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ORIGINAL ARTICLE

The 7-year follow-up of the Hungarian BICAMS validation cohort implies that cognitive performance may improve in multiple sclerosis patients

Aliz Nyári[1] · Zsófia Kokas[1] · Szabolcs Szamosi[1] · Zsanett Fricska-Nagy[1] · Judit Füvesi[1] · Zsigmond Tamás Kincses[1,2] · Tamás Biernacki[1] · László Vécsei[1,3] · Péter Klivényi[1] · Krisztina Bencsik[1] · Dániel Sandi[1]

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Abstract

Background Cognitive impairment (CI) is a frequent symptom of multiple sclerosis (MS) and has a great impact on the patients' quality of life, so screening is essential. The brief international cognitive assessment for multiple sclerosis (BICAMS) was developed for this purpose. However, longitudinal data is lacking with the use of the battery.

Objective This study is to assess the performance of patients after 5 and 7 years of the original BICAMS validation study and to identify any influencing factors.

Methods BICAMS was used to measure cognitive function of 52 relapsing-remitting MS patients (RRMS) from the original validation study after 5 years ($n = 43$) and again, after 7 years ($n = 42$). Patients filled out the fatigue impact scale (FIS) and multiple sclerosis quality of life-54 (MSQoL-54) questionnaire, and we evaluated expanded disability status scale (EDSS).

Results There was an improvement in the BVMT-R and the CVLT-II assessments at both the 5-year ($p<0.001$ and $p=0.025$) and the 7-year retest ($p<0.001$ and $p=0.002$). The prevalence of CI significantly decreased at the 5-year mark ($p=0.021$) but remained stable after that. There was no deterioration in MSQoL scores during the study. The basic cognitive performance is the most important influencing factor, but the duration of the disease, the EDSS score, and the escalation of the therapy also affect the cognitive scores.

Conclusion This is the longest longitudinal study utilizing the BICAMS battery, reinforcing its feasibility as a clinical screening tool. It seems that cognitive performance may improve in the long term and early initiation of effective therapy may influence this outcome.

Keywords Cognitive impairment · Multiple sclerosis · BICAMS · Fatigue · Quality of life

Introduction

Multiple sclerosis (MS) is one of the most common debilitating, progressive neuroinflammatory disorders affecting young- and middle-aged people. In addition, even though it has been well known that it leads to severe physical impairment, only during the last two decades have clinicians recognized the prevalence and functional impact of cognitive impairment (CI) that it leads to.

CI is quite frequent yet underdiagnosed with prevalence rates of 43–70% [1–3], and can appear already at the earliest stages of the disease [4]. It has also been shown that cognitive and psychological symptoms have similar (or according to some assessments an even more substantial) influence on the quality of life (QoL) of MS patients than physical damage [5, 6]. Thus, it is increasingly recognized that psychopathological disturbances must be appropriately monitored and controlled as part of the patient care process to preserve the patient's general well-being and QoL [5, 7, 8].

Considering all the above, it is not surprising that in 2018, the National MS society in the USA has recommended the

✉ Dániel Sandi
sandi.daniel@med.u-szeged.hu

[1] Department of Neurology, Albert Szent-Györgyi Faculty of Medicine and Clinical Center, University of Szeged, Szeged, Hungary

[2] Department of Radiology, Albert Szent-Györgyi Faculty of Medicine and Clinical Center, University of Szeged, Szeged, Hungary

[3] ELKH - SZTE Neuroscience Research Group, Szeged, Hungary

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early screening of cognition to reveal as early as possible the factors that can most contribute to working and educational difficulties [9]. Also, when the criteria of the MS care unit was defined in 2019 as the standard establishment of MS management, one of the minimum requirements was to be able to recognize and manage CI from the beginning [10].

For these reasons, it is of utmost importance that cognitive functions can be monitored regularly and repeatedly in a standardized and sensitive manner. In everyday clinical practice, however, this measurement is not easy, as it usually requires time-consuming batteries and special equipment not readily available in most centers. Therefore, there is a need for an easy-to-use, short, but sensitive and specific screening test; and the Brief international cognitive assessment for sclerosis multiplex (BICAMS) battery created in 2011 meets this need. It consists of three parts (SDMT, symbol digit modalities test; CVLT-II, California verbal learning test; BVMT-R, brief visual memory test revised), measures the most frequently impaired functions, and can be completed in 15 min and does not require special equipment or specialist [7].

Since its release in 2011, BICAMS has been adapted into almost 30 languages in Europe, North and South America, and the Middle East [11]. The first two national validations were undertaken by members of the BICAMS group themselves; our adaptation in 2015 was the first beyond the BICAMS group and the third study overall [7, 12, 13]. These evaluations all prove that the test can sensitively detect the presence of cognitive impairment in MS patients. It is no coincidence that the aforementioned 2018 CI guideline recommends its regular use as a standard screening test in daily practice, in addition to routine measurement of depression, anxiety, and fatigue. Although the constantly increasing numbers of validation studies confirm that BICAMS is a sufficient baseline screening test, data is still scattered on its use in long-term follow-up evaluations. Considering the above elaborated reasons, our aim in this pilot study was:

1. To assess whether BICAMS is suitable for routine, long-term clinical follow-up by measuring the long-term changes in the cognitive functions of patients who participated in the validation of BICAMS in our center in 2013–2014
2. To monitor the patient's changeovers in QoL
3. To determine the factors contributing most to the patients' cognitive performance over time

Patients and methods

Patients

In this follow-up pilot study, we evaluated 52 of the original 65 patients treated at the MS Outpatient Unit of the Department of Neurology of the University of Szeged, whom participated in the Hungarian BICAMS validation process. The same inclusion and exclusion criteria were used during the validation process [12].

The inclusion criteria were as follows:

1. Age 18 years or older.
2. The first language is Hungarian.
3. Diagnosed RRMS based on the revised McDonald's criteria [14].
4. Patients should have been in remission and not received steroid therapy for at least 30 days during the evaluation.
5. EDSS scores between 0-6.5 points.

The exclusion criteria were as follows:

1. Secondary (SPMS) or primary progressive (PPMS) disease course.
2. Acute infection or an acute relapse during the assessment.
3. Diagnosis of psychiatric or personality disorder (except mood disorders).
4. History of chronic alcohol abuse.
5. History of drug abuse or dependence.

We assessed the patients after 5 years and again after seven years since the baseline examination. The baseline surveys took place during the winter of 2013–2014, the 5-year control examinations in the spring-summer of 2019, while the 7-year follow-up was undertaken in the spring of 2021.

During the follow-up period, 13 patients dropped out of the study (one died, three moved away. Four patients switched to SPSM, and due to their conditions they could have only been partially tested, or not tested at all. As the number of SPMS patients were only four, thus very low to begin with, it would not have been possible to make a proper statistical analysis as the group would have had no statistical strength. In one patient, the test became irrelevant due to the development of a co-morbidity, one patient's MS diagnosis was revised as an MS-mimic condition and three patients no longer wanted to participate in the study after validation).

All in all, of the 52 patients who participated in the assessment: 43 could be tested at the 5-year mark, 42 at the 7-year mark, and 33 patients participated in both at 5- and 7-year control assessment.

All sociodemographic and clinical data on the patients (including sex, educational state, age, age at disease onset, disease duration, EDSS score, clinical course, and clinical disease activity) and data on disease-modifying therapy (DMT), therapy escalation, and all relevant changes during the follow-up period were obtained and updated from the Multiple Sclerosis Register of Szeged [15]. Disability

progression was defined according to the international standards. Thus, an increase of ≥1.5 points from an EDSS score of 0 point, ≥1 point from a baseline EDSS score of between 1.0 and 4.5, or ≥0.5 points from a baseline EDSS score ≥5.0 points was considered a significant progression. The escalation approach emphasizes starting a moderate-acting DMT or "platform" DMT (β-interferon, glatiramer-acetate, teriflunomide, dimethyl-fumarate) and transitioning to high-efficacy therapies (fingolimod, siponimod, cladribine, natalizumab, ocrelizumab and alemtuzumab); or between high-efficacy drugs (from fingolimod, cladribine, and natalizumab to the highest efficacy drugs ocrelizumab and alemtuzumab) when disease activity is detected.

Methods

All patients have completed the validated Hungarian version of the BICAMS battery at the given time points. BICAMS consists of three individual tests: the symbol digit modalities test (SDMT) [16] measuring information processing; BVMT-R (brief visuospatial memory test revised) [17] measuring visuospatial memory and CVLT-II (California verbal learning test 2nd edition) [18] to assess immediate verbal recall. The same test version of the BICAMS was used at each time point. Similar to the validation process, *z*-scores were calculated for SDMT, while *T*-scores were utilized for the BVMT-R and CVLT-II.

Scores 1.5 SD below normal for *z*-scores and *T*-scores below 40 were considered impaired. Similar to the original evaluation and other studies utilizing the BICAMS battery, cognitive impairment was defined as impairment on ≥1 tests [12, 13].

Due to the potential influence on the cognitive performance of fatigue [19–21], all of the patients at baseline, 40 patients at the 5-year mark and 39 patients at the 7-year mark had completed the Hungarian version of the fatigue impact scale (FIS) (missing data is due to incomplete filling of the questionnaire) [22].

To monitor the alterations in the patient's QoL, we used the MSQoL-54 questionnaire adapted to Hungarian native speakers [23]. MSQoL-54 is a self-reported questionnaire comprising 54 questions about physical and mental well-being.

Statistical analysis

Descriptive statistics (mean, standard deviation, median, and inter-quartile range [IQR]) were used to describe the demographic and clinical data. Due to the non-normal distribution of the data, non-parametric tests were utilized—Friedman's ANOVA and Wilcoxon signed rank test as suitable. To determine a given variable's impact on the evaluated subscale of BICAMS, we utilized the model-free, partial least squares regression (PLS) analysis. PLS is able to analyze data with predictive variables that are numerous in number relative to the low number of observations and also highly correlated—which is the case with our clinical and cognitive data [24]. PLS creates orthogonal principal components predicting the *Y* variable through the linear combination of *X* variables [25]. The dependent variables in our evaluation were the total SDMT, BVMT-R, and CVLT-II scores at 5 years and 7 years, while the predictive factors were the clinical and sociodemographic data and FIS scores at baseline and the presence of DMT escalation during the observational period. Any given predictive factor was considered to have a meaningful practical impact if the variable importance of projection (VIP) score was ≥1 [26]. The higher the score, the more influential the variable is. In case of a predictor was found to be important, it was dichotomized (if it was not originally dichotomous) based on clinical relevance (e.g., EDSS score ≤3 points and >3 points), and the Mann-Whitney *U* test was used to compare the BICAMS subscale scores between the two groups.

Results

Demographic and clinical characteristics

Among the examined patients, 14 were men and 38 were women, the sex ratio being 1:2.7. The demographic and clinical data of the patients who participated in the follow-up and those who dropped out are presented in Table 1. There was no significant difference between the two groups, with the exception of the patients' age at the baseline test.

At baseline, 22 patients (42.3%) received platform therapies (β-interferon, glatiramer-acetate, dimethyl-fumarate or teriflunomide) and 30 patients (57.7%) were on high-efficacy DMT (natalizumab or fingolimod). During the follow-up period, 18 patients (34.6%) were escalated to higher efficacy DMT.

We also compared patients who had cognitive assessments at all three time points with those who only had 5- and 7-year follow-up assessments regarding all their clinical, demographical, and baseline cognitive data. We found no difference between the two groups.

Raw scores on the BICAMS subtests and the prevalence of cognitive impairment

Statistically no significant differences were observed in SDMT scores between the baseline and 5- and 7-year follow-up ($p = 0.319$). The difference was significant in case of the BVMT-R and the CVLT-II tests between both the baseline and 5-year retest ($p < 0.001$ and $p = 0.025$ respectively) and the 5- and 7-year interval ($p = 0.001$

Table 1 Clinical and demographic data of the study population

Demographic and clinical data		Patients in the follow-up ($N = 52$)	Drop outs ($N = 13$)	Significance (p)
Sex	Male (%)	14 (26.92%)	2 (15.38%)	0.492
	Female (%)	38 (73.08%)	11 (84.62%)	
Education	12 years or less (%)	23 (44.23%)	6 (46.15%)	1.000
	13 years or more (%)	29 (55.77%)	7 (53.85%)	
Age at test (±SD)		40.06±11.64	49.31±9.90	0.008*
Disease duration (±SD)		12.29±7.85	11.08±7.26	0.603
Median EDSS score (IQR)		2.25 (2.25)	2.00 (4.50)	0.680
FIS score (±SD)		55.21±40.82	57.50±42.38	0.867
SDMT score (±SD)		55.69±15.27	55.46±16.79	0.965
BVMT-R score (±SD)		22.83±8.09	21.38±10.44	0.649
CVLT-II score (±SD)		55.56±10.33	54.85±10.55	0.830
Cognitive impairment	Yes	23 (44.23%)	7 (53.84%)	0.553
	No	29 (55.77%)	6 (46.14%)	

SD standard deviation, *IQR* inter-quartile range, *EDSS* expanded disability status scale, *FIS* fatigue impact scale, *SDMT* symbol digit modalities test, *BVMT-R* brief visuospatial memory test revised *CVLT-II* California verbal learning test second edition

and $p = 0.002$ respectively). Table 2 shows the mean raw scores for each subtest.

Fewer patients were defined as cognitively impaired at the 5-year and 7-year follow-up than at initial testing. At baseline, 23 out of 52 patients (44.2%) had CI, while at 5 years 12 out of 43 (27.9%) and at 7 years 8 out of 42 (19.0%). The difference was significant between the baseline and the 5th year ($p = 0.021$) but not significant between the 5th and the 7th year ($p = 0.219$).

The change in EDSS scores

EDSS score at baseline (IQR) was 2.25 (2.00), 3.00 (3.75) points at the 5-year interval, and 3.00 (4.50) points at the 7-year interval. The mean EDSS score of the cohort worsened statistically significantly in both periods ($p = 0.013$ and $p = 0.016$). All in all, 18 patients (34.6%) had a significant EDSS score progression during the follow-up period.

Fatigue

The total FIS score and the cognitive components of FIS were stable throughout the study, with none of these measures found to be statistically different from baseline values (Table 3).

Quality of life

No statistically significant worsening of any MSQoL-54 subscale parameter was observed, suggesting that QoL in this patient cohort remained stable. Results from the subscales of the MSQol-54 questionnaire following a 5-year and 7-year retest of the patients are presented in Table 4.

Factors influencing the cognitive performance on the BICAMS test

We evaluated the effect of several baseline demographic and clinical parameters which may have influenced the performance of the BICAMS battery at follow-up. The

Table 2 Mean raw score of each BICAMS subtest at baseline, at 5 years and at 7 years

	Baseline Mean±SD	5 years Mean±SD	p-value	7 years Mean±SD	p-value
SDMT	54.68±16.55	52.47±17.33	0.319	53.97±16.45	0.319
BVMT-R	22.83±8.08	26.33±7.67	<0.001*	29.72±7.68	0.001*
CVLT-II	55.56±10.33	57.65±14.00	0.025*	64.12±12.14	0.002 *

*Denotes significant result

SDMT symbol digit modality test, *CVLT-II* California verbal learning test, *BVMT-R* brief visual memory test revised, *SD* standard deviation

Table 3 Fatigue, cognitive fatigue scores, and prevalence

FIS score	Baseline		5 years		7 years		Significance (*p*)
	N	Score (mean±SD)	*N*	Score (mean±SD)	*N*	Score (mean±SD)	
Total score	52	55.21±40.82	40	58.85±41.63	39	49.97±41.01	0.144
Cognitive subscale	52	12.25±10.84	40	13.23±11.16	39	9.95±10.55	0.686

FIS fatigue impact scale

PLS analysis established that baseline disease duration and EDSS scores affected the performance on all three subtests both at 5 and 7 years' periods. Furthermore, therapy escalation during the evaluation had a significant positive influence on BVMT-R and CVLT-II performances. In addition, the baseline FIS score also had a noticeable effect on the SDMT and the BVMT-R performance: the higher the FIS total and cognitive subscale score, the worse the scores on BICAMS subtests (Fig. 1).

We also surveyed whether differences in the BICAMS raw scores can be measured based on the identified predictors. According to our model, baseline cognitive performance was the most robust predictor of cognitive deterioration in long term. We also found that worse BICAMS test results can be observed on longer disease duration and a higher EDSS score at baseline (Tables 5 and 6), while improvement can be perceived upon escalation of therapy (Table 7); however, these factors already had a significant influence at most of the baseline scores as well.

Discussion

The BICAMS battery has been validated in several countries and has become widely accepted as an effective screening tool for cognitive impairment in MS patients [11]. However, more data is needed on the longitudinal follow-up with this battery in support of its use in everyday clinical settings.

The 2-year long follow-up study of the Norwegian validation cohort showed that mean SDMT and CVLT-II raw scores improved significantly from baseline to 12 months and remained stable until the end of the 2nd year, while the BVMT-R score did not change essentially [27]. The other follow-up study of the Irish validation cohort presenting data over 5 years demonstrated stability in the SDMT and improvement in the CVLT-II and BVMT-R tests [28]. Our results are highly similar to this longer term evaluation. Regarding the prevalence of definitive CI, while 44.2% of the patients were cognitively impaired at baseline, the proportion was reduced to 27.9% after 5 years and 19% by the end of the study. The earlier mentioned validation cohort follow-ups and shorter duration follow-up studies with patients on teriflunomide treatment have also yielded similar results [27–32]. There are multiple possible reasons

Table 4 MSQoL-54 scores at the baseline, 5-year and 7-year intervals

MSQoL-54 scale	Baseline		5-year		7-year		Significance (p)
	N	*Mean±SD*	*N*	*Mean±SD*	*N*	*Mean±SD*	
Physical health	52	60.29 ±30.33	42	57.98±32.08	38	60.13±34.40	0.746
Role limitations due to physical problems	52	52.40±44.90	42	57.14±46.94	38	58.55±42.82	0.392
Pain	52	69.90±26.25	42	66.27±26.58	38	73.99±22.93	0.439
Energy	52	47.92±19.92	42	45.33±19.63	38	51.47±22.40	0.236
Health perceptions	52	49.62±24.66	42	45.63±23.67	38	51.05±24.77	0.408
Social function	52	71.96±22.33	42	64.13±26.71	38	63.49±31.92	0.079
Health distress	52	63.85±24.29	42	60.48±23.91	38	67.50±24.76	0.659
Sexual function	47	76.66±30.01	37	73.24±26.88	32	70.06±32.23	0.272
Role limitations due to emotional problems	51	64.71±42.90	42	58.73±47.03	38	69.30±44.10	0.404
Emotional well-being	52	62.31±19.57	42	57.81±18.20	37	63.14±19.39	0.496
Cognitive function	52	70.48±21.06	42	63.93±27.91	36	72.36±26.34	0.733
Overall Quality of Life	52	61.48±16.48	42	56.06±21.61	38	63.95±19.53	0.767
Change in health	51	44.12±25.29	42	44.64±19.55	38	40.79±20.48	0.774
Satisfaction with sexual function	47	57.98±36.16	38	53.95±33.65	33	54.55±35.05	0.124

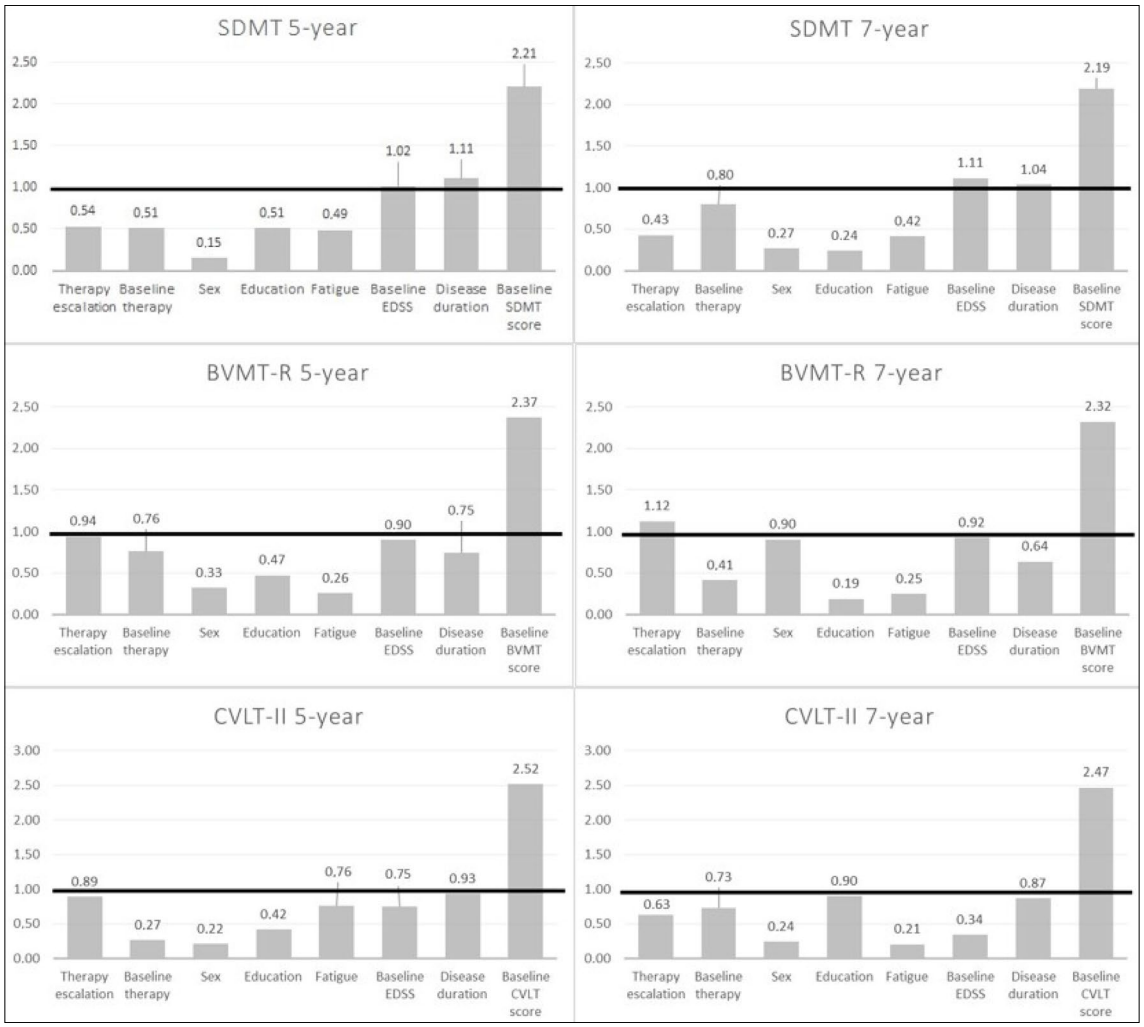

Fig. 1 Variable importance in projection (VIP) scores of the different factors contributing to the different subscales of BICAMS. SDMT, symbol digit modalities test; BVMT-R, brief visuospatial memory test revised; CVLT-II, California verbal learning test second edition; EDSS, expanded disability status scale; FIS, fatigue impact scale

Table 5 The difference between the BICAMS subtest raw scores of patients with different baseline disease duration

BICAMS subtests	0-14 years		≥15 years		Significance (*p*)
	N	*Mean±SD*	*N*	*Mean±SD*	
SDMT (baseline)	32	61.23±11.24	20	50.15 ±16.89	0.023*
SDMT (5-year)	32	57.50±12.82	20	41.13±16.89	0.009*
SDMT (7-ear)	32	59.35±11.69	20	46.06±16.35	0.013*
BVMT-R (baseline)	32	25.58±6.72	20	20.8 ±8.52	0.016*
BVMT-R (5-year)	32	28.23±6.13	20	23.25±9.06	0.040*
BVMT-R (7-year)	32	31.31±5.27	20	27.29±10.06	0.304
CVLT-II (baseline)	32	57.58±9.17	20	53.54±11.19	0.178
CVLT-II (5-year)	32	61.37±11.29	20	51.38±16.15	0.037*
CVLT-II (7-year)	32	67.69±8.41	20	58.65±14.97	0.052

SDMT symbol digit modalities test, *BVMT-R* brief visuospatial memory test revised, *CVLT-II* California verbal learning test second edition, *EDSS* expanded disability status scale, *denotes significant difference on the level of $p<0.05$

Table 6 The difference between the BICAMS subtest raw scores of patients with different baseline EDSS scores

BICAMS subtests	EDSS 0-3 points		EDSS ≥3.5 points		Significance (*p*)
	N	*Mean±SD*	*N*	*Mean±SD*	
SDMT (baseline)	39	59.05±12.43	13	45.62±18.84	0.021*
SDMT (5-year)	39	55.33±14.87	13	41.08±16.21	0.007*
SDMT (7-year)	39	58.23±12.32	13	43.42±16.67	0.004*
BVMT-R (baseline)	39	24.03±7.47	13	19.23±9.08	0.081
BVMT-R (5-year)	39	27.71±6.33	13	22.45±9.94	0.062
BVMT-R (7-year)	39	31.10±5.74	13	26.17±10.79	0.157
CVLT-II (baseline)	39	56.59±9.44	13	52.46±12.54	0.228
CVLT-II (5-year)	39	59.68±12.91	13	52.42±15.89	0.157
CVLT-II (7-year)	39	64.87±10.58	13	62.17±15.89	0.779

SDMT symbol digit modalities test, *BVMT-R* brief visuospatial memory test revised, *CVLT-II* California verbal learning test second edition, *EDSS* expanded disability status scale, *denotes significant difference on the level of $p<0.05$

Table 7 The difference between the BICAMS subtest raw scores of patients who underwent and who did not undergo therapy escalation during the observation period

BICAMS subtests	No, or linear DMT change		Escalation		Significance (*p*)
	N	*Mean±SD*	*N*	*Mean±SD*	
SDMT (baseline)	34	53±16.10	18	60.78±12.42	0.181
SDMT (5-year)	34	49.20±16.91	18	56.42±14.48	0.263
SDMT (7-year)	34	51.92±16.81	18	57.11±11.98	0.513
BVMT-R (baseline)	34	20.44±8.34	18	27.33±5.31	0.004*
BVMT-R (5-year)	34	24.93±8.21	18	29.83±4.80	0.042*
BVMT-R (7-year)	34	27.44±8.93	18	32.89±3.85	0.020*
CVLT-II (baseline)	34	53.91±11.38	18	58.67±7.28	0.252
CVLT-II (5-year)	34	55.52±15.08	18	63.17±9.06	0.174
CVLT-II (7-year)	34	62.24±13.26	18	66.72±10.19	0.445

SDMT symbol digit modalities test, *BVMT-R* brief visuospatial memory test revised, *CVLT-II* California verbal learning test second edition, *EDSS* expanded disability status scale, *denotes significant difference on the level of $p<0.05$

behind these aforementioned outcomes. One that several previous studies have suggested is the role of the practice effect in better scores during retesting. It is an effect that has been explained by factors like increased familiarity with the content of the test and the test procedure and may also be related to reduced anxiety and habituation to the testing situation [27, 33]. However, the attributes of this effect is not well determined. A meta-analysis concluded that at least a 16-month interval was necessary to eliminate this working memory effect [34], while others have shown that it depends on the cognitive domain tested [33]. However, the fact that the follow-up intervals were 5 and 7 years between the tests and that no increment was observed in the SDMT scores make the learning effect an unlikely explanation for the observed outcome. It is also important to note, however, that without a control group, learning effect cannot be properly measured; thus, these explanations discuss probabilities, and further investigations are needed on the matter.

A growing number of studies in the literature confirm that initial CI is associated with a worse clinical-radiological course and increased risk of progressive transformation is RRMS patients and could support treatment decisions in these patients [35–37]. Baseline cognitive performance can predict future clinical progression and also seems to determine longitudinal cognitive performance [38]. Our longitudinal study also corroborates these findings as based on our data, baseline cognitive score is the most important predictor for future performance. However, other important predictors can be identified, but their effect is less robust, compared to baseline cognitive results.

The impact of DMT on cognition needs to be better understood, as data from well-conceived evaluations on homogenous, large populations with long follow-up periods are lacking. Some earlier short-term longitudinal studies on small populations, usually utilizing only one short test for one cognitive domain (prominently SDMT or paced auditory serial addition test- PASAT), implied that some DMTs (e.g., natalizumab) might improve cognition. Still, the effect size of these studies is negligible at best. Regarding the use of BICAMS, only three recently published phase IV. clinical studies with a follow-up period of 2 years on teriflunomide-treated patients can be found so far. They all agree that after 2 years of treatment, there is an improvement compared to the baseline cognitive state in patients who are in a stable condition with therapy, which is related to the effect of treatment [30–32]. Our results also imply some role of therapy escalation; however, the significant impact could only be measured in case of BVMT-R scores, unlike in the teriflunomide follow-up cohorts. The reason behind this is unknown at the time requiring further analysis on large cohorts.

In cross-sectional and longitudinal studies, higher EDSS scores were found to predict worse cognitive performance [39–42]. Our results imply the same as the earlier

evaluations. Based on our results, longer disease duration has a negative impact on cognition as well. As cognitive decline can be considered a symptom of "silent progression" and tends to accumulate slowly over time, the found connection between disease duration and the BICAMS scores are understandable [43].

Sex and education have been established to be predictive factors for cognitive performance [39, 40, 42]; however, there were no associations found in our cohort, which is somewhat surprising. In our opinion, the low patient numbers can explain this lack of connection.

The role of fatigue in CI has been suggested for some time. However, despite being a prominent and disabling symptom in MS, which impacts the ability to participate in employment and education, evidence increasingly suggests that cognitive dysfunction cannot be clearly attributed to overall fatigue [44]. Studies found no association with memory performance, cognitive speed, language, or visuospatial processing; however, weak evidence point toward an association with working memory, and strong evidence proved an association with alertness/vigilance [45]. We detected some effect of subjective fatigue scores on the SDMT and the 7-year CVLT-II performances; nevertheless, we could not replicate it on a group level. Thus, clear conclusions cannot be drawn from our results, but the implied connections warrant further investigation of the subject on large cohorts.

Studies confirm that the HRQoL of MS patients is mainly determined by psychopathological factors in both the early and the later stages of the disease. Thus, regular psychopathological assessments and periodic feedback regarding a patient's HRQoL are urged, especially since different determinants influence the HRQoL of men and women [5]. Furthermore, stability or improvement in quality of life is an indicator of appropriate therapy and patient care. We found no deterioration in HRQoL in the study, which is in line with data from randomized controlled trials (RCTs) and long-term studies in RRMS showing stable psychopathological and physical outcomes during adequate DMD treatments associated with prevention or improvement in HRQoL deterioration [32, 46].

Overall, there are limitations to our study, which should be taken into account. On the one hand, we performed a pilot study; thus, the cohort number is currently too small to yield sufficient statistical power for detailed analysis. On the other hand, a group of healthy controls followed over the same period would have improved the implications of our results for assessing cognitive impairment associated with normal aging, as well as the determination of the extent of the practice effect, but longitudinal data from the control group were not available for the present study.

There are some strengths of our study as well. At present, it is the most comprehensive longitudinal study evaluating cognition with the BICAMS battery in a homogenous sample of RRMS patients. Also, several other clinical and psychopathological parameters affecting cognition were taken into consideration, further strengthening our results.

Conclusions

We can conclude that according to our 7-year follow-up assessment, BICAMS is a feasible screening test for cognitive impairment in everyday clinical practice. Although this pilot study was performed on a small cohort, our results imply that some clinical parameters (EDSS score, disease duration, therapy escalation) may influence the cognitive performance of patients. Furthermore, we emphasize the role of baseline CI in the long term. We hypothesize that baseline cognitive performance could be used to assess the risk of future cognitive decline and disease progression, potentially contributing to treatment decisions.

Notably, the cognitive performance of the patients might be improved with timely and adequate therapy, based on our findings. However, much more data are needed from large cohorts to enforce these initial results, which our group is currently working on. We emphasize the regular measurement of HRQoL, not only at the onset of the disease but also during long-term follow-up. This is because patients' well-being cannot be defined by a single parameter; the measurement of the physical state (EDSS), the activity shown on the MRI, and the measurement of psychopathological symptoms (cognition, fatigue, and mood disorders) should all determine the therapeutic decisions.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Szeged (Approval numbers: 207/2015 SZTE RKEB and 124/2013-SZTE RKEB). Participation in the study was based on written informed consent.

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