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ORIGINAL COMMUNICATION

The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS): results from the German validation study

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Abstract

Background Recent research has convincingly shown that the ability to work mainly depends on the cognitive status in multiple sclerosis (MS). An international committee of experts recommended a brief neuropsychological battery to evaluate cognitive performance in MS. BICAMS comprises three tests, the Symbol Digit Modalities Test (SDMT), the learning trials of the California Verbal Learning Test II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R).

Objective To validate BICAMS on a sample of German MS patients and healthy controls (HCs).

Methods According to the international guidelines for validation, examiner's instructions were standardized and translated into German. Due to the availability of better normative data for future applications in routine clinical care and classification of individual performance degree, the Rey Auditory Verbal Learning Test (RAVLT) (German version: Verbaler Lern- und Merkfähigkeits-Test, VLMT) was chosen instead of CVLT-II. 172 MS patients and 100 HCs entered the study. BICAMS was administered at baseline and retest (after 3–4 weeks).

Results The groups did not differ in age, gender or education. Mean age of MS patients was 43.33 years (SD 11.64); 68% were female and 86.9% had relapsing-remitting MS. Patients performed significantly worse than HCs on the SDMT ($p < 0.01$) and on BVMT-R ($p < 0.05$) but not on VLMT. In addition, BICAMS was shown to be reliable over time: $r = 0.71$ for BVMT-R, $r = 0.72$ for VLMT and $r = 0.85$ for SDMT. SDMT z-score proved to be a good predictor for the ability to work in a full-time ($p < 0.001$) as well as in a part-time job ($p < 0.001$). VLMT z-score turned out to be a significant predictor only for the ability to work in a part-time job, while BVMT-R z-score showed no significant predictive value.

Conclusion In this German validation study with the VLMT, the modified BICAMS (BICAMS-M) turned out to reliably detect cognitive problems in MS patients and to monitor cognitive performance over time. SDMT revealed the best predictive value for working ability. Moreover, only the SDMT was able to predict the ability to work in a part-time or full-time job. Following these results, application of the SDMT is recommended for medical statements on working ability of MS patients.

Keywords Multiple sclerosis · BICAMS · Cognition · Working ability · Validation

Abbreviations

BICAMS	Brief International Cognitive Assessment in Multiple Sclerosis
BICAMS-M	Modified Brief International Cognitive Assessment in Multiple Sclerosis
BL	Baseline
BRB-N	Brief Repeatable Battery of Neuropsychological tests
BVMT-R	Brief Visual Memory Test Revised
CVLT-II	California Verbal Learning Test II
EDSS	Expanded Disability Status Scale
HCs	Healthy controls
LÄK	Landesärztekammer
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis

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MS	Multiple sclerosis
N	Population size
p	Probability of an event or outcome in a statistical experiment
PPMS	Primary progressive multiple sclerosis
r	Pearson's *r*, correlation coefficient
RAVLT	Rey Auditory Verbal Learning Test
RRMS	Relapsing-remitting multiple sclerosis
RT	Retest
SD	Standard deviations
SDMT	Symbol Digit Modalities Test
SPMS	Secondary progressive multiple sclerosis
SPSS	Statistical Package for the Social Sciences
VLMT	Verbaler Lern- und Merkfähigkeitstest

Introduction

Cognitive problems are of major impact in patients with multiple sclerosis (MS). Recent data convincingly showed that the ability to work is a direct function of cognitive status [1]. Further, cognitive difficulties and fatigue are two of the most relevant factors in terms of burden and costs of MS in Europe, both having a strong influence on working ability from disease onset, and being independent of the degree of physical disability [2]. In addition, there is evidence from an 8-year follow-up study that cognitive impairment may even be predictive for disability progression and cortical thinning [3]. These results highlight the importance of regular cognitive assessments in standard clinical care.

For this purpose, BICAMS was introduced as an international consensus instrument to screen cognitive status in patients with MS [4]. BICAMS consists of three neuropsychological tests assessing information processing speed and working memory by SDMT [5], verbal short-term memory and learning by CVLT-II [6], and visuo-spatial short-term memory and learning by BVMT-R [7]. These three tests have been evaluated by an expert panel and have been recommended as international standard to assess cognitive decline in MS based on their excellent psychometric properties. In total, the application of BICAMS takes 15–20 min and allows not only determination of cognitive status at a single time point but also monitoring of cognitive evolution over time by offering parallel versions of test material [4].

So far, BICAMS has been translated and validated in Iran [8], Belgium [9], Argentina [10], Canada [11], Greece [12], Brazil [13], Hungary [14], Ireland [15], Lithuania [16], Italy [17], the Czech Republic [18], Turkey [19] and Japan [20]. The present study provides data of the German validation of BICAMS based on the official protocol for the international standards for validation [21]. Additionally, the predictive value of BICAMS for working ability was assessed in this German population.

Methods

Subjects

A total of 172 MS patients and 100 HCs entered the study. All participants were recruited from the ambulatory MS clinic of the University Hospital Hamburg, and the Neurological Practice and Neuropoint Academy, Ulm. All participants provided their informed written consent and the study was approved by the ethical committees of the University of Hamburg and the LÄK, Baden-Württemberg, Stuttgart.

Procedures

According to the international guidelines for validation, the examiner's instructions were standardized and translated into German [21]. For the SDMT and the BVMT-R, the original test versions were applied, since test stimuli are independent of language. Instead of CVLT-II, the Rey Auditory Verbal Learning Test (RAVLT [22]; German version: Verbaler Lern- und Merkfähigkeits-Test, VLMT [23]) was chosen as verbal short-term memory and learning test. This decision was taken based on availability of extensive normative data in Germany for VLMT allowing graduation of impairment degree in future clinical trials and clinical standard care. Before participants performed the BICAMS battery written informed consent was obtained from each subject followed by a short demographic interview for age, education and working ability. Three categories generally used in Germany were taken to categorize the employment status of the participants: (a) work disabled/retired (b) working in a half-time job and (c) working in a full-time job. For assessing test–retest reliability, all participants completed the BICAMS battery at baseline (BL) and were retested (RT) with the recommended parallel versions [6, 7] after 3–4 weeks.

Neuropsychological test procedures

Patients and HCs were investigated by trained personnel for administration and scoring of BICAMS.

The tests were administered in a standardized manner with a fixed order: first SDMT, second the five learning trials of VLMT, and last the three learning trials of BVMT-R.

SDMT is a measure for information processing speed and working memory. Subjects have to assign as fast and as accurate as possible the numbers 1–9 to predefined symbols in 90 s. Since for the Rao SDMT Version of the Brief Repeatable Battery of Neuropsychological tests (BRB-N) no equivalent alternate version is available [21] and since

learning effects by applying the test twice are minor [24], the same SDMT version was applied to test for RT reliability.

The VLMT learning trials are a measure for verbal short-term memory and learning. It consists of a list of 15 words and 5 learning trials. The examiner reads aloud and consecutively the 15 words to the participant who in return has to immediately recall as many words as possible. This procedure is repeated five times. The sum score is derived from the number of correctly recalled words. The VLMT provides three parallel versions, to minimize learning effects between testing sessions. For the BL examination, version A was applied, while for the RT the equivalent version C was used.

The BVMT-R learning trials are a measure of visuospatial short-term memory and learning. Subjects have to encode six geometrical figures and memorize their precise location during presentation of 10 s. Immediately afterwards, subjects have to draw the memorized figures in the right location. The procedure is repeated three times. Depending on figure and exact location accuracy, a scoring from zero to two points for each figure is given. The total recall score consists of the sum of the individual scores of the three trials. BVMT-R offers six parallel versions. According to the validation protocol, form one was used for BL testing, and form four for RT examination.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics version 24 software packages. The sample was checked for completeness and correctness of the data. To determine cognitive impairment, we calculated *z*-scores based on the performance of the HCs. Participants were defined as impaired if their score was 1.5 SD below the mean of the control group in one or more tests. Cronbach's alpha was determined to define internal consistency of BICAMS. Group differences in BICAMS performance were examined with *t* tests and the test–retest reliability was evaluated with Pearson's correlation analyses. In a last step, logistic regression was used to reveal whether BICAMS performance predicted self-reported vocational status in MS patients.

Results

Demographic characteristics

Descriptive statistics of the whole sample are presented in Table 1 and the vocational status is displayed in Table 2. The Chi-square analyses demonstrated that HCs and patients did not differ in age, $\chi^2(52) = 60.31$, $p = 0.20$, gender, $\chi^2(1) = 0.26$, $p = 0.61$, or education, $\chi^2(2) = 0.07$, $p = 0.97$.

Table 1 Descriptive data of the sample

	N (%)	Age (mean ± SD)	Female (%)	Years of education (mean ± SD)
HCs				
Total	100 (100)	43.04 ± 15.59	71.0	10.77 ± 1.58
Patients				
RRMS	146 (86.9)	41.43 ± 10.83	65.8	10.77 ± 1.56
SPMS	16 (9.5)	54.37 ± 09.27	81.3	10.19 ± 1.47
PPMS	6 (3.6)	54.00 ± 10.43	83.3	10.50 ± 1.23
Total	268 (100)	43.33 ± 11.64	68.0	10.74 ± 1.56

$N = 272$, $N = 4$ missings

RRMS relapsing-remitting MS, *SPMS* secondary progressive MS, *PPMS* primary progressive MS

Validity

Group differences

Group differences in BICAMS tests were analysed with *z*-scores using *t* tests (Table 3) between BL and RT. Patients performed significantly worse than HCs on SDMT ($p < 0.01$) and BVMT-R ($p < 0.05$) but not on VLMT at both time points (Table 3).

Using the previously reported criteria of cognitive impairment, 32.6% of patients turned out to be cognitively impaired at BL. Most patients showed impairment on BVMT-R (26.5%) when compared to the other single tests with 8.1% on VLMT and 19.2% on SDMT (Fig. 1).

Vocational status and BICAMS

To further analyse the validity of BICAMS, we evaluated the predictive value for working ability. Therefore, a multinomial logistic regression analysis was performed for the group of MS patients, including work-disabled patients as a reference group. The results showed that age ($p < 0.05$), education ($p < 0.05$), and SDMT *z*-score ($p < 0.001$) were reliable predictors for the ability to work in a full-time job. Young, better educated patients with a higher test score in SDMT showed the highest probability to work in a full-time job. For the prediction of the ability to work in a part-time job, only the SDMT *z*-score ($p < 0.001$) and VLMT *z*-score ($p < 0.05$) were significant predictors. Patients with higher test scores in SDMT and higher test scores in VLMT showed a higher probability to work in a part-time job. The BVMT-R *z*-score did not explain variance with respect to the vocational status (Table 4).

Table 2 Vocational status of the sample

	N (%)	Work disabled, *n* (%)	Part-time job, *n* (%)	Full-time job, *n* (%)
HCs				
Total	100 (100)	8 (8.0)	28 (28.0)	64 (64.0)
Patients				
RRMS	142 (54.2)	42 (29.6)	29 (20.4)	71 (50.0)
SPMS	15 (5.7)	11 (73.3)	3 (20.0)	1 (6.7)
PPMS	5 (1.9)	1 (20.0)	2 (40.0)	2 (40.0)
Total	262 (100)	62 (23.7)	62 (23.7)	138 (52.7)

$N = 272$, $N = 10$ missings

RRMS relapsing-remitting MS, *SPMS* secondary progressive MS, *PPMS* primary progressive MS

Table 3 Group differences at baseline (BL) and retest (RT) for all BICAMS measures

	Patients ($N = 172$)				HCs ($N = 100$)				*p*
	Raw score		*z*-score		Raw score		*z*-score		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SDMT BL	47.43	11.67	−0.74	1.00	56.07	11.64	0.00	1.00	< 0.001**
VLMT BL	55.35	11.43	0.02	1.11	55.16	10.27	0.00	1.00	> 0.05
BVMT-R BL	24.44	7.59	−0.49	1.27	27.37	5.96	0.00	1.00	< 0.05*
BICAMS BL	na	na	−0.41	0.90	na	na	0.00	0.79	< 0.001**
SDMT RT	50.04	14.01	−0.67	1.04	59.02	13.49	0.00	1.00	< 0.001**
VLMT RT	57.28	11.63	0.16	1.15	55.69	10.09	0.00	1.00	> 0.05
BVMT-R RT	23.63	7.84	−0.97	1.46	28.86	5.39	0.00	1.00	< 0.001**
BICAMS RT	na	na	−0.49	0.94	na	na	0.00	0.78	< 0.001**

$N = 272$

Comparison (*t* test) mean *z*-scores of SDMT, VLMT and BVMT-R in both groups (MS patients and HCs)

na not applicable

$^{**}p < 0.001$; $^{*}p < 0.05$

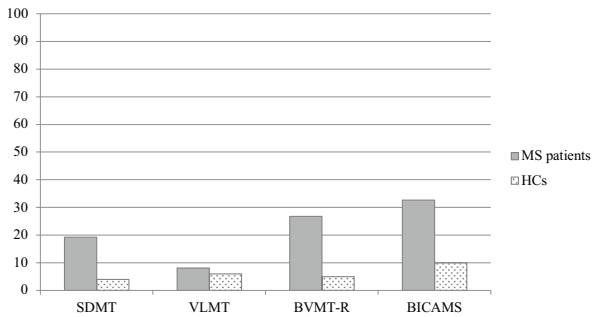

Fig. 1 $N = 272$. Frequencies (in %) of impaired (z-score ≤ -1.5) patients and HCs by mean z-scores (BL and RT) for single tests (SDMT, VLMT, BVMT-R) and total BICAMS (one or more tests are impaired)

Reliability

Internal consistency and retest reliability

Cronbach's alpha for BL and RT revealed satisfying levels of internal consistency for the three BICAMS tests at BL ($\alpha = 0.70$) and RT ($\alpha = 0.65$). The test–retest reliability was good for all three tests in both groups. According to Cohen [25], the correlation between BL and RT for the mean z-score of BICAMS was strong ($r = 0.85$). The analysis for the single tests of BICAMS showed the strongest correlation between BL and RT for the SDMT ($r = 0.85$, see Table 5) [25].

Discussion

BICAMS as a measure to evaluate cognitive impairment in MS, has been validated in several languages and countries [9–20]. The most well-known batteries of neuropsychological tests in MS are the BRB-N [26], the Minimal Assessment of Cognitive Function in MS (MACFIMS) [18] and the BICAMS [4]. BICAMS differs from the two others in application time (15–20 min [4, 15]) which makes it an interesting tool for standardized evaluation in standard clinical care and clinical trials. This study addresses the validation of

Table 4 Multinomial logistic regression analysis of vocational status in MS patients

Dependent variable Vocational status		95% CI for OR		
	B (SE)	Lower	OR	Upper
Full-time				
Age*	−0.04 (0.02)	0.93	0.96	0.99
Education*	0.52 (0.26)	1.02	1.68	2.78
SDMT *z*-score**	1.27 (0.27)	2.09	3.55	6.04
VLMT *z*-score	−0.10 (0.18)	0.64	0.91	1.29
BVMT-R *z*-score	0.05 (0.19)	0.73	1.06	1.52
Part-time				
Age	0.02 (0.02)	0.99	1.02	1.06
Education	0.40 (0.28)	0.86	1.50	2.60
SDMT *z*-score**	1.04 (0.28)	1.63	2.84	4.93
VLMT *z*-score*	0.43 (0.19)	1.06	1.54	2.24
BVMT-R *z*-score	−0.27 (0.20)	0.52	0.77	1.12

$N = 172$ ($N = 166$ MS patients, $N = 6$ missings on vocational status). OR (odds ratio) = exp (*B*). Reference group: work-disabled participants. Nagelkerke $R^2 = 0.37$, $\chi^2(10) = 440.33$, $p < 0.001$

*$p < 0.05$; **$p < 0.001$

Table 5 Retest reliability of the overall sample

	Pearson's *r*	*p*
SDMT	0.85	< 0.001
VLMT	0.72	< 0.001
BVMT-R	0.71	< 0.001
BICAMS	0.85	< 0.001

$N = 272$. Pearson's *r* of *z*-scores at BL and RT

BICAMS in Germany in accordance with the recommendation guidelines of the international validation protocol of BICAMS [21]. Since for methodological reasons CVLT-II was replaced by the RAVLT (German version: Verbaler Lern- und Merkfähigkeits-Test, VLMT), this modification step may be indicated in the future by referring to BICAMS-M to ensure differentiation from the original version.

In accordance with other studies, the SDMT showed a reliable predictive value for working ability [27–29]. Therefore, application of the SDMT can be recommended to categorize participants with respect to their ability to work full-time or part-time. To differentiate between the ability to work in a part-time job or to be completely unable to work, the VLMT showed an additional significant predictive value. Similar results in previous studies concerning the predictive value for working ability of the CVLT were reported [30, 31]. Thus, our data confirms previous research findings and can be regarded representative. Though test performance in VLMT did not vary between the two populations (MS patients and HCs), it is precise enough to identify participants' work status. However, a clear limitation in interpreting this finding is the lack of information about the Expanded Disability Status Scale (EDSS) in our study. Thus, no information on physical disability, its particular effect on working ability and a possible interaction with cognitive status can be given.

Since it is important to consider BICAMS as a measure to monitor cognitive performance over time, retest reliability was analysed: BICAMS overall showed good retest reliability, with SDMT showing the highest reliability index [25].

The present findings provide evidence for good psychometric properties of at least two of the three BICAMS measures in a German-speaking sample. SDMT and BVMT-R significantly differentiated between MS patients and HCs at BL and RT. However, the groups did not differ in performance on VLMT, neither at BL nor at RT assessment. Similar findings were reported by Dusankova et al. [18], showing that SDMT and BVMT-R were the most sensitive tests of the MACFIMS battery and exhibiting the largest differences between MS and HCs. Costers et al. [9] reported that MS patients and HCs showed differences mainly in SDMT and BVMT-R, but not in CVLT-II [9]. Furthermore, some other validation studies also reported that the SDMT and BVMT-R were able to dissociate between the MS and HCs, while CVLT-II was not [11, 17]. Thus, our findings of applying VLMT are consistent with studies using CVLT-II. Therefore, it can be assumed that verbal short-term memory and verbal learning (VLMT) represent a cognitive domain that is less suitable to discriminate MS patients from HCs than information processing speed (SDMT) and visuo-spatial short-term memory and learning (BVMT-R).

With respect to the limited time available in daily clinical care of patients in the German healthcare system, SDMT and BVMT-R can be recommended as mandatory, whereas the use of the VLMT is optional by giving additional information on the vocational status of patients (half-time job and work disabled).

According to Smerbeck et al. [32] performance on all three BICAMS tests is significantly influenced by nationality and should be considered in the interpretation of these findings. Therefore, the weakness of the VLMT in distinguishing MS patients from HCs might be attributed to the fact that patients in Germany were not severely cognitively impaired in verbal short-term memory and thus, differences to the control sample were hardly possible to detect. Previous studies highlighted cultural differences of cognitive performance and emphasized the importance of including nationality variables when normative data are being conducted [32–35].

Conclusion

The BICAMS battery was proposed as international consensus to quickly and reliably assess cognitive performance of MS patients in standard clinical care [21]. Our validation study verifies that the German version of BICAMS, the BICAMS-M, is a useful tool to detect cognitive deficits in MS patients and to reliably monitor cognitive performance over time. Since early detection of cognitive impairment is crucial for a holistic treatment concept and for disability quantification, BICAMS(-M) should be integrated as part of each neurological assessment for MS, at each level of cognitive rehabilitation, and it can be further applied for vocational guidance.

Author contributions MF: statistical data analysis, data interpretation, manuscript preparation. HS: Co-PI of study, study conceptualization, data collection, data interpretation, manuscript preparation. JP: data collection, data interpretation, manuscript preparation. SU: support of statistical analysis, data interpretation, review of manuscript. ML: data collection, study coordination. IKP: PI of study, study conceptualization, data collection, data interpretation, manuscript preparation.

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Compliance with ethical standards

Ethics approval and consent to participate The study was performed in accordance with the Declaration of Helsinki. It was approved in October 2014 by the ethical committee of the University of Hamburg, committee's reference number is PV4770, and in June 2014 by the Landesärztekammer (LÄK) Baden-Württemberg, Stuttgart, committee's reference number is F-2014-048. All participants were informed of the full details of the study and to give their confirmation to participate.

Consent for publication Not applicable. There are no details, images, or videos relating to an individual person included in this manuscript.

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest MF has nothing to disclose. HS has received travel Grants and honoraria for speaking at scientific meetings, participating in scientific advisory boards and consulting activities from Almirall, Bayer Healthcare, Biogen GmbH, Genzyme, Merck, Novartis and Teva. JP has received travel cost compensation from Bayer Pharma and honoria for speaking at scientific meetings from Novartis Pharma GmbH. SU has nothing to disclose. ML has received travel Grants, speaker's honoraria, financial research support, consultancy fees from Teva, Merck Serono, Genzyme -Sanofi, Novartis, Bayer, Biogen. IKP has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almiral, Bayer Pharma, Biogen GmbH, Desitin, Genzyme, Merck Serono, Novartis Pharma GmbH, Roche and Teva.

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