



# VALIDATION OF THE BRIEF INTERNATIONAL COGNITIVE ASSESSMENT FOR MULTIPLE SCLEROSIS (BICAMS) IN A LARGE COHORT OF RELAPSING-REMITTING MS PATIENTS

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**SUMMARY** – Cognitive impairment is one of the most frequently reported symptoms in persons with multiple sclerosis (MS). The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) has been recommended as a standardized international screening and monitoring tool for brief cognitive assessment. The aim of our study was to assess the reliability and validity of the Serbian version of the BICAMS. A total of 500 relapsing-remitting MS (RRMS) patients and 69 age-, gender- and education-matched healthy control (HC) subjects were examined. All participants performed the BICAMS test battery, which includes the oral version of the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test second edition (CVLT-II), and Brief Visuospatial Memory Test Revised (BVMTR). A randomly selected subset of patients were retested one to three weeks after baseline. Statistically significant differences between patients and HCs were evident on the SDMT and BVMTR ( $p < 0.001$ ). HCs had higher CVLT-II scores but this difference did not reach statistical significance ( $p = 0.063$ ). Cognitive impairment, defined as an abnormal test score on  $\geq 1$  subtest, was found in 62.9% of MS patients. There were statistically significant correlations between BICAMS scores and age, education, EDSS and disease duration in patient sample. Test-retest reliability was confirmed with Pearson correlation coefficient of 0.70 in all measures. This study supported the reliability and validity of the Serbian BICAMS, although the CVLT-II version tested here lacked sensitivity to detect MS compared to healthy volunteers.

**Key words:** *Multiple sclerosis; BICAMS; Cognition; Cognitive impairment; Validation*

## Introduction

Cognitive impairment is one of the most frequently reported symptoms that has significant impact on the working status of persons with multiple sclerosis

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(MS), responsible for their early retirement<sup>1</sup>. Cognitive dysfunction occurs in 30%-70% of MS patients<sup>2-4</sup>. This variation is based on different instruments used and population normative data<sup>5</sup>. The most frequently involved cognitive functions are attention, information processing speed, executive functioning, memory and visuospatial functions<sup>2,5,6</sup>.

Until about a decade ago, in order to obtain general assessment of MS patient cognitive functioning, two validated neuropsychological test batteries were widely used, i.e., the Rao's Brief Repeatable Battery (BRB-N)<sup>7</sup>, and the Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS)<sup>8,9</sup>. However, since trained examiners usually are needed for application of these batteries, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed in 2012 and recommended as validated and standardized international screening test for brief cognitive assessment of MS<sup>10</sup>. This international expert consensus committee has suggested that in order to enable international implementation of the BICAMS, multiple translations are warranted, as well as psychometric research. Therefore, consensus on the BICAMS validation protocol has been defined<sup>11</sup>. Until now, BICAMS has been translated and validated in numerous languages worldwide<sup>12</sup>.

The aim of our study was to translate and validate the Serbian version of the BICAMS. This investigation was performed as part of the multicenter cross-sectional study conducted at five university MS centers in Serbia and one in Montenegro in order to investigate the factors associated with work status in the relapsing-remitting (RR) MS patients (Observational, Multicenter Study of Factors Associated with Work Status and Employment of MS Patients in Serbia, OFELIA).

## Patients and Methods

### Patients

A cohort of 500 RRMS patients diagnosed according to the Revised McDonald criteria<sup>13</sup> were recruited at the following university clinical centers in Serbia and Montenegro: (1) Department of Neurology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; (2) Department of Neurology, Military Medical Academy, Medical Faculty, Defense University, Belgrade, Serbia; (3) Department of Neurology,

Kragujevac Clinical Center, Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia; (4) Department of Neurology, Clinical Center of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; and (5) Department of Neurology, Clinical Center of Montenegro, Podgorica, Montenegro.

According to the OFELIA study protocol, our cohort comprised all MS patients treated with interferon beta-1a s.c. in the above-mentioned clinical centers in Serbia and Montenegro. Thus, 261 RRMS patients treated with interferon beta-1a s.c. from January 2004 to December 2013, and 239 disease-modifying therapy (DMT) naïve RRMS patients, as well as 69 age-, gender-, and education-matched healthy control (HC) subjects were recruited. Treatment naïve patients were matched according to the Expanded Disability Status Scale (EDSS)<sup>14</sup> stratification and annual relapse rate in the previous year in each of EDSS clusters. Patient recruitment took place from January 2015 to August 2017. HC group was recruited among unaffected relatives and friends of MS patients.

The inclusion criteria were subjects over 18 years of age and able to give informed consent. All MS patients treated with interferon beta-1a s.c. in the above-mentioned clinical centers in Serbia and Montenegro and treatment naïve RRMS patients were recruited. Participants were excluded from the study if any of the following exclusion criteria existed: history of other major medical, neurological or psychiatric disorders, history of substance dependence or current substance abuse, an MS relapse that had occurred within eight weeks preceding evaluation, and inability to comply with study requirements. All patients and HCs were Caucasian Serbian-speaking individuals. This study was non-interventional and was not obligatory for safety data to be collected.

All MS patients and HC subjects underwent the BICAMS battery<sup>10</sup>, which comprised of oral version of the Symbol Digit Modalities Test (SDMT)<sup>15</sup>, the California Verbal Learning Test (CVLT-II)<sup>16</sup>, and the Brief Visuospatial Memory Test revised (BVMT-R)<sup>17</sup>. The SDMT<sup>15</sup> is a measure of attention and processing speed. It comprises series of nine symbols, each in association with a single digit. After short practice, patients have to pair as many of the symbols with the digit as they can in 90 seconds. In

the oral version, both the examiner and the patient are given one sheet and the patient is required to say the correct number while the examiner writes down. Total score is based on the number of correct answers. The CVLT-II<sup>16</sup> is a measure of verbal learning and memory. It comprises a list of 16 words that the participant must learn. After the examiner has read a list of 16 words, the patient is asked to repeat as many of the items, in any order. The procedure is repeated five times. Words have been translated to Serbian and culturally adapted. The outcome measure is the total number of recall items over the five learning trials. The BVMT-R<sup>17</sup> is a measure of visuospatial memory. Participants are asked to remember a page with six simple abstract designs for ten seconds. The procedure is repeated three times. Each design is scored 0, 1 or 2 points, based on accuracy and location. Total score is the sum of individual scores of the three trials. The above tests were performed by neurologists in each of the centers. Examiners had previously attended training sessions, and scoring was performed by blinded observers in each of the centers. Validation was performed according to the international standards<sup>11</sup>.

The study protocol was approved by the Ethics Committees of each participating institution, and all patients and HCs gave their written informed consent to participate in the study.

### Statistical analysis

Test-retest reliability was performed in a subgroup of MS patients and controls, using Pearson correlation coefficient. Retest was performed in 80 MS patients and 30 HCs at the Department of Neurology in Belgrade. According to the expert consensus committee recommendations, retest was performed at an interval ranging from one to three weeks and correlation coefficient ( $r$ ) was considered adequate if  $>0.70$ .

### Results

Five hundred RRMS patients and 69 HCs were recruited to the study. Their demographic and patient clinical characteristics are presented in Table 1. Median EDSS score was 2.0 with mean disease duration of 9.2 years. There were no statistically significant differences between HCs and patients according to age, gender and education.

Table 1. Patient and control subject characteristics

	MS patients	Healthy controls	P
N (male/female)	500 (149/351)	69 (25/44)	0.277
Age at examination (years) (mean $\pm$ SD, range)	39.9 $\pm$ 9.4 (17-70)	40.3 $\pm$ 11.5 (20-65)	0.736
Education (years) (mean $\pm$ SD, range)	14.0 $\pm$ 2.9 (6-25)	14.1 $\pm$ 3.4 (6-22)	0.706
Disease duration (years) (mean $\pm$ SD, range)	9.2 $\pm$ 6.7 (1-36)	-	
EDSS (median, IQR)	2.0 (2.0)	-	

MS = multiple sclerosis; SD = standard deviation; EDSS = Expanded Disability Status Scale; IQR = interquartile range

There was a statistically significant difference in two tests of the BICAMS battery (SDMT and BVMT) between MS patients and HCs ( $p < 0.001$ ) (Table 2). The results indicated that HCs had a higher CVLT test score compared to MS patients but this difference did not reach statistical significance.

Table 2. Mean raw scores in MS patients and healthy controls in BICAMS battery

	MS patients	Healthy controls	P
<b>SDMT</b>			
Mean $\pm$ SD	45.9 $\pm$ 16.7	56.3 $\pm$ 12.9	<0.001
Cohen's d	0.70		
Effect size ( $r$ )	0.33		
<b>CVLT</b>			
Mean $\pm$ SD	50.0 $\pm$ 11.7	52.7 $\pm$ 9.6	0.063
Cohen's d	0.25		
Effect size ( $r$ )	0.13		
<b>BVMT</b>			
Mean $\pm$ SD	18.8 $\pm$ 7.4	22.6 $\pm$ 5.8	<0.001
Cohen's d	0.57		
Effect size ( $r$ )	0.27		

MS = multiple sclerosis; SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visuospatial Memory Test

Table 3 outlines conversion of raw scores to scale scores ( $M=10$ ,  $SD=3$ ) using the cumulative frequency distribution of each raw measure.

Table 3. Raw score to scaled score conversion

Scaled score	Raw score		
	CVLT	SDMT	BVMT
2	0-32	0-24	0-3
3	33-36	25-29	4-8
4	37-38	30-35	9-12
5	39-43	36-40	13-15
6	44-47	41-45	16-17
7	48-49	46-50	18-19
8	50-51	51-52	20
9	52-53	53-55	21
10	54-55	56-57	22
11	56-57	58-60	23
12	58-59	61-62	24-25
13	60-62	63-66	26
14	63-64	67-68	27
15	65-66	69-70	28
16	67-69	71-75	29
17	70-75	76-80	30-31
18	$\geq 76$	$\geq 81$	32

CVLT = California Verbal Learning Test; SDMT = Symbol Digit Modalities Test; BVMT = Brief Visuospatial Memory Test

Table 4. Final regression models for BICAMS measures

Measure	Predictor	Unstandardized $\beta$ coefficient	Standard error $\beta$	T	Standardized $\beta$	Total R square
SDMT	(Constant)	10.870	5.211	2.086		0.494
	Age	-0.162	0.246	-0.658	-0.508	
	Age <sup>2</sup>	0.000	0.003	-0.081	-0.063	
	Gender	1.237	0.826	1.498	0.163	
	Education	0.325	0.136	2.392	0.271	
CVLT	(Constant)	6.418	5.998	1.070		0.359
	Age	-0.108	0.274	-0.394	-0.328	
	Age <sup>2</sup>	0.000	0.003	0.097	0.081	
	Gender	-0.448	0.885	-0.506	-0.057	
	Education	0.518	0.139	3.717	0.451	
BVMT	(Constant)	16.575	6.870	2.413		0.215
	Age	-0.407	0.314	-1.296	-1.193	
	Age <sup>2</sup>	0.004	0.004	0.995	0.915	
	Gender	0.002	1.013	0.002	0.000	
	Education	0.302	0.160	1.890	0.254	

SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visuospatial Memory Test

Normal control regression models for each of the three tests are presented in Table 4. These regression models allow the calculation of predicted (scaled) score based on the age, gender and education. Afterwards, z-score was calculated by dividing the difference between the predicted scale score and the actual scale score by the standard error of the residual (RSE) of the regression model.

Most patients showed impairment on SDMT (52.7%) when compared to other single tests, CVLT (9.7%) and BVMT (31.8%) (Table 5). According to the previously reported criteria for cognitive impairment, 62.9% of patients turned out to be cognitively impaired (Fig. 1).

Table 5. Prevalence of cognitive impairment in MS patients and healthy controls

	MS patients	Healthy controls	p
SDMT	52.7%	7.7%	0.001
CVLT	9.7%	3.4%	0.111
BVMT	31.8%	13.6%	0.004

MS = multiple sclerosis; SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visuospatial Memory Test

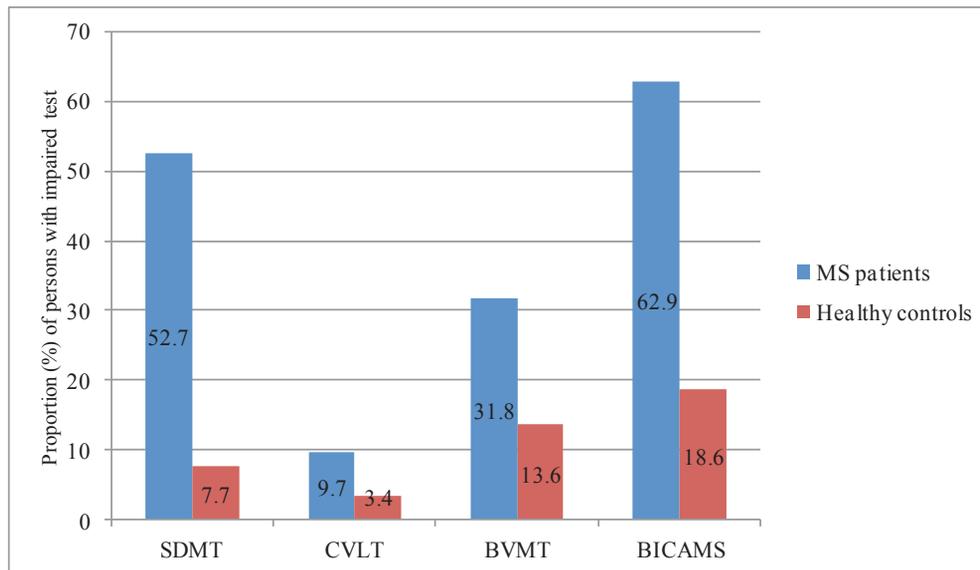


Fig. 1. Frequencies (%) of impaired ( $z$ -score  $\leq 1.5$ ) MS patients and healthy controls by mean  $z$ -scores for single tests (SDMT, CVLT and BVMT) and total BICAMS (at least one test impaired).

MS = multiple sclerosis; SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visuospatial Memory Test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis

Table 6 presents correlations of MS patient findings on three BICAMS tests with age, education, EDSS and disease duration. It has to be emphasized that CVLT did not correlate with disease duration. SDMT and BVMT, as well as CVLT correlated significantly with all demographic and clinical variables in MS patients, and with demographic variables in HCs. Test-retest reliability was confirmed with Pearson correlation coefficient of 0.70 in all measures.

### Discussion

Although it is well known that cognitive impairment is frequent in persons with MS, until now, cognitive screening is not performed routinely, which may be a consequence of limited availability of neuropsychologists<sup>18</sup>. The BICAMS has been proposed for assessing cognitive deficit in MS in small MS centers by health care professionals without experience

Table 6. Correlation between BICAMS and demographic and clinical characteristics in MS patients and healthy controls

MS patients	Age		Education		Disease duration		EDSS	
	r	p	r	p	r	p	r	p
SDMT	-0.225	0.001	0.339	0.001	-0.109	0.018	-0.466	0.001
CVLT	-0.232	0.001	0.298	0.001	-0.880	0.056	-0.320	0.001
BVMT	-0.271	0.001	0.190	0.001	-0.207	0.001	-0.360	0.001
Healthy controls								
SDMT	-0.605	0.001	0.521	0.001				
CVLT	-0.430	0.001	0.552	0.001				
BVMT	-0.374	0.002	0.394	0.002				

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visuospatial Memory Test

in neuropsychological testing. An international validation protocol was defined and until now the BICAMS has been validated in several languages and countries worldwide<sup>11</sup>. The current study aimed to evaluate the BICAMS in Serbian language.

According to the criteria of  $\geq 1$  test abnormal as recommended from previous studies<sup>19</sup>, 62.9% of our MS patients turned out to be cognitively impaired compared to 18.6% of age-, sex- and education-matched control subjects. These results are in line with the Czech, Irish and Canadian validation studies reporting on 58%, 57% and 58% of cognitively impaired MS patients, respectively<sup>19-21</sup>.

Our findings support the already published data implicating good psychometric properties of two of the three BICAMS measures in a Serbian sample<sup>22,23</sup>. Thus, SDMT and BVMTR significantly differentiated MS patients and HCs. Similarly, as already demonstrated by Costers *et al.*, we did not find significant differences in CVLT-II between MS patients and HCs<sup>22</sup>. On the other hand, recently Scorbe *et al.* identified statistically significant difference in CVLT-II score between MS patients and HCs. Additionally, these authors demonstrated, in contrast to other BICAMS validation studies, that CVLT-II identified impairment in a higher proportion of patients in comparison with both BVMTR and SDMT<sup>24</sup>. Having in mind these findings implicating the presented psychometric properties of BICAMS tests, Filser *et al.*<sup>23</sup> proposed the following: regarding the limited time available in the standard clinical care of MS patients in the German health care system, they recommended SDMT and BVMTR as mandatory, and the usage of Verbal Short-term Memory and Verbal Learning (VLMT) as optional<sup>23</sup>.

We found significant correlation of age, education, disease duration and EDSS with all three BICAMS tests. These findings are comparable with those demonstrated in recently published validation studies<sup>22,25</sup>.

Test-retest reliability was analyzed and BICAMS demonstrated good retest reliability. This might be important having in mind that cognitive performance should be monitored and followed-up over time.

Our validation study provided the Serbian BICAMS version, a screening battery for cognition in MS and demonstrated its strong psychometric properties. To the best of our knowledge, the present validation study comprised the highest number of MS patients until now. Since early detection and follow-up

of cognitive deficit is very important in MS, especially having in mind its potential impact on the quality of life<sup>26</sup>, the BICAMS should be considered to be accepted as a standard of MS care.

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## Sažetak

## VALIDACIJA KRATKE MEĐUNARODNE KOGNITIVNE PROCJENE MULTIPLE SKLEROZE U VELIKOJ KOHORTI BOLESNIKA S RELAPSNOM-REMITENTNOM MULTIPLOM SKLEROZOM

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Kognitivno oštećenje je jedna od najčešće prijavljivanih manifestacija kod osoba s multiplom sklerozom (MS). Kratka međunarodna kognitivna procjena multiple skleroze (engl. *Brief International Cognitive Assessment for Multiple Sclerosis*, BICAMS) je baterija testova preporučena za brzu kognitivnu procjenu, koja je međunarodno standardizirana. Cilj našeg istraživanja bio je procijeniti pouzdanost i validnost srpske verzije BICAMS-a. Ispitano je ukupno 500 bolesnika s relapsno-remitentnom MS (RRMS) i 69 zdravih kontrolnih osoba (ZK) ujednačenih po uzrastu, spolu i razini obrazovanja. Svim sudionicima u studiji napravljen je BICAMS, koji uključuje usmenu verziju Testa analogije simbola i brojeva (SDMT), Kalifornijski test verbalnog učenja (CVLT-II), drugo izdanje i revidirani kratki test vizualne memorije (BVMTR). Nasumično odabrana podskupina bolesnika je ponovno testirana 1-3 tjedna nakon prvog testiranja. Statistički značajne razlike između bolesnika s MS i ZK zabilježene su za SDMT i BVMTR ( $p < 0,001$ ). ZK su imali viši zbroj CVLT-II, ali ova razlika nije dostigla statističku značajnost ( $p = 0,063$ ). Kognitivno oštećenje definirano kao nenormalni rezultat testa na  $\geq 1$  subtestu utvrđeno je kod 62,9% bolesnika s MS. Postojale su statistički značajne korelacije između rezultata testova BICAMS-a i dobi, razine obrazovanja, proširene ljestvice onesposobljenosti (EDSS) i dužine bolesti u skupini bolesnika s MS. Pouzdanost test-retest je potvrđena Pearsonovim koeficijentom korelacije od 0,70 u svim mjerenjima. Ova studija je pokazala pouzdanost i validnost srpskog BICAMS-a, iako verzija CVLT-II koja je ovdje testirana nije bila osjetljiva za otkrivanje kognitivnih poremećaja kod MS u usporedbi sa ZK.

Ključne riječi: *Multipla skleroza; BICAMS; Kognicija; Kognitivno oštećenje; Validacija*