ARTICLE

The correlation between EDSS and cognitive impairment in MS patients. Assessment of a Brazilian population using a BICAMS version

Correlação entre EDSS e déficit cognitivo em pacientes com EM. Avaliação de uma população brasileira usando uma versão do BICAMS

Marco A. G. de Caneda[1], Maria Cecília A. de Vecino[1]

ABSTRACT

Multiple sclerosis (MS) may present with a cognitive impairment as disabling as the physical disabilities. Therefore, routine cognitive evaluation is pivotal. Valid and reliable neuropsychological tests are essential in follow-up and to define future therapeutic interventions. **Objectives:** To investigate the correlation between the disabilities of MS patients and their cognitive impairment assessed by the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). **Methods:** Forty patients with definitive diagnoses of MS were selected. The correlation coefficient (r) between the Expanded Disability Status Scale (EDSS) and the neuropsychological tests of BICAMS were calculated. **Results:** The correlation was clinically substantial and significant with r = 0.55 (p < 0.01) in the Symbol Digit Modalities Test (SDMT), 0.54 (p < 0.01) in the Brief Visuospacial Memory Test (BVMT) and 0.40 (p < 0.05) in the California Verbal Learning Test (CVLT). **Conclusion:** BICAMS has easy and satisfactory application and evaluation for routine visits and presents a significant correlation with the EDSS. Its use may be indicated for screening and monitoring of cognitive impairment in patients with MS.

Keywords: multiple sclerosis; cognition disorders; disabled persons.

RESUMO

A esclerose múltipla (EM) pode apresentar um déficit cognitivo (DC) tão devastador quanto suas debilidades físicas. Uma avaliação cognitiva rotineira é essencial e testes neuropsicológicos (TNs) validados e confiáveis são fundamentais no acompanhamento e definição de futuras intervenções terapêuticas. **Objetivos:** Investigar a correlação entre o estado de incapacidade física de pacientes com EM e o comprometimento cognitivo, avaliado pelo Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). **Métodos:** Foram calculados coeficientes de correlação (r) entre a Expanded Disability Status Scale (EDSS) e resultados dos testes do BICAMS em quarenta pacientes com diagnóstico definitivo de EM. **Resultados:** A correlação foi clinicamente substancial e significativa, com r = 0.55 (p < 0.01, no Symbol Digit Modalities Test (SDMT), 0.54 (p < 0.01) no Brief Visuospacial Memory Test (BVMT) e 0.40 (p < 0.05) no California Verbal Learning Test (CVLT). **Conclusão:** O BICAMS é de fácil e satisfatória aplicação e avaliação em visitas de rotina e apresenta uma correlação significativa com a EDSS. Seu uso pode ser indicado como rotina no acompanhamento do (DC) em portadores de EM.

Palavras-chave: esclerose múltipla; transtornos cognitivos; pessoas com deficiência.

Multiple sclerosis (MS) is the most prevalent neurological disorder of the central nervous system in young adults. It affects about two million people worldwide, with a varied prevalence of 1/100,000 in equatorial areas to 30-80/100,000 in Canada, USA and North Europe[1], and 18/100,000 in southern South America[2].

Since the initial descriptions by Charcot, 1877, cognitive impairment has been mentioned as one of the characteristics of this disease[3] and may be present in its very early stages[4,5,6,7]. The process can remain latent, but is continuous and associated with clinical activity. The most frequently affected cognitive domains include memory, especially acquisitive difficulties, information processing speed, visuospacial perception and attention[5,7].

Once cognitive abnormalities emerge, there is a tendency toward progression[8] with impact on the quality of life[9], which can affect performance at work, social activities, physical independence, progress of rehabilitation, treatment compliance and in family living or affective relationships as a whole[6,10,11].

[1]Hospital Moinhos de Vento, Instituto de Ensino e Pesquisa, Departamento de Neurologia, Grupo de Esclerose Múltipla, Porto Alegre RS, Brasil.

Correspondence: Marco AG de Caneda; Serviço de Neurologia do Hospital Moinhos de Vento; Rua Ramiro Barcelos, 910; 90035-001 Porto Alegre RS, Brasil; E-mail: mcaneda@terra.com.br

Twenty years ago, a systematic review concluded that the duration of the disease and the individual physical state (measured by the Expanded Disability Status Scale - (EDSS) did not influence the results of neuropsychological tests in MS by more than 10% to 15%[12]. This conclusion was based on previous studies that indicated a virtually non-existent correlation between the physical state and cognition in these patients. This concept was subsequently corroborated by studies characterized by a great heterogeneity in the samples and methodologies[13].

Currently, despite some conflict about the association between cognitive impairment and the physical state[9], there are several studies suggesting a cognitive decline that is definitely identifiable by neuropsychological tests, and correlated with the disability state in MS[5,9,10,12,14].

Cognitive complaints are rarely considered in routine evaluation. This approach is considered complicated, expensive, particularly difficult in the early stages of the disease[14] and takes too long (30-120 minutes)[1]. Difficulties ranged from the lack of a suitable place to perform complex tests, which often require multiple sessions, to the need for specialized staff such as neuropsychologists available.

The neuropsychological tests (NTs) provide assessment of the cognitive state and are used for the diagnosis of impairment and decision-making about medical and/or cognitive treatment[15]. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) consists of a recently-proposed battery of NTs[1,15] that favor centers with teams with few professionals. The full battery of tests does not take more than 15 minutes, making it ideal for use in daily clinical practice. The objective of this study was to investigate the applicability of a version of BICAMS in the Portuguese language, estimating its correlation with the physical disability of subjects with MS.

METHODS

Participants

We selected patients with relapsing-remitting type MS, defined by the McDonald criteria 2010[16], who had regular neurologic attendance in the city of Porto Alegre, Rio Grande do Sul, southern Brazil. All patients provided an informed consent form and the study was approved by the local research ethics committee under registration number 1.477.109.

Patients were excluded if any of the following criteria were met: (a) immunological clinical conditions other than MS that affect the central nervous system; (b) physical or cognitive impeditive disabilities secondary to conditions other than MS; (c) any prior impairment secondary to MS that precluded the application of BICAMS tests; (d) an impeditive psychiatric illness, previous or under development, in treatment or not; (e) prior history or current abuse of alcohol or other psychoactive substances and (f) an MS attack treated with corticosteroids at high doses, or untreated, in the last six weeks.

Procedures and evaluation tools

Patients included were evaluated during regular visits. The EDSS and NTs were applied individually by the same neurologist, in the same session. An appropriate explanation about the goals and way of carrying out each test was performed. The order of application of the test components of BICAMS was (1) the Symbol Digit Modalities Test (SDMT), (2) California Verbal Learning Test II (CVLT-II), and (3) the Brief Visuospatial Memory Test Revised (BVMT-R)[4,8,11,15]. Individual disease duration was considered to be from the initial manifestation of neurological signs or symptoms suggestive of the disease.

Data analysis

The abnormality of the NTs was established by the parameters previously described in the literature, and the results obtained were compared with normative healthy controls and MS patients. The association of EDSS and NTs was estimated by Pearson's correlation coefficient (r). The coefficient of determination (R^2) was also calculated[17]. Confidence intervals (CI) of correlation coefficients were calculated by the bootstrap resampling method, in the percentile mode[18]. A simple linear regression analysis was performed to identify the impact and to predict possible variations in cognition relative to the state of the disability. In the same way, we used a multiple regression analysis to evaluate the effect of age, disease duration and level of education in the NTs. Statistical significance was set at a value of $p < 0.05$. The calculations for statistical analysis were performed with use of IBM®™ package SPSS®™, version 23, 2015, available for limited free use at *statistics trial software, www-01.ibm.com*.

RESULTS

Six patients were excluded by the cited criteria. The BICAMS showed an excellent applicability and very fast performance. The material required for implementation was extremely inexpensive. The tests were easily understood by patients and the evaluation of results was simple and accessible to the examiner. The normal distribution of the dependent variables was assessed by the Shapiro-Wilk test. The demographics, EDSS and BICAMS tests scores with their respective means are shown in Table 1.

When compared with the aggregate mean described in healthy controls in previous studies, which considered one standard deviation (SD) below the mean score as an abnormal test[14], 70% of individuals in the sample had abnormality in one of three tests, 32% in two and 17% in all three tests. Within the limits of at least two tests with 1 SD below the mean of healthy controls for establishment of cognitive impairment, the prevalence of cognitive prejudice was 32%.

Table 1. Demographic characteristics of our sample, EDSS and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) components scores.

Patient	Gender	Age (yrs)	TD(yrs)	Formal education level	EDSS	SDMT	CVLT	BVMT
1	♀	24	3	2	2	60	60	29
2	♂	42	7	1	6.5	21	40	10
3	♀	35	3	2	2	51	50	29
4	♀	60	5	3	3.5	73	63	20
5	♀	53	5.5	3	3.5	50	51	25
6	♀	52	3.5	2	2.5	48	62	29
7	♀	46	20	2	3.5	40	58	23
8	♀	51	7	2	3.5	38	44	25
9	♂	54	18	1	7	30	36	11
10	♀	39	0.5	1	3	45	37	14
11	♀	42	9.5	1	4.5	32	45	11
12	♀	34	2.5	2	3.5	52	50	31
13	♀	32	2.5	2	3	51	44	29
14	♀	51	2	1	3	42	34	35
15	♀	67	15	2	3.5	39	36	20
16	♀	38	20	3	4.5	58	45	26
17	♀	65	36	3	7	20	37	14
18	♀	44	7	3	2	57	42	27
19	♀	40	7	3	4	48	45	14
20	♀	44	9	4	1.5	66	63	24
21	♀	45	13	4	3.5	54	53	23
22	♂	46	19	3	3	43	45	24
23	♂	49	11	3	3.5	44	52	29
24	♀	35	5	4	2.5	59	47	20
25	♂	25	3	2	2.5	53	50	32
26	♀	35	2	4	3.5	60	60	20
27	♂	36	8	4	4	74	36	28
28	♀	51	23	3	3.5	25	57	23
29	♀	34	3	4	2	69	43	21
30	♂	40	7	2	1.5	50	52	22
31	♂	38	12	2	4	79	62	35
32	♀	51	21	3	4.5	23	50	18
33	♀	55	5.5	2	3.5	45	44	30
34	♀	22	2.5	2	1.5	53	46	29
Mean	3.25♀:1♂	43	9.7	-	3.4	48.5	48.2	23.5
SD	-	-	-	-	1.3	14.9	8.6	6.7

TD: time of disease; Formal Education Level: (1) ≤ 8 years; (2) >8–11 years; (3) >11 –18 years and (4) >18 years; EDSS: expanded disability status scale; SDMT: symbol digit modalities test; *CVLT: California verbal learning test; BVMT: brief visuospatial memory test; SD: standard deviation.

On other hand, considering 2 SD below the aggregate mean of healthy controls to define an abnormal test[19], 29% of our patients had impairment of only one test and 15% had abnormality in two or all three tests. If the requirement was for abnormality in at least two tests with 2 SD below the average of healthy controls for a definitive cognitive impairment, 15% of our patients tested presented with cognitive

damage. As previously described in the literature[10], an EDSS around 3.5 was the cut-off for the presence of minimal impairment, with 1 SD below the aggregate mean of controls in one test.

Only the SDMT showed some association with disease duration, age had no significant impact on the performance of any test in our sample. However, the formal

education level had a significant influence on the SDMT ($p < 0.01$) and CVLT ($p < 0.05$), which suggests some protective effect in the NTs.

The mean of SDMT was 48.5 points (SD = 14.9), similar to a previously-described aggregate mean of 43.5 (mean SD = 14.1) for patients with MS. Around 67% of patients exhibited a result below the aggregate mean of normal controls previously described (56.3, mean SD = 10.3)[3-7,10,13,20-24] in this test. The coefficient r with the EDSS was negative, -0.55 (95%CI: -0.74 to -0.27); of marked and high significance, $p < 0.01$ (Figure 1A) and the coefficient R^2 estimated was 0.30 (Table 2). The linear regression analysis estimated a drop of three points in the SDMT, about 6% of the mean score, for each 0.5 points progression in the EDSS (Figure 1B).

The CVLT had an average of 48.2 points (SD = 8.6), a very close result to the aggregate mean of 51 (mean SD = 11.5) in MS patients reported in the literature. This test showed 73% of patients below the average of healthy controls (58.4 points; mean SD = 8.3)[4,8,13,22,23,24,25]. The coefficient r with the EDSS was negative, - 0.40 (95%CI: -0.57 to -0.11), indicative of a moderate[26] correlation, with a $p < 0.05$ (Figure 2A), and the coefficient R^2 for this association was 0.16 (Table 2). The linear regression analysis (Figure 2B) showed that for each increase of 0.5 in the EDSS, the score in the CVLT decreases 1.5 points, or 3% of the mean score in our sample.

The BVMT showed a mean of 23.5 points (SD = 6.7), above the aggregate mean of patients with MS, which is 20.7 points (mean SD = 7.5). This test had lower abnormality rates, with 58% of patients below the average of normal controls previously reported (26.2 points; mean SD = 5.3)[4,11,22,23,24,25]. However, there was a marked inverse correlation with the EDSS, with a coefficient r of -0.54 (95%CI: -0.71 to -0.25), highly significant, $p < 0.01$ (Figure 3A), and a coefficient R^2 of 0.29 (Table 2). With the linear regression there was an estimation of a decrease about 1.5 points in the BVMT, or 6% of the mean score, for each 0.5 points of progression in the EDSS (Figure 3B).
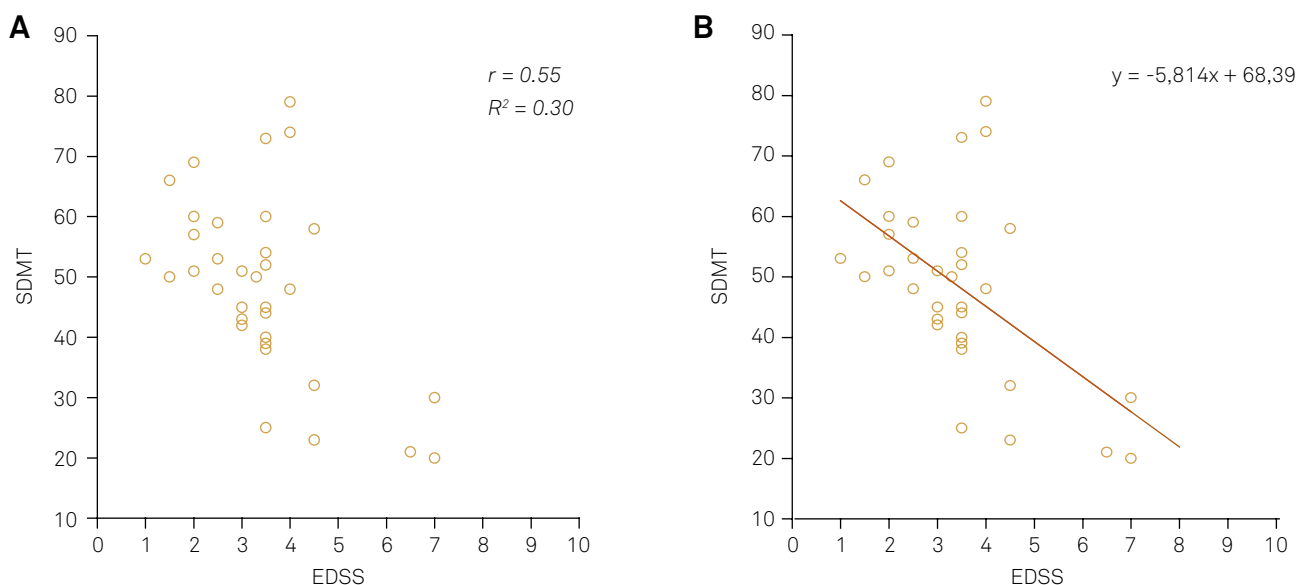
DISCUSSION

There is some disagreement regarding the definition of an abnormal cognitive test. Some studies take a result of 1 SD below the mean of normal controls as sufficient to define it[14]. In contrast, other authors argue that this lenient cut-off point, despite producing an increase in the sensitivity of the battery, may cause a dramatic reduction in its specificity[19]. Likewise, it is possible to consider as a parameter of cognitive impairment an abnormality present in one or two cognitive domains[7,9,10] or even combinations of these found in two

Table 2. Correlation coefficients EDSS x Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS).

Variable	EDSS		
	r (95%CI)	R^2	p
SDMT	-0.55 (-0.74 to -0.27)	0.30	0.0008**
CVLT	-0.40 (-0.57 to -0.11)	0.16	0.03***
BVMT	-0.54 (-0.71 to -0.25)	0.29	0.001**

EDSS: expanded disability status scale; r: Pearson's correlation coefficient; R^2: determination coefficient; **$p < 0.01$ significant; *** $p < 0.05$ significant; CI: Confidence interval; SDMT: symbol digit modalities test; CVLT: California verbal learning test; BVMT: brief visuospatial memory test.
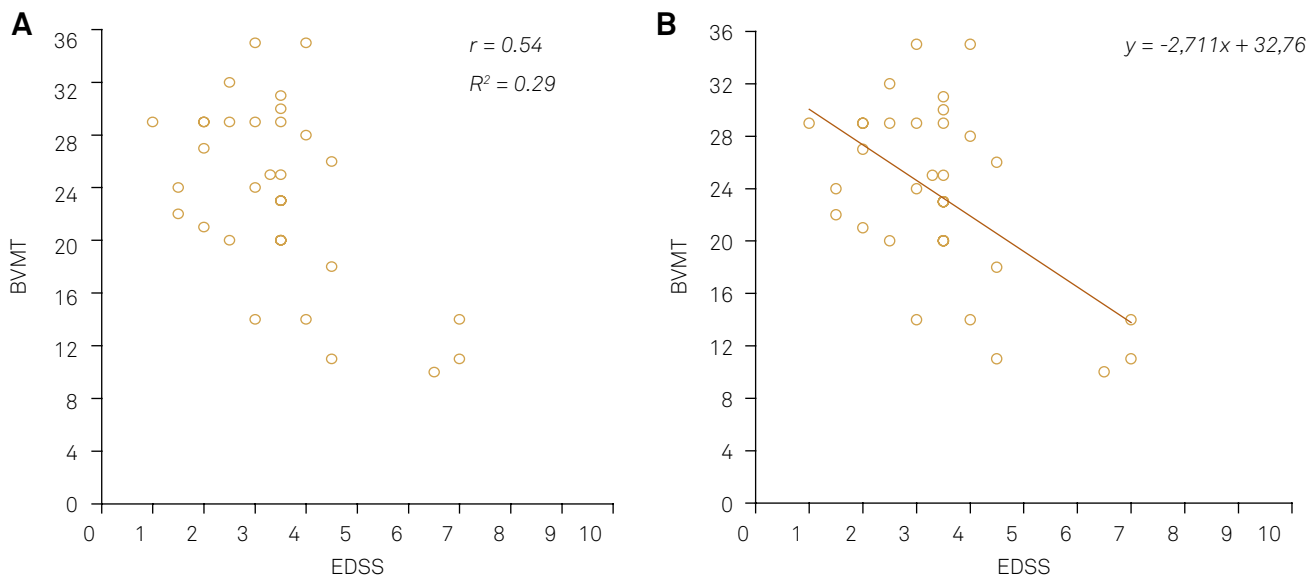

EDSS: expanded disability status scale; SDMT: symbol digit modalities test.

Figure 1. A: Correlation EDSS X SDMT; B: Linear Regression EDSS X SDMT.
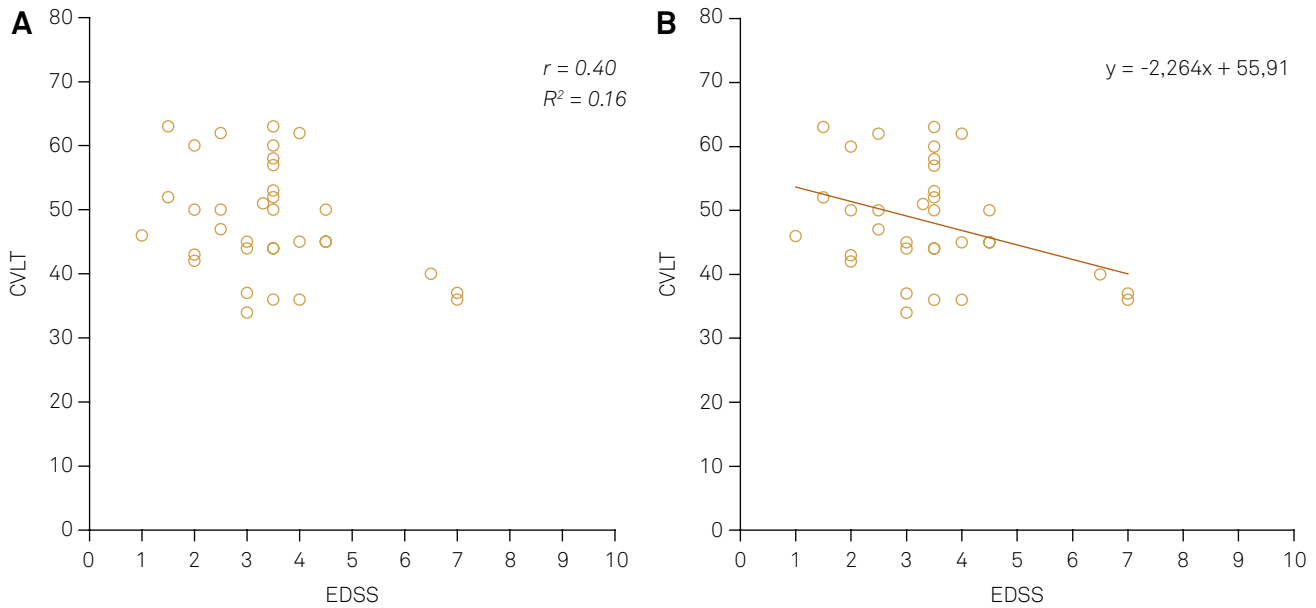
EDSS: expanded disability status scale; CVLT: California verbal learning test.

Figure 2. A: Correlation EDSS X CVLT; B: Linear Regression EDSS X CVLT.

EDSS: expanded disability status scale; BVMT: Brief visuospatial memory test.

Figure 3. A: Correlation EDSS X BVMT; B: Linear Regression EDSS X BVMT.

or three tests of a battery[4,7,14]. In many studies, the batteries of NTs were much more extensive than BICAMS, some containing five or ten different tests[3,4 6,12,13]. However, it is possible that the BICAMS test can accurately detect cognitive impairment, since each test involves more than one simple cognitive domain[4,8,11,15].

Adopting the rigidity of 2 SD below the mean of controls as an abnormality, and two abnormal tests as a determinant standard, the prevalence of cognitive impairment was 15% in our study. With these same criteria, the mean cognitive impairment prevalence in previous studies was around 40%[3,5,9,10,20]. Table 3

Using the more liberal criterion of 1 SD below average of controls in two tests, to define a NTs abnormality and cognitive impairment, the aggregate mean prevalence rises to approximately 60%[5,14], whereas in our study this was 32%. It is necessary to take into account that none of these studies used BICAMS. In turn, previous publications using BICAMS, considered a test with results of 1.5 SD below the mean of healthy controls in just one NTs as abnormal, and like definition of cognitive impairment. These studies found a prevalence of cognitive impairment of 58%[4] and 57%[23], which is very close to the 55% of our work under these same parameters. Table 3

summarizes these previous findings comparing them to those obtained by us.

Many studies have shown a significant correlation between the EDSS and cognitive impairment[3,10,14,19], including some prospective trials[6,9]. This association may reflect a greater cognitive decline in patients with a longer duration of disease[14]. However, our results did not find this correlation consistently, compared with those previously reported[19]. Aging had no significant impact on any test in the battery, which is comparable to results previously described[19,27]. In contrast, the level of formal education had significant influence on the SDMT ($p < 0.01$) and CVLT ($p < 0.05$). This effect of protection on the NTs is a replication of previous data widely suggested by other authors[8,19,25,28,29]. Interestingly, a study performed in the last decade[5] suggested cut-off points for the SDMT accordance with educational level of patients and considered differences of 1, 1.5 and 2 SD below the mean of normal controls as cognitive impairment, reinforcing the importance of the impact of this variable on NTs.

The present study was developed in the city of Porto Alegre, in the southernmost state of Brazil, just over 800 miles from Buenos Aires, Argentina and 1400 miles of Santiago de Chile. These capitals and our city have many similarities: ethnic background (with important European descent, particularly Iberian, Italian and German), climatic, cultural and socio-economic features, with a Human Development Index around 0.80. Thus, it is interesting to compare indicators for cognitive impairment in MS between them.

In a study published in 2011, performed in Buenos Aires, the prevalence of cognitive impairment was 43%[3]. Another paper, released in the following year, from Santiago de Chile, showed a rate of 36%[20]. These studies did not use the BICAMS, but applied rigid parameters for cognitive impairment, setting 2 SD below the mean of normal controls in at least two NTs, in which our rate was 15%. Of course, the use of different assessment tools prevents a simple direct comparison, since the test battery used in the cited studies, the Neuropsychology Brief Repeatable Battery Test (BRB-N)[5], is much more extensive than BICAMS. The BRB-N and BICAMS have the SDMT[23] as a common test, in which our sample presented a prevalence of abnormality of 42%, with the same parameters for definition of an abnormal test – a very similar rate to other Latin Americans cited papers. Beyond this, the cognitive impairment rates found by these authors are comparable to ours when using 2 SD present in just one NTs as a definition parameter (Table 3).

The score obtained by patients with MS in the SDMT in previous publications ranges from 34.9 to 56.3 with a mean of 43.5 (mean SD = 14.1)[3,7,10,13,20,21,22,23,24], close to our result of 48.5 (SD = 14.9). Importantly, in the study that showed the lower score[7], the population assessed was of older patients (mean age 61.8 years) and with longer duration of disease (mean 34.5 years) compared to ours, which possibly influenced its results. On the other hand, the highest scores of SDMT were obtained in a study where the subjects had a mean EDSS of 2.6, lower than our sample.

In the Chilean publication mentioned[20], the MS patients had a mean score of 41 (SD = 13.6) in the SDMT, and three years later, an Argentinian[30] study showed a mean of 38.5 (SD = 14). Although our study showed a higher mean in the SDMT than these publications, the differences in rates are not statistically significant, staying within the limits of standard deviations. In 2015, a study performed in Brazil showed a mean score of 36 (SD = 16) in MS patients[25]. In this study the mean EDSS of patients was 4.2, higher than ours, which could be the cause of this different results. Table 4 shows the comparison between various study results obtained in patients with MS in this test.

Some publications have shown a consistent correlation between the SDMT and EDSS[5,6,9,30]. Just as in our study, in these papers the correlation coefficients between the

Table 3. Comparison of the prevalence of cognitive impairment in patients with multiple sclerosis in the literature.

AbNT	SD	Sepulcre et al. (2006)[5]	Patti et al. (2009)[14]	Deloire et al. (2010)[9]	Cáceres et al. (2011)[3]	Nogales et al. (2012)[20]	Dusankova et al. (2012)[4] *	Goretti et al. (2014)[8]	Patti et al. (2015)[15]	O'Connell et al. (2015)[27]*	Caneda and Vecino (2016)
						Prevalence					
1	1	90%	59%	-	-	-	-	-	-	-	70%
2	1	83%	37%	-	-	-	-	-	-	-	32%
3	1	73%	22%	-	-	-	-	-	-	-	17%
1	1.5	78%	-	-	-	-	58%	-	-	57%	55%
2	1.5	57.6%	-	-	-	-	34%	-	-	-	23%
3	1.5	52.5%	-	-	-	-	13%	-	-	-	11%
1	2	66%	-	-	-	62%	-	-	75%	-	44%
2	2	40.6%	-	48%	43%	36%	-	-	54%	-	15%
3	2	30.5%	-	-	-	18%	-	40%	44%	-	9%

AbNT: abnormal neuropsychological test; SD: standard deviation below normal controls; *Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) applied.

Table 4. Comparison of some mean scores in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) tests and correlation coefficients in the literature.

Reference (n)	Mean Score SD				
	SDMT	CVLT	BVMT	r: EDSS x SDMT	r: EDSS x CVLT
Caneda et Vecino (40)	48.5(14.8)	48.2(8.6)	23.5(6.7)	0.55	0.40
Cáceres et al[3] (111)	38.4(13.4)	-	-	-	-
Dusankova et al[4] (367)	50 (13)	52 (11)	23 (7)	-	-
Sepulcre et al[5] (59)	36.8(16.8)	-	-	0.59	-
Duque et al[6] (44)	51.6(14.3)	-	-	0.45	-
Smestad et al[7] (84)	34.9(13.4)	-	-	-	-
Deloire et al[9] (58)	-	-	-	0.40	-
Patti et al[10] (125)	43.2(14.4)	-	-	-	-
Lynch et al[12] (164)	-	49.6(10.9)	-	-	0.30
Olivares et al[13] (33)	48.3(13.2)	64.2(ND)	-	-	-
Nogales et al[20] (129)	41 (13.7)	-	-	-	-
Hoogs et al[22] (132)	49 (15.2)	51.6(12.8)	19.4 (7)	-	-
Spedo et al[25] (58)	35.9(16.1)	42.1(12.4)	19.9(8.6)	-	-
O'Conell et al[27] (67)	46 (12.9)	45.3(10.2)	17.9(7.1)	-	-
Nicollai et al[23] (192)	46.4(12.9)	49.9(12.1)	23.7 (8)	-	-
Giedraitiené et al[24] (50)	42.7(13.9)	55.9 (10)	23.1 (7)	-	-

EDSS: expanded disability status scale; SMDT: symbol digit modalities test; CVLT: California verbal learning test; BVMT: brief visuospatial memory test; SD: standard deviation; r: Pearson's correlation coefficient; ND: not defined.

EDSS and the SDMT would be classified as moderate[26], and therefore clinically significant.

In the study by Dusankova et al.[4], the CVLT was the test with the lowest occurrence of impairment among patients with MS, the lowest decline regarding disease duration and the lowest correlation with the Minimal Assessment of Cognitive Function in Multiple Sclerosis, considered the gold standard battery for cognitive impairment in this study. The patients had a mean of 52 points, very close to our 48.2. In other studies, this findings was similar, ranging from 42 to 51.6 points[12,22,23,24,25]. Only one paper[13] showed a significant discrepancy, with a mean in the CVLT of 64 in patients with MS[2]. Draws attention the fact that in this study there was no significant difference between MS patients and healthy controls in the CVLT, with a mean of 66.5 points, a result that has not been replicated in subsequent studies[4,20].

A consistent association between the CVLT and EDSS, with a coefficient r of - 0.30, was shown in a study by Lynch et al.[12] This coefficient, which was statistically significant, is lower than ours; however is important to consider the differences in methodology and number of patients in the samples between the studies. Table 4 shows the comparison between our results and the CVLT obtained in earlier studies in patients with MS.

The BVMT has been little explored in the literature. In previous studies, MS patients had a mean of 23 (SD = 7)[4], 23.1 (SD = 7)[24] and 23.7 points (SD = 8)[23], nearly identical to the results of our study, of 23.5 (SD = 6.7). In other publications[22,25]

the scores of MS patients were 19.6 and 19.9, different rates that, in relation to ours, have no statistical significance and were within the limits of standard deviations. Table 4 shows the various results obtained in the BVMT of former studies in patients with MS.

One of the possible limitations of our study is the strict selection and limited sample size derived from a MS center. This may generate distortions when extrapolating its results, although this study presents a suitable size for its propositions, and was derived from an earlier pilot study. Besides this, the lack of NTs rates in local healthy controls can result in some difficulty in defining abnormality parameters in our tests. Lastly, it is known that psychological factors, such depression or anxiety, can exert some influence on the tests and ideally these variables must be controlled.

It is possible that the well-established clinical properties of the BICAMS and its widespread use should encourage a major renovation of concepts and definitions in the particularities of MS. For example, in the concepts of benign disease, treatment failure, No Evidence of Disease Activity, which is becoming an important secondary endpoint in clinical trials, and the use of MRI as a defining criterion, which possibly has insufficient sensitivity to detect pathological neurodegenerative changes that can be reflected much more in the effects on cognitive aspects. All these issues must be a priority and a boost in the development of future studies based on the BICAMS in our population.

References

1. Van Schependom J, D'hooghe MB, Cleynhens K, D'hooge M, Haelewyck MC, De Keyser J et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur J Neurol. 2014;21(9):1219-25. doi:10.1111/ene.12463

2. Cristiano E, Rojas J, Romano M, Frider N, Machnicki G, Giunta D et al. The epidemiology of multiple sclerosis in Latin America and the Caribbean: a systematic review. Mult Scler. 2013;19(7):844-54. doi:10.1177/1352458512462918

3. Cáceres F, Vanotti S, Rao S.Epidemiological characteristics of cognitive impairment of multiple sclerosis patients in a Latin American country. J Clin Exp Neuropsychol. 2011;33(10):1094-8. doi:10.1080/13803395.2011.603690

4. Dusankova JB, Kalincik T, Havrdova E, Benedict RH. Cross cultural validation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Clin Neuropsychol. 2012;26(7):1186-200. doi:10.1080/13854046.2012.725101

5. Sepulcre J, Vanotti S, Hernández R, Sandoval G, Cáceres F, Garcea O et al. Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. Mult Scler. 2006;12(2):187-95. doi:10.1191/1352458506ms1258oa

6. Duque B, Sepulcre J, Bejarano B, Samaranch L, Pastor P, Villoslada P. Memory decline evolves independly of disease activity in MS. Mult Scler. 2008;14(7):947-53. doi:10.1177/1352458508089686

7. Smestad C, Sandvik L, Landrø NI, Celius EG. Cognitive impairment after three decades of multiple sclerosis. Eur J Neurol. 2010;17(3):499-505. doi: 10.1111/j.1468-1331.2009.02889.x

8. Goretti B, Niccolai C, Hakiki B, Sturchio A, Falautano M, Minacapelli E. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): normative assessment for gender, age and education corrections in the Italian population. BMC Neurology. 2014;14(1):171. doi:10.1186/s12883-014-0171-6

9. Deloire M, Ruet A, Hamel D, Bonnet M, Brochet B. Early cognitive impairment in multiple sclerosis predicts disability outcome several years later. Mult Scler. 2010;16(5):581-7. doi:10.1177/1352458510362819

10. Patti F, Nicoletti A, Messina S, Bruno E, Fermo SL, Quattrocchi G et al. Prevalence and incidence of cognitive impairment in multiple sclerosis: a population- based survey in Catania, Sicily. J Neurol. 2015;262(4):923-30. doi:10.1007/s00415-015-7661-3

11. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18(6):891-8. doi:10.1177/1352458511431076

12. Lynch SG, Parmenter BA, Denney DR. The association between cognitive impairment and physical disability in multiple sclerosis. Mult Scler. 2005;11(4):469-76. doi:10.1191/1352458505ms1182oa

13. Olivares T, Nieto A, Sánchez MP, Wollmann T, Hernández MA, Barroso J. Pattern of neuropsychological impairment in the early phase of relapsing-remitting multiple sclerosis. Mult Scler. 2005;11(2):191-7. doi:10.1191/1352458505ms1139oa

14. Patti F, Amato MP, Trojano M, Bastianello S, Tola MR, Goretti B et al. Cognitive impairment and its relation with disease measures in midly disabled patients with relapsing-remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS). Mult Scler. 2009;15(7):779-88. doi:10.1177/1352458509105544

15. Benedict RH, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): international standards for validation. BMC Neurol. 2012;12(1):55. doi:10.1186/1471-2377-12-55

16. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302. doi:10.1002/ana.22366

17. Altmann D. Relation between two continuos variables. In: Altmann DG. Practical statistics for medical research. London: Chapmann & Hall; 1994. Chap. 11. p. 277-321.

18. Costa GGO. Intervalo de confiança e teste de significância Bootstrap para coeficientes de correlação linear referente à hipótese de um valor não nulo. GEPROS. 2010;5(2):177-86.

19. Silva AM, Cavaco S, Moreira I, Bettencourt A, Santos E, Pinto C et al. Cognitive reserve in multiple sclerosis: protective effects of education. Mult Scler. 2015;21(10):1312-21. doi:10.1177/1352458515581874

20. Nogales-Gaete J, Aracena R, Díaz V, Zitko P, Eloiza C, Cepeda-Zumaeta S et al. Evaluación neuropsicológica en 129 pacientes chilenos con esclerosis multiple recurrente remitente previo a inicio de fármacos inmunomoduladores. Rev Med Chile. 2012;140(1):1437-44. doi:10.4067/S0034-98872012001100009

21. Sheridan LK, Fitzgerald HE, Adams KM, Nigg JT, Martel MM, Puttler LI et al. Normative Symbol Digit Modalities Test perfomance in a community-based sample. Arch Clin Neuropsychol. 2006;21(1):23-8. doi:10.1016/j.acn.2005.07.003

22. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH et al. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. Int J MS Care. 2011;13(2):57-63. doi:10.7224/1537-2073-13.2.57

23. Niccolai C, Portaccio E, Goretti B, Hakiki B, Giannini M, Pastò L.et al. A comparison of the brief international cognitive assessment for multiple sclerosis and the brief repeatable battery in multiple sclerosis patients. BMC Neurol. 2015;15(1):204. doi:10.1186/s12883-015-0460-8

24. Giedraitiené N, Kizlaitiené R, Kaubrys G. The BICAMS battery for assessment of Lithuanian: speaking multiple sclerosis patients: relationship with age, education, disease disabiltiy, and duration. Med Sci Monit. 2015;21:3853-9. doi:10.12659/MSM.896571

25. Spedo CT, Frndak S, Marques VD et al. Cross-cultural adaptation, reliability, and validity of the BICAMS in Brazil. Clin Neuropsychol. 2015;26(6):836-46. doi:10.1080/13854046.2015.1093173.

26. Cohen J. Differences between Correlation Coefficients. In: Cohen J, Statistical power analysis for the behavioral sciences. 2nd ed. Printed in USA. Laurence Erlbaum; 1988. Chap. 4:109-39.

27. O'Conell K, Langdon D, Tubridy N, Hutchinson M, McGuigan C. A preliminary validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) tool in an Irish population with multiple sclerosis. Mult Scler Relat Disord. 2015;4(6):521-5. doi:10.1016/j.msard.2015.07.012

28. Sumowski JF, Chiaravalloti N, Wylie G, Deluca J. Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. J Int Neuropsychol Soc. 2009;15(4):606-12. doi:10.1017/S1355617709090912

29. Modica CM, Bergsland N, Dwyer MG, Ramasamy DO, Zivadinov R, Benedict RH. Cognitive reserve moderates the impact of subcortical gray matter atrophy on neuropsychlogical status in multiple sclerosis. Mult Scler. 2016;22(1):36-42. doi:10.1177/1352458515579443

30. Vanotti S, Cores EV, Elzagurre B, Angeles M, Rey R, Villa A et al. Normatization of the symbol digit modalities test: oral version in a Latin American country. Appl Neuropsychol Adult. 2015;22(1):46-53. doi:10.1080/23279095.2013.831866