Multiple Sclerosis and Related Disorders 37 (2020) 101458

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Brief international cognitive assessment for multiple sclerosis (BICAMS): A danish validation study of sensitivity in early stages of MS

Lisbet Marstrand[a,*], Ole Østerberg[b], Trine Walsted[a], Amalie C. Skov[a], Karen I. Schreiber[a], Finn Sellebjerg[a]

[a] Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Global stakeholder partnership, LEO Pharma, Denmark

ARTICLE INFO

Keywords:
Multiple sclerosis
Cognitive impairment
Brief international cognitive assessment for ms
Symbol digit modalities test
California verbal learning test-ii
Brief visuospatial memory test revised

ABSTRACT

Background: Cognitive impairment is highly prevalent in multiple sclerosis (MS). Due to the lack of specialized neuropsychological resources in many MS clinics, a brief cognitive monitoring tool that can be administered by other MS clinic staff is needed. BICAMS (Brief International Cognitive As-sessment for Multiple Sclerosis) has been developed and recommended by MS experts to monitor MS-related cognitive impairment. International validations of the tool are warranted.

Objective: The primary aim of the study was to establish a Danish translation of BICAMS as a feasible cognitive monitoring tool and to provide a Danish contribution to the international validation of BI-CAMS. A secondary aim was to determine if BICAMS correlated with self-reported cognition. The study population comprised people with MS (pwMS) with relatively early MS and newly diagnosed.

Methods: 65 pwMS were compared to healthy controls (HCs) matched on age, sex and education. PwMS and controls completed the BICAMS test battery which includes the Symbol Digit Modalities Test (SDMT, oral version), California Verbal Learning Test-II (CVLT-II) and the Brief Visuospatial Memory Test-Revised (BVMT-R). In addition, self-reported cognition, fatigue, depression and quality of life were assessed. To evaluate the reliability of the BICAMS test, all participants were retested 2–3 weeks later with alternate versions of the tests.

Results: Mean age of the MS group was 37.2 years; 63% were female and all pwMS had a relapsing-remitting disease course. MS disease duration was relatively short; mean disease duration was 3.9 years and 32 of 65 pwMS (49%) were newly diagnosed with MS, i.e. diagnosed within the last 2 years. Mean EDSS was 1.8 with a span from 0–4. Comparison of the groups showed that the MS group performed significantly below the control group on the 3 BICAMS measures: SDMT ($p < 0.005$), CVLT-II ($p < 0.05$) and BVMT-R ($p < 0.05$). When the results were controlled for influence from depression and fatigue by regression analysis, group differences were limited to the SDMT ($p < 0.05$) and the BVMT-R ($p < 0.05$) and these group differences were only found at the retest session. The BICAMS measures were reliable over time ($r = 0.90$ for SDMT, $r = 0.82$ for CVLT-II and $r = 0.68$ for BVMT-R). 32.3% of the MS population was cognitively impaired on at least one of the 3 BICAMS tests (defined as -1.5 SD compared to HCs). In the MS group 20% were impaired on the SDMT; 16.9% were impaired on the BVMT-R and 10.7% were impaired on the CVLT-II. There was no relationship between BICAMS test-scores and subjectively reported cognition, fatigue or depression.

Conclusion: The Danish translation of BICAMS was a reliable and feasible cognitive assessment tool. This finding was confirmed even in an MS population characterized by relatively early MS and high cognitive reserve. Frequency of cognitive dysfunction detected by BICAMS in this study was relatively low due to population characteristics.

1. Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (Thompson, 2018). In Denmark the prevalence of MS is among the highest in the world with approximately 300 per 100.000 citizens being affected (Koch-Henriksen et al., 2018). MS is associated with a range of physical, psy-chiatric and cognitive symptoms. A large proportion of people with MS (pwMS) (40–75%) have

* Corresponding author.
E-mail address: lisbet.marstrand@regionh.dk (L. Marstrand).

https://doi.org/10.1016/j.msard.2019.101458
Received 27 May 2019; Received in revised form 26 August 2019; Accepted 18 October 2019

cognitive im-pairment, primarily reduced information processing speed, memory and executive functions, and these symptoms may appear already in the early course of the disease (Trenova et al., 2016; Filippi et al., 2018). Cognitive symptoms have a negative impact on a broad range of aspects for pwMS: employment (Clemens and Langdon, 2018), daily activities (Benedict et al., 2017; Goverover et al., 2017), quality of life (Ruet and Brochet, 2013), disease management (Bruce et al., 2010), and many aspects of psychosocial functions (Kavaliunas et al., 2019). Cognitive impairment in MS is often subtle and is not necessarily detected in routine clinical consultations. Self-reporting of cognitive functioning is confounded by other fac-tors such as depression. Hence, objective assessment of cognitive functions in MS is needed.

A full neuropsychological assessment of cognitive functions is time-consuming and requires expert personnel and specialized equipment, which may not be available at many MS clinics. This in turn poses an obstacle for the implementation in routine clinical practice and, consequently, there is an inherent risk of cognitive impairment being underdiagnosed in pwMS.

The BICAMS is a set of three tests selected by a consensus panel of MS experts as part of an interna-tional initiative to develop a brief cognitive monitoring tool with adequate reliability, validity, sensitivity and specificity to assess cognitive impairment in MS (Langdon et al. 2012). The BICAMS consists of the oral ver-sion of the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II) and the Brief Visuospatial Memory Test Revised (BVMT-R), these can be performed by health care personal without any formal neuropsychological training (e.g. MS nurses). It takes approximately 15 min to conduct and, as such, the BICAMS represents a useful tool for implementation in routine clinical practice to detect early and unrecognized cognitive impairment in MS.

It has been emphasized that cultural norms of specific populations are markedly different, and that this might interfere with the reliability of cognitive testing. Hence there is a need for validation studies in individual countries. To facilitate international implementation of BICAMS, validation recommendations have been proposed to ensure the reliability and validity of the test battery across different countries (R.H. Benedict et al., 2012). Currently, the BICAMS has been validated in several countries according to these recom-mendations, and according to a recent systematic review and meta-analysis, BICAMS has up till now been validated across 11 languages and in 14 countries (Corfield and Langdon, 2018).

The objective of the present study was to validate BICAMS in a Danish population of pwMS. A popula-tion of pwMS with relapsing-remitting multiple sclerosis (RRMS) was selected to ensure homogeneity of studied group. Furthermore, persons with relatively short disease duration were selected for the study to address BICAMS sensitivity in the early stages of the disease. A secondary objective of the study was to evaluate self-reported cognition vs. BICAMS measures. The validation of BICAMS in the Danish patient popu-lation followed the international standards for validation (R.H. Benedict, R.H. et al., 2012).

2. Materials and methods

2.1. Study design and population

This was an open-label study conducted at a single centre (the Danish Multiple Sclerosis Center (DMSC) at Copenhagen University Hospital Rigshospitalet) to validate BICAMS.

People diagnosed with RRMS as defined by the 2010 revised McDonald criteria (Polman et al., 2011) and attending the DMSC or other Danish MS clinics in the period between Q2 2018 to Q4 2018 were asked to participate in the study. Both newly diagnosed, treatment naïve pwMS and pwMS who had previously received treatment for MS were eligible for the study. All pwMS were on first- or second-line treatment. The inclusion criteria were: Expanded Disability Status Scale (EDSS) score of 0 – 5.0 (both inclusive) at screening; no evidence of relapse within 30 days prior to enrolment; 18–59 years of age and fluent in Danish. The exclusion criteria were: neurological, psychiatric or medical conditions besides MS and depression that might affect cognition; a history of learning disabilities; seizures; uncorrected visual acuity problems; corticosteroid treatment within two months of enrolment; current MS exacerbation; current use of legal or illegal drugs that could impact cognitive functions.

A matching group of healthy controls (HCs) with similar age (± 2 years), gender and education were re-cruited. All participants gave written informed consent before entering the study.

To asses test-retest reliability, all participants completed the BICAMS at baseline and were retested with alternate versions of the tests after 1–3 weeks. The study was done in full accordance with the Declara-tion of Helsinki as adopted by the World Medical Association as well as Danish laws and regulations.

2.2. Assessment

2.1.1. Baseline assessments

At baseline, subjects' eligibility to participate in the study was evaluated and informed consent was obtained. Demographic data were then collected, including age, gender, disease duration, years of education and employment status. EDSS was registered from the latest neurological assessment. Furthermore, timed 25-foot walk (T25-FW), 9-hole peg test and low contrast visual acuity test were assessed and noted for each participant.

2.2.1. Brief international cognitive assessment for multiple sclerosis (BICAMS)

The BICAMS consists of a set of three individual tests: the SDMT (oral version), CVLT-II and BVMT-R tests (Langdon et al. 2012). The SDMT is designed to evaluate information processing speed. The CVLT-II assesses verbal learning and memory. In the CVLT-II, the examiner reads out a list of a total of sixteen words within four different semantic categories. The BVMT-R assesses visuospatial memory. In the BVMT-R, the subject is presented with a piece of paper with six abstract symbols for 10 s. The paper is then removed, and the subject is asked to replicate the six symbols on a blank piece of paper. The test is repeated in three trials.

In accordance with the BICAMS validation protocol (R.H. Benedict, 2012), initially all verbal material of the BICAMS including instructions was translated into Danish.

The SDMT in two alternate forms adapted by Benedict and cow-orkers (R.H. Benedict et al., 2012 (b)) based on the original version (Smith, 1973) were applied in this study.

Following collection of demographic data and other baseline assessments, the BICAMS was conducted. 1–3 weeks after the initial test all participants were retested in a follow-up session. In the follow-up sessions alternate test forms were used to reduce practice effects. The instruction and administration of the BICAMS test and retest was done by the same neuropsychologist or neuropsychologist student during the entire study.

In addition to BICAMS, questionnaires were applied to measure self-reported cognition, fatigue, de-pression, and quality of life. Self-reported cognition was assessed with the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), which is a validated measure of subjective cognitive deficits related to MS (Benedict et al., 2003). Fatigue was measured with the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009). Depression was measured with Beck's Depression Inventory (BDI-II) (Beck et al., 1961). In the MS group, quality of life was measured with Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001).

2.3. Data collection and statistical analysis

All statistical tests were performed using a two-sided test at a 5%

significance level. Results from the analyses are presented with point estimates, 95% confidence intervals and p-values. Data from all subjects (pwMS and HCs) were included in the statistical analyses and no imputation of missing data was made.

For the comparison of categorical variables between the MS and HC group, chi-square and Fisher's ex-act test were applied, and for continuous variables Students *t*-test or Wilcoxon test were applied to test for group differences. Furthermore, for continuous variables, the effect size was calculated using Cohen's d sta-tistic (Cohen et al., 1998). To evaluate the relationship between assessments at test and retest, Pearson or Spearman correlation coefficients were calculated.

The distribution of BICAMS test data predicting cognitive impairment (SDMT, CVLT-II and BVLT-R) was visualized by group with histograms and QQ-plots. Based on these plots the raw test scores were scaled scores ($M = 10$; SD = 3) using the cumulative frequency distribution of each measure (Bland et al., 1986; Testa et al., 2009). For the BICAMS tests, raw or scaled scores regression models were applied on the control group with the test result as response variable, age, age2, BDI score and FSMC-total as continuous explanatory variables, and sex and educational level as categorical explanatory variables. The estimated regression models from the control group were used to calculate predicted values for the MS group, and the predicted values were subtracted from the observed test results of the pwMS group.

Receiver operating curves (ROC) were plotted to illustrate the predictive ability of the different BI-CAMS tests. The confidence limits were estimated using a bootstrap approach (Carpenter and Bithell, 2000).

3. Results

3.1. Demographics

Demographic data for the entire study population are presented in table 1. The HC group and the MS group did not differ in age, gender or education. Mean age was 37.2 years in the MS group and 36.8 years in the control-group. For both groups, 63% were females. Mean years of education (YOE) was 15.2 years in the MS group and 15.9 years in the control group. All pwMS had a RRMS disease course. In the MS group, the mean EDSS score was 1.8 and the range was 0–4. Average disease duration was 3.9 years.

Table 1
Demographic and clinical profiles of the population at baseline.

Demographic parameter	MS	HC
Number of subjects, N (female/male)	65 (41/24)	65 (41/24)
Age, years (SD, range)	37.2 (8.8, 19–56)	36.8 (9.6, 18–56)
Years of education, years (SD, range)	15.2 (2.4, 10–20)	15.9 (2.1, 10–20)
EDSS (SD, range)	1.8 (1.2, 0–4)	NA
Disease duration, years (SD, range)	3.9 (2.7, 1–10)	NA
MSQN-S	20.5 (13.3)	11.2 (5.5)
FSMC	53.6 (22.2)	24.5 (4.9)
BDI-II	7.8 (7.4)	3.3 (3.5)
MSIS-29	51.3 (20.0)	NA
25FWT (seconds)	3.5 (0.5)	4.1 (1.6)
9-HPT (seconds)	17.0 (2.0)	18.9 (5.3)
LCVA (right eye)	25.0 (7.0)	25.2 (9.8)

Abbreviations: EDSS = Expanded Disability Scale Score; HC = healthy control; MS = multiple sclerosis; SD = standard deviation; NA = not applicable; MSQN-S = Multiple Sclerosis Neuropsychological Questionnaire – Self form; FSMC = Fatigue Scale for Motor and Cognitive Functions; BDI-II = Beck Depression Inventory-II; MSIS-29 = Multiple Sclerosis Impact Scale; 25FWT = timed 25-foot walk; 9-HPT = 9-Hole Peg Test; LCVA = Low contrast visual acuity.

Table 2
BICAMS scores at baseline and follow up.

		HCs	MS	P val-ue
SDMT	Baseline	66.0 (9.6)	61.0 (10.0)	< 0.005
Follow up	66.3 (9.1)	60.5 (10.0)	< 0.001	
CVLT-II	Baseline	68.6 (6.4)	65.4 (9.9)	< 0.05
Follow up	69.6 (5.7)	67.7 (9.0)	= 0.154	
BVMT-R	Baseline	29.6 (3.7)	27.4 (5.8)	< 0.05
Follow up	30.5 (3.6)	28.9 (5.0)	< 0.05	

Abbreviations: MS = multiple sclerosis; HC = healthy control; SDMT = Symbol Digit Modalities Test; CVLT-II = California Verbal Learning Test-II; BVMT-*R* = Brief Visuospatial Memory Test-Revised. Numbers in parentheses denote standard deviation.

3.2. Validation of bicams

3.2.1. BICAMS test scores at baseline and follow-up

For each of the BICAMS tests, the parameter estimates, corresponding standard errors and p-values from the regression analyses are tabulated (table 2). BICAMS test score values are shown in table 2. PwMS scored significantly lower than the control group on SDMT ($p < 0.005$), CVLT-II ($p < 0.05$) and BVMT-R ($p < 0.05$) at the first visit. When data were analysed with regression analysis controlling for the effects of depression and fatigue, group differences were limited to the SDMT ($p < 0.05$) and the BVMT-R ($p < 0.05$) and these group differences were only found at the re-test session (table 3). The effect sizes of the BICAMS tests were small to medium at baseline and at follow-up; at baseline a medium effect size was found for the SDMT ($d = 0.51$), a small to medium effect size was found for the BVMT-T ($d = 0.45$), and a small effect size was found for the CVLT-II ($d = 0.38$) (table 4). Cognitive impairment has previously been defined as a score 1.5 standard devia-tions below the average on one or more BICAMS tests. Using this criterion 21 out of 65 (32.3%) of the pwMS were cognitively impaired at baseline whereas 20% in the HC group were cognitively impaired (Fig. 1). In the patient group, 14 out of 65 (21.5%) were impaired on one of the BICAMS tests, 4 out of 65 pwMS were impaired on two BICAMS tests (6.2%) and 3 out of 65 pwMS (4.6%) were impaired on all three BICAMS tests. Most pwMS were impaired on the SDMT (20%); 16.9% were impaired on the BVMT-R and 10.7% were impaired on the CVLT-II (Fig. 1).

By using a BICAMS test result of 1.5 SD below the mean as a criteria of impairment, the SDMT classi-fied 20% of pwMS and was the most sensitive test to measure cognitive dysfunction in the population. The CVLT-II and the BVMT-R correctly classified 10.8% and 16.9% of participants, respectively. The sensitivity was relatively low, but specificity was high (see table 5).

Analysis of covariates influencing the BICAMS test results demonstrated that EDSS and YOE both had a significant impact (table 6).

There was no difference in BICAMS administration time between the two groups ($p = 0.711$). Mean administration time in the MS group was 17 min, ranging from 11–25 min. Thus, in both groups, the time consumption was within the predicted range of 15–20 min.

3.2.2. Reliability

The test-retest reliability data for the MS group are presented in table 3. All three BICAMS-tests demonstrated reliability over time. The SDMT showed the strongest correlation.

Strength of correlations were modest to strong (range from 0.90 for the SDMT to 0.68 for the BVMT-R).

Practice effects were found between baseline assessments and follow-up for the CVLT-II and the BVMT-R in the MS group despite the use of alternate test forms. In the HC group a close to significant practice effect was found for the BVMT-R only. No practice effects were found for the SDMT.

Table 3
Test-retest correlations; means and practice effect calculations paired statistics were calculated.

MS	Pearson's r	P-value	Baseline Mean	SD	Follow-up Mean	SD	t	Cohen's d	P-value
SDMT	0.90	< 0.01	60.98	9.97	60.46	10.63	0.94	0.12	0.35
CVLT-II	0.82	< 0.01	65.43	9.88	67.71	9.02	−3.18	−0.39	< 0.01
BVMT-R	0.68	< 0.01	27.40	5.74	28.88	4.96	−2.76	−0.34	< 0.01
HCs									
SDMT	0.84	< 0.01	65.97	9.60	66.29	9.13	−0.50	−0.06	0.62
CVLT-II	0.58	< 0.01	68.57	6.40	69.60	5.65	−1.49	−0.18	0.14
BVMT-R	0.41	< 0.01	29.58	3.74	30.52	3.56	−1.92	−0.23	0.06

SDMT – Symbol Digit Modalities Test; CVLT-II – California Verbal Learning Test-II; BVMT-R-Brief Visuospatial Memory Test-Revised. Numbers between parentheses denote standard deviation.

Table 4
Effect sizes of BICAMS test.

Visit	BICAMS test	Cohen's D
Baseline	SDMT	0.51 (0.16; 0.86)
	CVLT-II	0.38 (0.03; 0.73)
	BVMT-R	0.45 (0.10; 0.80)
Follow-up	SDMT	0.61 (0.25; 0.96)
	CVLT-II	0,25 (−0.10; 0.06)
	BVMT-R	0.38 (0.03; 0.73)

SDMT – Symbol Digit Modalities Test; CVLT-II – California Verbal Learning Test-II; BVMT-R-Brief Visuospatial Memory Test-Revised.

3.3. Relationship between bicams measures and subjective cognition

Self-reported cognition in the MS group as assessed by the MSNQ did not correlate with any of the BI-CAMS measures (r ranging from −0.18 to −0.21). Self-reported cognition did, however, correlate moderately with depression at the baseline assessment ($r = 0.54$, $p < 0.01$).

3.4. Relationship between bicams measures and depression, fatigue and quality of life

BICAMS measures did not correlate with depression in the MS-group as measured by the BDI (SDMT: $r = -0.18$, $p < 0.01$; CVLT-II: $r = -0.04$, $p = 0.75$; BVMT-R: $r = -0.075$, $p = 0.55$). Furthermore, BI-CAMS scores did not correlate with fatigue in the MS group. In the MS group a measure of QOL (MSIS-29) correlated with the SDMT-score ($r = -0.34$, $p < 0.01$), while no correlations were found for the CVLT-II or the BVMT-R.

4. Discussion

The BICAMS has been suggested by MS experts as an assessment and monitoring tool for cognition in MS, i.e. a tool that reliably identifies the typical cognitive deficits associated with MS. Specific purposes of the tool are monitoring of cognition over time, feasibility in the clinics by healthcare professionals without neuropsychological test experience and quick administration time (15–20 min). BICAMS as a measure to reliably evaluate cognitive impairment in MS has so far been validated in several languages and countries (Corfield and Langdon, 2018). This study addressed the recommendations outlined in the international vali-dation protocol for BICAMS (R.H. Benedict et al., 2012) and is the first to publish Danish validation data. The study aimed to evaluate the BICAMS in a Danish population, and to study whether BICAMS discriminated between pwMS and healthy controls, as well as whether BICAMS demonstrated test-retest reliability.

Regarding the practical purposes of BICAMS, the expected BICAMS administration time of 15–20 min was confirmed with administration times ranging from 11 to 25 min in the MS-group. Thus, our data confirm the feasibility of BICAMS as a quick monitoring tool in the clinic.

Table 5
Sensitivity and specificity of BICAMS test using recommended cut-off of 1.5 standard deviation.

BICAMS test	AUC	Sensitivity	Specificity
SDMT	0.585	20.0%	95.4%
CVLT-II	0.569	10.8%	89.2%
BVMT-R	0.585	16.9%	93.8%

SDMT – Symbol Digit Modalities Test; CVLT-II – California Verbal Learning Test-II; BVMT-R-Brief Visuospatial Memory Test-Revised; AUC-Area under the curve.

Table 6
Values from regression analysis of covariates influencing the BICAMS performance.

	Odds ratio	95% Confidence inter-val	P-value
Gender	14.00	[0.95 – 206.36]	0.055
Age	1.01	[0.90 – 1.12]	0.853
BDI-II	0.88	[0.76 – 1.02]	0.087
EDSS	0.30	[0.09 – 0.92]	0.035
YOE	1.74	[1.07 – 2.83]	0.026

BDI-II -Beck Depression Inventory-II, EDSS-Expanded Disability Status Scale, YOE-years of education.

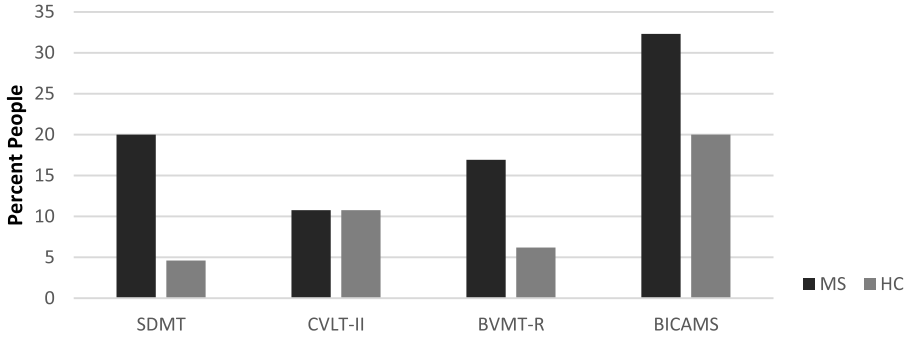

Fig. 1. $N = 130$. Frequencies in% of impaired ($z = < -1.5$) patients with multiple sclerosis (MS) and healthy controls (HCs) by mean scores at baseline for each test (SDMT, CVLT-II, BVMT-R) and total BICAMS (one or more test are impaired).

The study population was characterized by relatively early MS, exclusively RRMS disease course and a low burden of disease as measured by EDSS (mean 1.8). Consequently, there was only a small difference in BICAMS test performances between pwMS and controls. EDSS and YOE both had a significant impact on BICAMS test results as confirmed in other studies where lower levels of education predict cognitive function in pwMS (Borghi, 2013). BICAMS was able to identify cognitive impairment in 32.3% of the MS-sample using the criteria of impairment defined by one or more abnormal tests. This result is comparable to 32.6% in the German validation study (Filser et al., 2018). The finding of cognitive impairment even in early stages of MS is comparable to other studies addressing the prevalence of cognitive impairment in early stages of MS (Amato, 2001; Jønsson, 2006; Glanz, 2007;DiGiuseppe, 2018). Other BICAMS validation studies have found somewhat higher frequencies of cognitive impairment: For example, 57.9% in the Canadian validation study (Walker et al., 2016) and 52% in the Hungarian study (Sandi et al., 2015). The difference in frequencies be-tween our study and other studies are likely attributable to differences in population characteristics, since prevalence rates of cognitive impairment in MS are highly dependent on the patient group studied. It is of significance that different disease courses have been associated with different cognitive profiles (Ruet et al., 2013). Furthermore, the population was characterized by a relatively high educational level compared to other studies (Filser et al., 2018; Niccolai et al., 2015; Spedo et al., 2015). Thus, cognitive reserve might also have been a factor influencing the results. Regarding representativeness of the MS population and inclusion procedures in the present study, the pwMS were not selected for the study but were recruited via advertisement. Thus, pwMS with more pronounced cognitive impairment might not have entered the study. The present study controlled for both depression (BDI) and fatigue (FSMC) in the regression analysis which may result in lower impairment frequencies. After accounting for depression and fatigue, only the SDMT and the BVMT-R were able to discriminate between the MS group and the control group, and this was only the case at the follow-up session. The CVLT-II did not discriminate between groups at any time point. Similar findings have been reported in the Hungarian study (Sandi et al., 2015), the Canadian study (Walker et al., 2016), the Belgian study (Costers et al., 2017) and the German study (Filser et al., 2018). It has been suggested that the lack of discrimination between groups on the verbal memory measure may be related to higher education level/cognitive reserve. However, in our study a regression analysis revealed that YOE did not correlate with the CVLT-II outcome. An alternative explanatory factor could be a difference in the distribution of memory impairment in MS populations between validation studies. Changes in MS cognition over time may be in memory and executive functions, hence disease duration and the number of included pwMS with progres-sive MS in the validation studies could matter.

As in other BICAMS validation studies, no correlation was found between BICAMS measures and sub-jectively reported cognition. Subjectively reported cognitive complaints, typically in the memory domain, often co-occur with depression, in the absence of objective cognitive deficits (Jessen et al., 2014). Thus, the findings support the need for objective measures of cognition in the clinic. It could be argued that depres-sion is an important factor to be considered when monitoring cognitive functions in MS. Depression is a highly prevalent symptom in the MS population with life time prevalence rates as high as 50% (Chwastiak et al., 2002; Skokou et al., 2012). Depression is associated with reversible affection of cognitive functions, i.e. attention, memory and executive functions (Mathews and Macleod, 2005; McDermott and Ebmeier, 2009). In this study we did not make an a priori correction for depression, which is an important limitation of the study. However, correlation analyses did not show any association between depression and cognition.

It is of note that using the suggested criterion for cognitive impairment of 1.5 standard deviations be-low the mean, as much as 20% of the healthy controls were also characterized as cognitively impaired. While the BICAMS tests identified a statistically significant effect at the group level, the effect sizes were small to medium. Thus, the precision of the tests at the individual level is less than perfect. Hence, for the clinical use of BICAMS national norms based on a larger representative population are warranted to evalu-ate individual performances. Furthermore, normalization using linear regression modelling to control for demographic effects on test performance, i.e. a regression-based norms approach, is relevant.

Evaluation of test-rest reliability of the three BICAMS measures confirmed good reliability over time for the SDMT ($r = 0.90$) and the CVLT ($r = 0.82$), while an acceptable reliability was found for the BVMT-T ($r = 0.68$). Reliability in this study was evaluated over a period of 1–3 weeks. Alternate test forms were applied at baseline and follow-up to reduce practice effects. Despite the use of alternate forms some practice effects were observed. This finding is important when using BI-CAMS as a monitoring tool over time, since improvement between sessions cannot necessarily be attributed to actual improvement over time. If scores decline between sessions, a true decline might be plausible, but a finding of no change between sessions also might be attributed to a true decline. Regarding the clinical implementation of BICAMS, it remains to be decided what is a reliable change between assessments, and control procedures for test-retest artefacts may be relevant.

5. Conclusion

Data from this Danish validation study support the suggestion of BICAMS as a highly effective tool for detection of cognitive impairment in pwMS and for reliable monitoring of cognitive performance over time. Furthermore, data support BICAMS' feasibility in a clinical setting. This finding was confirmed even in a MS study population with early MS, low burden of disease measured by EDSS and an apparently high cognitive reserve. Results were comparable to those reported in studies from other cultures when accounting for population differences regarding factors such as disease duration, MS course, degree of impairment and educational level. The relatively comparable results and equivalent frequencies across studies and countries support the international applicability of BICAMS.

Role of funding source

This study was financially supported by Novartis Healthcare A/S Denmark and the Danish Multiple Sclerosis Society.

Disclosures:

Lisbet Marstrand has served on scientific advisory boards, served as a consultant, received support for congress participation, received speaker honoraria from Biogen and Novartis.

Ole Østerberg is an employee of LEO Pharma.

Trine Walsted have nothing to disclose

Amalie C. Skov have nothing to disclose.

Karen I. Schreiber has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria from Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva.

Finn Sellebjerg has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva.

Declaration of Competing Interest

None

Acknowledgements

This study was financially supported by Novartis and the Danish Multiple Sclerosis Society. The authors would like to thank all participating persons in the study. We also thank Dr. Dawn Langdon for her advice and support during the study.

References

Amato, M.P., et al., 2001. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol 58 (10), 1602–1606.
Beck, A.T., et al., 1961. An inventory for measuring depression. Arch Gen Psychiatry 4 (6), 561-571.
Benedict, R.H., et al., 2003. Screening for multiple sclerosis cognitive impairment using a self-admistered 15-item questionnaire. Mult Scler 9, 95–101.
Benedict, R.H., et al., 2012a. Brief international cognitive assessment for ms (BICAMS): international standards for validation. BMC Neurol 12 (55), 1–8.
Benedict, R.H., et al., 2012b. Reliability and equivalence of alternate forms for the symbol digit modali-ties test: implications for multiple sclerosis clinical trials. Multiple Sclerosis Journal 18 (9), 1320–1325.
Benedict, R.H., et al., 2017. Neuropsychology of multiple sclerosis: looking back and moving forward. J. Int Neuropsychol Soc. 23 (9–10), 832–842.
Borghi, M., et al., 2013. Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. PLoS ONE 8 (7), 1–9.
Bruce, J., et al., 2010. Treatment adherence in multiple sclerosis: association with emotional status, per-sonality, and cognition. Journal of Behavioural Medicine 33 (3), 219–227.
Carpenter, J., Bithell, J., 2000. Bootstrap condence intervals: when, which, what? a practical guide for medical statisticians. Stat Med 19, 1141–1164.
Chwastiak, L., et al., 2002. Depressive symptoms and severity of illness in multiple sclerosis: epidemio-logic study of a large community sample. Am J Psychiatry 159 (11), 1862–1868.
Clemens, L., Langdon, D., 2018. How does cognition relate to employment in multiple sclerosis? a sys-tematic review. Mult Scler Relat Disord 26, 183–191.
Cohen, J., 1988. Statistical power analysis for the behavioral sciences, Second ed. Routledge, New York.
Corfield, F., Langdon, D., 2018. A systematic review and meta-analysis of the brief cognitive assess-ment for multiple sclerosis (BICAMS). Neurol Ther 7, 287–306.
Digiuseppe, G., et al., 2018. Prevalence of cognitive impairment in newly diagnosed relapsing-remitting multiple sclerosis. Int J MS Care 20 (4), 153–157.
Filippi, M., et al., 2018. Multiple sclerosis. Nat. Rev. Disease Primers 4 (43), 1–27.
Filser, M., et al., 2018. The brief international cognitive assessment in multiple sclerosis. Journal of Neu-rology 265, 2587–2593.
Glanz, B.I., et al., 2007. Cognitive dysfunction in patients with clinical isolated syndromes or newly diag-nosed multiple sclerosis. Mult Scler 13, 1004–1010.
Goverover, Y., et al., 2017. Evidenced-Based cognitive rehabilitation for persons with multiple sclerosis: an updated review of the literature from 2007 to 2016. Arch Phys Med Rehabil 2, 390–407.
Hobart, J., et al., 2001. The multiple sclerosis impact scale (MSIS-29): a new patient-based outcome measure. Brain 124 (5), 962–973.
Jessen, F., et al., 2014. A conceptual framework for research on subjective cognitive decline in preclinical alzheimer's disease. Alzheimers Dement 10 (6), 844–852.
Jønsson, A., et al., 2006. Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. J. Neurol. Sci. 245 (1–2), 77–85.
Kavaliunas, A., et al., 2019. Cognitive function is a major determinant of income among multiple sclerosis patients in sweden acting independently from physical disability. Multiple Sclerosis Journal 25 (1), 104–112.
Koch-Henriksen, N., et al., 2019. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset. Neurol. 29 (90).
Langdon, D.W., et al., 2012. Recommendations for a brief international cognitive assessment for multi-ple sclerosis (BICAMS). Mult. Scler. 18, 891–898.
Mathews, A., Macleod, C., 2005. Cognitive vulnerability to emotional disorders. Annu Rev Clin Psychol 1, 167–195.
McDermott, L., Ebmeier, K., 2009. A meta-analysis of depression severity and cognitive function. J Affect Disord 119 (1–3), 1–8.
Penner, I.K., et al., 2009. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 15 (12), 1509–1517.
Polman, C.H., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the mcdonald crite-ria. Ann. Neurol. 69, 292–302.
Ruet, A., Brochet, B., 2013. Ask the experts: cognitive impairment in multiple sclerosis: progress, prevalence and management. Neurodegener Dis Manag 3 (4), 307–311.
Skokou, M., et al., 2012. Depression in multiple sclerosis: a review of assessment and treatment ap-proaches in adult and pediatric populations. ISRN Neurology. 2012, 1–6.
Smith, A., 1973. Symbol Digit Modalities Test. Western Psychological Services, Los Angeles, CA.
Testa, S.M., et al., 2009. Accounting for estimated iq in neuropsychological test performance with regres-sion-based techniques. Journal of the international Neuropsychological Society 15, 1012–1022.
Thompson, A., et al., 2018. Multiple sclerosis. lancet (London, england), 391(10130), 1622–1636.
Trenova, A.G., et al., 2016. Cognitive impairment in multiple sclerosis. Folia Med (Plovdiv) 58 (3), 157–163.
Walker, L., et al., 2016. Brief international cognitive assessment for multiple sclerosis (BICAMS): canadian contribution to the international validation project. J. Neurol. Sci. 362, 147–152.

Update

Multiple Sclerosis and Related Disorders

Volume 38, Issue , February 2020, Page

DOI: https://doi.org/10.1016/j.msard.2020.101942

Multiple Sclerosis and Related Disorders 38 (2020) 101942

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Corrigendum

Corrigendum to "Brief international cognitive assessment for multiple sclerosis (BICAMS): A Danish validation study of sensitivity in early stages of MS" [Multiple Sclerosis and Related Disorders 37 (2020) 101458]

Lisbet Marstrand[a,*], Ole Østerberg[b], Trine Walsted[a], Amalie C. Skov[a], Karen I. Schreiber[a], Finn Sellebjerg[a]

[a] Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Global stakeholder partnership, LEO Pharma, Denmark

The authors regret that there are 2 errors in the published article:

1) in table 1 data from MS and control group respectively have been switched on the 3 parameters: 25FWT, 9-HPT and LVCA;

2) in table 2 one line concerning follow-up is placed in the wrong column for all 3 tests.

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.msard.2019.101458
* Corresponding author.
E-mail address: lisbet.marstrand@regionh.dk (L. Marstrand).

https://doi.org/10.1016/j.msard.2020.101942