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ARTICLE

Longitudinal analysis of verbal episodic memory in patients with relapsing-remitting multiple sclerosis

Análise longitudinal da memória episódica verbal em pacientes com esclerose múltipla remitente-recorrente

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ABSTRACT

Objective: A 4.5-year follow-up study was conducted to characterize baseline verbal episodic memory (VEM) and its behavior and to assess the effects of relapsing-remitting multiple sclerosis (RRMS) on this domain. **Methods:** Twenty-nine patients with RRMS underwent two neuropsychological assessments performed an average of 4.5 years apart. Twenty-six control participants underwent a single neuropsychological assessment. A significance level of $p < 0.005$ was adopted to denote a significant difference between the groups on the Mann Whitney and Wilcoxon paired statistical analyses. **Results:** No statistical difference was found in the results of the VEM tests between the first and second neuropsychological assessments of the patients. However, a statistical difference was evident between the patient and control groups in the results of the VEM tests. **Conclusion:** The patient group showed changes in the VEM relative to the control group. After approximately 4.5 years of disease, the patient performance on the VEM stabilized or improved.

Keywords: multiple sclerosis; cognition; longitudinal studies.

RESUMO

Objetivo: Neste estudo, propomos a caracterização da Memória Episódica Verbal (MEV) basal e o seu comportamento após o período de 4,5 anos de doença, a fim de avaliar o efeito da EMRR neste domínio. **Métodos:** Vinte e nove pacientes com EMRR foram submetidos a duas avaliações neuropsicológicas realizadas entre um intervalo de tempo médio de 4,5 anos. Vinte e seis controles foram submetidos à avaliação neuropsicológica única. Considerou-se nível de significância $p < 0,005$ para delinear diferença significante entre os grupos nas análises estatísticas *Mann Whitney* e *Wilcoxon* pareado. **Resultados:** Não houve diferença estatística nos resultados dos testes de MEV entre a primeira e segunda avaliação neuropsicológica realizada pelos pacientes. Houve discrepância estatística nos resultados dos testes de MEV entre o grupo dos pacientes e controles. **Conclusão:** O grupo de pacientes apresentou alterações de MEV quando comparado aos controles. Após 4,5 anos aproximadamente os pacientes estabilizaram ou melhoraram seu desempenho em MEV.

Palavras chave: esclerose múltipla; cognição; estudos longitudinais.

Patients with multiple sclerosis (MS) clinically present with a myriad of neurologic symptoms, including cognitive decline, regarded as having the greatest impact on key aspects of their daily living, such as managing domestic tasks, participating in society and holding down a job[1].

According to reviews of the scientific literature, one third of MS patients with the relapsing-remitting (RRMS) clinical form show cognitive impairments that are often milder than that found in the progressive subtypes of the disease[2,3].

Cognitive impairments can vary, but an impact on episodic memory is evident in the early stages of the disease. A 10-year longitudinal study revealed that decline in information processing speed and verbal episodic memory (VEM) in early RRMS patients predicted progression to the secondary progressive MS clinical form. Given that secondary progressive MS is a more severe stage of the disease, assessing these cognitive domains in the early stages of MS is vital[4].

A scientific review of the related literature[1] reported that episodic memory is one of the most common deficits found in MS, occurring in 40–65% of patients. Evidence on the nature of the episodic memory disorder in MS patients is conflicting. Some authors hold that episodic memory problems are characterized by impairment in the retrieval of learned information over the course of time. Others have shown reduced

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assimilation of new information in patients relative to controls, yet once the information has been acquired, delayed recall and recognition ability in patients had proven to be similar to those of healthy controls[5].

Numerous cross-sectional studies investigating the prevalence and pattern of cognitive dysfunction in MS are available in the literature. However, there is a dearth of studies on the evolution of the disease, from a cognitive viewpoint, over the course of time. The results of longitudinal studies in the literature are conflicting, reporting cognitive improvement, stability or decline in patients over time[6].

The objective of this study was to conduct a longitudinal assessment of VEM at two time points, consisting of a baseline assessment and another at 4.5 years of disease later, to assess the impact of RRMS on the VEM over this period. In order to characterize the VEM in RRMS patients at baseline, results were compared against those of the healthy controls. The characterization of sociodemographic and clinical variables, as well as correlation between attention and executive functions and VEM, were analyzed at the baseline assessment.

METHODS

Participants

The study sample comprised 29 patients with RRMS (19 women and 10 men), whereas the control group comprised 26 healthy subjects (17 women and nine men). Patients were recruited from the clinic for demyelinating diseases of the Department of Neurology of the Clínicas Hospital of the São Paulo University School of Medicine.

The study sample included patients diagnosed with RRMS based on the McDonald criteria (2010)[7]. All patients underwent an initial cognitive assessment to establish a baseline. In addition, only patients with an IQ within or above the mean expected IQ for age (mean = 106.60; SD = 7.65) were included, on the premise that patients of lower intelligence may have worse cognitive performance. Patient IQ was determined at baseline using the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-III)[8].

The exclusion criteria included: patients who had evolved to progressive clinical subtypes, patients with deficits that prevented assessment, patients with other central nervous system disease, patients with relapse less than 30 days before the study, patients using corticosteroids for the last 90 days before the examination, patients with a Mini-Mental State Examination (MMSE) score below the cut-off. Owing to the lack of normative MMSE data for the Brazilian population for the age stratum of the present sample, cut-off scores for the educational level were employed[9].

The control group was formed by selecting healthy participants matched for age, educational level and gender with the patients in the study group. Volunteers using psychoactive or neuroleptic medications or with a history of alcohol or illegal drug abuse were excluded. Control participants scoring below the cut-off on the MMSE for educational level[9] and above the cut-off on the Hospital Anxiety and Depression Scale (8 for symptoms of anxiety and 9 for depression) were excluded[10].

Instruments and procedures

The patients underwent a comprehensive cognitive assessment, which included specific tests of VEM such as the Hopkins Verbal Learning Test[11] and the Logical Memory subtest of the Memory Wechsler Scale[12] (Table 1). The same protocol was used for the assessments at the study baseline and endpoint.

The interval between the two neuropsychological assessments applied to the patient group ranged from 3.1 to 5.7 years with a mean and standard deviation of 4.5 (0.7) years.

The mood assessment of the patients was carried out at both baseline and follow-up using the Beck Depression Inventory[13] and the Hospital Anxiety and Depression Scale[10].

Patients, specifically, underwent the neurologic examination at two time points to identify the degree of physical disability by completing the Expanded Disability Status Scale[14] applied by the neurologist.

The healthy participants from the control group were given a single neuropsychological assessment using the same instrument that was applied to the patient group (Table 1).

Table 1. Neuropsychological instruments used and cognitive domains assessed.

Cognitive domains assessed	Neuropsychological instruments used
Attention	
Sustained	Trail Making Test A
Divided	Trail Making Test B
Selective	Stroop Test Victoria – part 3
Information Processing Speed	Symbol Digit Modalities Test
Short-term memory (verbal and visual-spatial)	
Immediate	Digit Span - Forward (WAIS-III) Corsi Blocks - Forward (WMS)
Working	Digit Span - Backward (WAIS-III) Letter-Number Sequencing (WAIS-III) Corsi Blocks - Backward (WMS)
Episodic memory (verbal and visual-spatial)	
Immediate Recall	HVLT*, BVMT, Logical Memory (WMS)*
Delayed Recall	HVLT*, BVMT, Logical Memory (WMS)*, ROCF
Recognition	HVLT* and BVMT
Executive functions	
Mental Flexibility	Modified Wisconsin Card Sorting Test
Verbal Fluency	Controlled Oral Word Association Test
Visual-spatial functions	
Visual-construction	Rey-Osterrieth Complex Figure (ROCF)
Language	
Naming	Boston Naming Test

WAIS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; HVLT: Hopkins verbal learning test-revised; BVMT: brief visuospatial memory test-revised; ROCF: Rey-Osterrieth complex figure; *Measures assessing verbal episodic memory.

Additional clinical data for the patients were drawn directly from medical records held at the neurology clinic of the Clínicas Hospital (Hospital das Clínicas) of the São Paulo University School of Medicine. All patients were using disease modifying therapies, although there were some changes and interruptions during the follow-up period (non-adherence to treatment) for different reasons such as the presence of collateral effects, pregnancy and due to patients seeking alternative treatment.

All study participants signed the free and informed consent form when asked to undergo the examinations.

Statistical analysis

Statistical analyses were carried out using the SPSS V20 for Windows 8.1 software package. Cognitive data extracted from the sample were expressed as mean, standard deviation, median and measures of spread. Raw scores were converted into Z-scores to allow comparison of the data. Data on the use of medication by patients were expressed as absolute medians.

Sociodemographic data for the control and patient groups were compared using the Student's t-test.

The normality of cognitive data extracted from the neuropsychological tests of patients was analyzed by the Shapiro-Wilk test. Given that most of the variables exhibited a non-normal distribution, non-parametric statistical tests were applied.

Cognitive data collected from patients at the first and second neuropsychological assessments were analyzed using the Wilcoxon paired statistical test. The Mann Whitney statistical test was used to compare the cognitive data from the baseline neuropsychological assessments of patients versus controls.

Spearman's correlation was used to better characterize patient deficits in VEM at the baseline assessment and to determine a possible relationship or interdependence among the clinical, sociodemographic and physical disability variables of patients for VEM.

The following clinical variables were investigated: disease duration, time since last relapse, number of relapses, use of disease modifying therapies, and use of antidepressants. Sociodemographic variables were: age, education and gender. Lastly, the variable for physical disability was assessed by the EDSS (Expanded Disability Status Scale).

Because executive functioning and attention play a role in the memorization and learning process, instruments assessing these cognitive domains were also correlated with the VEM tests using Spearman's correlation. Variables showing a level of significance of $p \leq 0.05$ on this statistical test were included in the covariance analysis. Thus, it was possible to check whether differences between patient and control performances on the VEM test persisted even after controlling for the effects of the attention and executive functioning tests.

RESULTS

Sociodemographic data for the control and patient groups are given in Table 2. There was no statistically significant difference between the groups for age, educational level or gender. Clinical and physical disability data for the patient group at the baseline assessment are given in Table 3. At the follow-up, mean disease duration was 7.25 years (SD = 2.33), time since diagnosis was 5.57 years (SD = 1.85) and the mean number of relapses was 4.10 (SD = 2.63). Twenty-five patients were on a disease modifying drug and 13 out of the 29 patients discontinued this. Ten patients were using an antidepressant at the follow-up.

The results of the longitudinal analysis, shown in Table 4, indicate patient stability in VEM, with statistically significant improvement on the immediate recall of the Hopkins Verbal Learning Test ($p = 0.019$) and delayed recall of the Logical Memory test ($p = 0.042$). In addition, there were statistically significant improvements by patients on the tests assessing sustained attention (Trail Making Test A) and working memory (WAIS-III Digit span), as well as on the semantic verbal fluency (animals) and naming tasks (Boston Naming Test). At the follow-up, patient scores on the MMSE ranged from 27 to 30 points, with a mean and standard deviation of 29.17 (0.84).

The results of the baseline assessment of control participants were statistically better than those of the patients. The patients had worse performance than the controls on the VEM tests for the immediate recall task of the Hopkins Verbal Learning Test ($p = 0.001$; $p = 0.006$) and for the delayed recall of the Logical Memory test ($p = 0.013$; $p = 0.003$).

Table 2. Sociodemographic data of sample of patients and controls.

Variable	Controls (n = 26)	Patients at baseline (n = 29)	P (controls vs patients at baseline)	Patients at follow-up (n = 29)
Age (years)			0.667	
Mean (SD)	30.62 (8.47)	29.62 (8.55)		34.34 (8.52)
Median (min-max)	28.00 (20.00–53.00)	27.00 (18.00–48.00)		33.00 (23.00–52.00)
Education (years)			0.291	
Mean (SD)	15.46 (3.56)	14.55 (2.74)		15.62 (3.12)
Median (min-max)	15.00 (11.00–24.00)	15.00 (10.00–19.00)		16.00 (10.00–22.00)
Gender (female/male)	17/09	19/10	0.992	19/10

p: statistical significance between patient and control groups at baseline according to the Student's t-test.

Table 3. Clinical data of patients at baseline and follow-up.

Variable	Baseline		Follow-up	
	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)
Disease duration (years)	2.16(0.25–7.05)	2.64(1.94)	6.68(3.62–12.69)	7.25(2.33)
Time since diagnosis (years)	0.30(0.00–5.01)	0.96(1.30)	5.26(3.32–10.66)	5.57(1.85)
Number of relapses	2.00(1.00–7.00)	2.66(1.77)	4.00(1.00–11.00)	4.10(2.63)
Time since last relapse (months)	7.70(0.40–41.96)	13.65(12.23)	28.90(2.70–107.03)	36.08(26.85)
EDSS	1.00(0.00–3.00)	1.21(0.94)	1.00(0.00–4.00)	1.14(1.21)
Disease modifying therapies (DMTs) (y/n)	-		25/04	
Interferon (Betaferon, Avonex, Rebif)	-		12	
Glatiramer acetate (Copaxone)	-		9	
Natalizumab (Tysabri)	-		1	
Rituximab (Mabthera)	-		1	
Fingolimod (Gilenya)	-		2	
Antidepressants (y/n)	-		10/19	
Poor adherence to DMTs (y/n)	-		13 / 16	

Disease duration: (date of neuropsychological assessment – date of first relapse); Time since last relapse = (date of neurologic assessment – date of last relapse); EDSS: Expanded Disability Status Scale.

The statistically significant poorer performances of patients also occurred in the attention, semantic verbal fluency and naming processes. Comparison of quantitative results for the sample of patients and controls on the neuropsychological test battery is given in Table 5.

Also, regarding the VEM, no statistically significant difference in the recognition phase of the Hopkins Verbal Learning Test was evident on comparison of the patient and control groups, or comparison of the longitudinal performance of patients.

Spearman's analysis revealed a strong positive correlation between attention and executive tasks with VEM tasks, suggesting that mnemonic impairments were accompanied by attentional and executive deficits (Table 6). The executive function tests exhibiting this correlation were the Modified Wisconsin Card Sorting Test (assessing strategy and mental flexibility) and the Letter-Number Sequencing and Digit Span subtests of the WAIS-III (both assessing verbal working memory). One attention test (Symbol Digit Modalities Test) correlated with the VEM tests. The Symbol Digit Modalities Test provides a more accurate assessment of information processing speed.

On the analysis of covariance using the attention and executive function tests cited above (Modified Wisconsin Card Sorting Test, Letter-Number Sequencing, Digit Span, and Symbol Digit Modalities Test), the patient group at baseline differed from the control group on the VEM tests even when including the attention and executive functioning measures (Table 7).

No correlation was found between VEM and sociodemographic status or clinical and physical disability data for patients at baseline or follow-up.

With regard to mood, patients in the sample had mean scores below the cut-off point on the scales assessing this parameter at both baseline and follow-up.

At the baseline, only three patients (3%) had mild depression while the remainder were classified as having minimal or nonsignificant depression with a mean and standard deviation of 6.68 (5.22), where a score of up to 10 points defines minimal depression/nonsignificant.

At the follow-up, the mean score for the sample was below the cut-off point for mood, i.e. no significant symptoms of anxiety (mean = 7.14, SD = 3.20) or depression (mean = 5.15, SD = 3.04).

DISCUSSION

In the present study, the group of RRMS patients showed VEM deficits at the baseline assessment compared to the group of healthy controls. These changes were characterized by poor patient performance on encoding (immediate recall) and retrieval (delayed recall) of information on VEM tasks. The groups did not differ statistically on the recognition stage assessing storage. According to a systematic review on the subject[1], this result can be expected for the neuropsychological profile of MS, but the nature of decline in episodic memory, however, is controversial.

Chiaravalloti e DeLuca[1] discussed whether the nature of VEM impairment is characterized by ineffective performance at the stages of information encoding, retrieval or both these stages[5]. There is evidence in the literature showing that impairments in working memory[15], processing speed[1], strategies[16] and resistance to distractibility[5] can negatively impact episodic memory functioning. Other studies have shown deficits in delayed recall, even in patients receiving sufficient help to assimilate the information at the encoding stage, suggesting

Table 4. Data in Z-scores obtained by patients on cognitive tests – baseline vs. follow-up.

Neuropsychological instruments	Patients at Baseline		Patients at Follow-up		p-value
	Median (min-max)	M (SD)	Median (min-max)	M (SD)	
HVLT – Immediate recall	-0.80 (–2.20–1.00)	-0.97 (0.84)	-0.50 (–2.20–1.70)	-0.48 (0.94)	0.019*
HVLT – Delayed recall	-0.80 (–2.20–1.30)	-0.81 (0.85)	-0.10 (–3.00–1.10)	-0.48 (1.08)	0.092
HVLT – Recognition	0.60 (–2.20–0.80)	0.18 (0.76)	0.70 (–3.00–1.00)	-0.06 (1.19)	0.829
BVMT – Immediate recall	0.90 (–2.20–1.50)	0.49 (1.35)	0.50 (–2.00–1.70)	0.36 (0.98)	0.681
BVMT – Delayed recall	1.00 (–2.20–1.50)	0.53 (0.95)	1.00 (–3.00–1.50)	0.53 (1.10)	0.497
BVMT – Recognition	0.00 (0.00–0.00)	0.00 (0.00)	0.00 (–1.90–0.00)	-0.18 (0.53)	0.102
Letter-number sequencing	0.40 (–1.00–2.00)	0.38 (0.78)	0.70 (–0.70–2.00)	0.62 (0.75)	0.190
Digit span (WAIS-III)	0.70 (–1.00–2.50)	0.58(0.80)	1.00 (–0.30–3.00)	1.13(0.98)	0.002*
Corsi blocks (WMS-R)	-0.60 (–1.50–1.60)	-0.38 (0.67)	0.00 (–1.80–1.40)	-0.17(0.79)	0.175
Logical memory – immediate recall	-0.30 (–1.90–1.60)	-0.21 (0.86)	-0.10 (–1.80–3.50)	0.12(0.99)	0.178
Logical memory – delayed recall	-0.10 (–1.30–1.30)	-0.16 (0.66)	0.00 (–1.00–2.40)	0.22(0.87)	0.042*
Stroop test Victoria - part 3	-0.50 (–2.20–1.50)	-0.46 (1.07)	-0.20 (–2.30–1.70)	-0.18(0.97)	0.234
Trail making test A	-0.10 (–2.20–0.70)	-0.33 (0.77)	0.00 (–2.90–1.40)	0.01(0.87)	0.028*
Trail making test B	-0.10 (–2.20–0.90)	-0.44 (0.93)	0.00 (–3.00–1.00)	-0.52(1.20)	0.750
FAS form of the COWA test	-0.90 (–2.20–1.10)	-0.80 (0.78)	-0.80 (–2.60–0.70)	-0.90(0.84)	0.463
Animals	-0.60 (–1.70–1.10)	-0.56 (0.71)	0.00 (–1.40–2.20)	0.08(0.83)	<0.001*
Symbol digit modalities test	-0.80 (–2.40–0.60)	-0.79 (0.88)	-0.70 (–2.00–1.00)	-0.71(0.82)	0.509
Modified Wisconsin card sorting test	0.70 (–2.20–0.70)	0.17 (0.89)	0.70 (–3.00–0.70)	0.16(0.88)	0.726
Boston naming test	-0.60 (–2.20–0.10)	-0.90 (0.76)	-0.20 (–2.60–1.10)	-0.40(0.94)	0.004*

*p < 0.05; HVLT: Hopkins verbal learning test; BVMT: Brief visuospatial memory test; WAIS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; HVLT: Hopkins verbal learning test-revised; BVMT: brief visuospatial memory test-revised; COWA: controlled oral word association.

Table 5. Cognitive data at baseline for patient vs.control groups.

Neuropsychological instruments	Patients at Baseline		Control		p-value[1]
	Median (min–max)	M (SD)	Median (min–max)	M (SD)	
HVLT – Immediate recall	-0.80 (–2.20–1.00)	-0.97 (0.84)	0.15 (–1.30–1.30)	-0.05 (0.82)	< 0.001*
HVLT – Delayed recall	-0.80 (–2.20–1.30)	-0.81 (0.85)	0.00 (–1.70–1.00)	-0.08 (0.93)	0.006*
HVLT– Recognition	0.60 (–2.20–0.80)	0.18 (0.76)	0.80 (–0.80–0.80)	0.29 (0.65)	0.495
BVMT – Immediate recall	0.90 (–2.20–1.50)	0.49 (1.35)	0.80 (–2.20–2.00)	0.69 (0.89)	0.826
BVMT – Delayed recall	1.00 (–2.20–1.50)	0.53 (0.95)	1.05 (–2.20–1.50)	0.78 (0.81)	0.314
BVMT – Recognition	0.00 (0.00–0.00)	0.00 (0.00)	0.00 (0.00–0.00)	0.00 (0.00)	> 0.999
Letter-number sequencing	0.40 (–1.00–2.00)	0.38 (0.78)	0.55 (–1.00–4.00)	0.81 (1.25)	0.300
Digit span (WAIS-III)	0.70 (–1.00–2.50)	0.58 (0.80)	0.70 (–1.00–4.00)	0.85 (1.11)	0.553
Corsi blocks (WMS-R)	-0.60 (–1.50–1.60)	-0.38 (0.67)	0.00 (–2.00–2.00)	-0.12 (0.98)	0.184
Logical memory – immediate recall	-0.30 (–1.90–1.60)	-0.21 (0.86)	0.35 (–1.00–1.90)	0.38 (0.81)	0.013*
Logical memory – delayed recall	-0.10 (–1.30–1.30)	-0.16 (0.66)	0.50 (–1.30–2.40)	0.47 (0.81)	0.003*
Stroop test Victoria – part 3	-0.50 (–2.20–1.50)	-0.46 (1.07)	0.55 (–2.10–2.50)	0.36 (0.89)	0.007*
Trail making test A	-0.10 (–2.20–0.70)	-0.33 (0.77)	0.05 (–2.20–1.60)	-0.05 (0.95)	0.227
Trail making test B	-0.10 (–2.20–0.90)	-0.44 (0.93)	0.20 (–3.00–2.00)	0.12 (1.17)	0.023*
FAS form of the COWA test	-0.90 (–2.20–1.10)	-0.80 (0.78)	-0.45 (–1.50–1.30)	-0.40 (0.75)	0.050
Animals form of the COWA test	-0.60 (–1.70–1.10)	-0.56 (0.71)	0.05 (–1.70–2.30)	0.08 (0.98)	0.009*
Symbol digit modalities test	-0.80 (–2.40–0.60)	-0.79 (0.88)	-0.40 (–1.50–1.60)	-0.14 (0.90)	0.017*
Modified Wisconsin card sorting test	0.70 (–2.20–0.70)	0.17 (0.89)	0.70 (–1.60–0.70)	0.30 (0.70)	0.731
Boston naming test	-0.60 (–2.20–0.10)	-0.90 (0.76)	-0.30 (–2.20–1.30)	-0.37 (0.88)	0.007*

1: comparison between patient and control groups at baseline using the Mann Whitney test. *p < 0.05;
HVLT: Hopkins verbal learning test; BVMT: brief visuospatial memory test; WAIS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; COWA: Controlled Oral Word Association.

Table 6. Result of analysis of covariance between patient groups baseline vc controls corrected by neuropsychological tests Digits, SNL, SDMT and MWCST.

Variable	Working memory		Information processing speed	Executive function	p group
	p Dígitos	p SNL	p SDMT	p MWCST	
HVLT - Immediate recall	0.112	0.016*	0.948	0.310	0.001*
HVLT - Delayed recall	0.911	0.060	0.596	0.028*	0.028*
Logic Memory - Immediate recall	0.084	0.094	0.568	0.068	0.068
Logic Memory - Delayed recall	0.715	0.172	0.698	0.017*	0.017*

SNL: Sequence of numbers and letters; SDMT: Symbol Digit Modalities Test; MWCST: Modified Wisconsin Card Sorting Test. *: p > 0.05.

Table 7. Impact of the functioning of the other cognitive areas on the verbal episodic memory of the patients in the baseline

Cognitive domain	Cognitive ability	Neuropsychological test	p/r	Measures of episodic verbal memory			
				HVLT - Immediate recall	HVLT - Delayed recall	Logic memory - Immediate recall	Logic memory - Delayed recall
Attention	Selective	Stroop Test Victoria	r	0.027	0.062	-0.119	-0.074
			p	0.888	0.749	0.538	0.702
	Sustained	TMT A	r	0.271	-0.024	0.130	0.094
			p	0.155	0.900	0.501	0.627
	Divided	TMT B	r	0.303	0.173	0.311	0.344
			p	0.110	0.370	0.100	0.067
	Processing speed	SDMT	r	0.285	0.350	0.464*	0.415*
			p	0.134	0.063	0.011	0.025
Executive function	Verbal fluency to letters	COWAT - F.A.S	r	0.088	0.072	0.174	0.298
			p	*0.651*	0.712	0.366	0.117
	Verbal fluency semantic	COWAT - animals	r	0.165	0.278	0.115	0.080
			p	*0.393*	0.144	0.551	0.680
	Strategy training and mental flexibility	MWCST	r	0.560*	0.229	0.391	0.423
			p	*0.005*	0.232	0.036	0.022
	Verbal working memory	SNL-WAIS	r	0.560*	0.183	0.347	0.218
			p	0.002	0.341	0.066	0.255
		Dígits-WAIS	r	0.401*	0.260	0.063	-0.067
			p	0.031	0.174	0.747	0.730

SNL: Sequence of numbers and letters; TMT: Trail Making Test; SDMT: Symbol Digit Modalities Test; COWAT: Controlled Oral Word Association Test; MWCST: Modified Wisconsin Card Sorting Test; BNT: Boston Naming Test. *: p < 0.05.

accelerated forgetting in MS[5]. Based on the current findings of deficits at both the encoding and delayed recall stages, the nature of the episodic memory impairment might be explained in both phases by the brain areas affected[5].

In the present study, the results on tests assessing processing speed, strategy building and working memory correlated with those of VEM tests at the baseline assessment, thereby corroborating the findings in the literature outlined in the previous paragraph. However, the covariance analysis, even when including the effects of the executive function and attention tests on the VEM tests, revealed that the patient and control groups differed at baseline. This finding may be explained by other attentional and executive processes that impact episodic memory but have yet to be correlated. Another hypothesis is that mnemonic impairments occur independently of attentional and executive processes.

The scores obtained by patients on VEM tasks showed no correlation with sociodemographic status or with clinical and physical disability data of patients at baseline or follow-up. These variables have been the focus of studies to ascertain whether they impact cognitive functioning or otherwise, although a review has shown conflicting results in the literature[2].

In the longitudinal analysis of the present study, the patients showed stabilization or improvement in VEM performance, corroborating the findings of some longitudinal studies[17,18,19,20,21,22,23,24], yet contrasting with others showing decline[4,6,25,26] in this domain.

These incongruent findings have been reported in recently-published systematic reviews on the subject[1,2,3].

In the longitudinal studies cited in the preceding paragraph, part of the sample that showed a worsening of VEM over time comprised participants who evolved or were diagnosed with more progressive clinical forms of MS. The present sample was homogenous for the clinical form of the disease. This might explain the cognitive stability of the patients studied, given that cognitive impairment tends to be milder in the relapsing-remitting form of MS.

Another aspect that supports the stability and cognitive improvement of the present sample over time is the mechanism of brain neuroplasticity. A recent systematic review on functional magnetic resonance imaging related to the execution of neuropsychological tasks[27] has shown that MS patients without cognitive dysfunction had different brain dynamics from control participants. The patients had greater brain activation, widely-distributed cortical recruitment and changes in functional connectivity in cognition-related regions. These findings suggest that increased recruitment of important cortical networks can attenuate the negative effect of MS on cognitive function.

On the other hand, episodic memory deficits, and likewise for other cognitive dysfunctions, are heterogeneous in MS where their degree of severity varies significantly between patients[5]. Based on this variability, in the present sample specifically, the patients did not show a relevant decline in VEM.

One point to consider that may influence the detection of cognitive impairments is the time interval between neuropsychological assessments. The short follow-up of the present study, coupled with the low rate of VEM impairment in the patients, may explain the longitudinal stability observed.

However, studies in the literature have shown that variation in follow-up time is an incongruent factor in terms of the impact of evolution of cognitive impairment. Some studies have detected cognitive impairments within follow-up periods of two years[16,24,26,28,29], reporting impairments in VEM and, particularly, attentional processes. Conversely, a systematic review[3] found that studies with a follow-up of three to five years showed inconsistent and slow cognitive changes, whereas a longer follow-up period (10-18 years) was needed to detect deficits.

In summary, the incongruence of the cognitive findings in patients with MS is due to the many different limitations inherent in longitudinal studies. These limitations include different criteria for determining cognitive impairment parameters, possible practice effects on the neuropsychological tests given the number of assessments administered per time interval, the choice of tests involving different levels of difficulty, and heterogeneous samples in terms of the clinical forms of the disease.

As outlined above, the healthy controls were not reassessed to better define the parameters of VEM impairments in the patients over time. In addition, the high cognitive variability among individuals with MS requires a larger sample size for greater representativeness of the data.

In conclusion, the results of this study revealed that the patients showed ineffective VEM relative to controls at the baseline assessment and attained improvement and stability in this cognitive domain over time. The clinical, sociodemographic and physical disability variables showed no correlation with patient performance on the VEM tests. An impact of the attention and executive functioning tests on VEM in the information encoding and retrieval stages was evident. The present sample was homogenous for the clinical form of the disease, a factor that may have enhanced the reliability of the results.

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