely affected the patient's capacity to resist the effects of proactive interference posed by story A (presentation and subsequent recall trials). There is some indirect evidence from previous studies that MS patients encounter increased difficulty in coping with tasks that impose greater demands for conscious control of cognitive resources. For instance, Coolidge et al. (1996) reported similar group effects (MS patients and healthy controls) on

immediate and delayed word list measures. These effects were present only when the lists contained distractor words attesting to the possible deleterious effects of interference. Further, a potentially interesting parallel may be drawn between the present data and the lack of a recency effect on the Rey Auditory Verbal Learning Test (Godoy, Perez, Sanchez-Barrera, Muela, Mari-Beffa, & Puente, 1995). More recently, Griffiths et al. (2005) conducted analyses of interference from a large cohort of MS patients who were administered the CVLT. They reported that patients showed significantly greater susceptibility to semantic interference when attempting to recall items from List B as compared to healthy controls. Apparently, patients may have encountered greater difficulty than controls in maintaining "separate" representations of items that belonged in the same semantic category across lists. It is conceivable that patients in the present study may have found it difficult to organize semantically the elements of story B while they were attempting actively to maintain elements of Story A in memory.

In addition to verbal learning, the present study examined the nature of group differences in the ability to retrieve already consolidated, word-level information (using the COWAT) in a series of analyses where a number of potential mediating factors were used as covariates. MS patients showed significantly reduced ability to retrieve words using either a semantic (category) strategy or a phonological/phonetic strategy. Group differences were stronger and more resistant to the effects of potential confounding factors on the semantic rather than on the phonological subtest. Group differences in the semantic subtest of the COWAT were also found for the first trial of the test (production of animal names), suggesting, that set shifting abilities, which may be involved in performance in subsequent trials using different retrieval strategies, did not account for the reduced performance of MS patients, at least in the semantic condition. Moreover, group differences on the semantic subtest of the COWAT remained significant when any of the measures of immediate or delayed recall ability were entered as covariates either separately or combined. Our findings are in agreement with the general conclusion of a meta-analysis (Zakzanis, 2000) which reported more severe deficits on semantic than phonetic fluency, although a second meta-analysis reported similar effect sizes for the two types of fluency tests (Henry & Beatty, 2005). Although our patients showed signs of difficulties in a measure of executive function (TMT A minus B), individual differences on this measure did not affect the size of the group differences on secondary memory and fluency. Conversely, group differences on verbal fluency measures appear to depend on measures which closely reflect information processing ability (Trails A and performance on the Grooved Pegboard). Although group differences were greater on semantic than phonemic fluency, they were both eliminated when individual differences on processing speed measures were taken into account. These findings are in agreement with previous reports that MS patients may display less efficient semantic memory searching ability difficulties which do not depend upon executive function abilities (Beatty, Monson, & Goodkin, 1989).

Finally, in agreement with previous reports, performance on cognitive tasks did not depend upon disease duration, and only one measure, delayed recall of story B, appeared to be affected by the level of physical disability as indexed by the patient's EDSS score (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988; Filippi et al., 1994; Lynch, Denney, & Parmenter, 2005). Self-reported presence of depressive symptoms did not affect any of the group differences in the present as in previous studies on memory in MS (Rao, Leo, & Aubin-Faubert, 1989).

To summarize, the present findings confirm previous reports of reduced ability to recall verbal information in relapsing remitting MS. Decline in memory performance was evident independent of individual differences in crystallized or fluid intelligence measures. Under learning conditions that did not pose special demands for cognitive resources, recall deficits were fully accounted for by deficient encoding of the material to be learned. When the ability to recall verbal information in story form was subject to proactive interference, initial encoding deficits did not account for later difficulty to recall the story content. General slowing of information processing and response ability, for the most part, accounted for the reduced ability of the patients to retrieve stored lexical entries from long term storage.

As the relation between the location of demyelinating lesions in our patients and the pattern of cognitive deficits is crucial, it cannot be ascertained at present if verbal fluency and verbal learning/recall deficits share a common pathophysiologic substrate. This notion could be tested in future studies by examining the relation between lesion size, number and location with cognitive and disability measures. Tests of non-verbal memory (e.g. with faces and spatial locations) should be conducted in future studies to extend the present findings.

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