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Original article

A two-year longitudinal follow-up of cognitive performance assessed by BICAMS in newly diagnosed patients with MS

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ABSTRACT

Background: : Cognitive impairment is common in patients with multiple sclerosis (MS) and may occur at any stage and with any subtype of the disease. Screening and monitoring of cognitive function should therefore be implemented into everyday clinical neurology practice. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed for this purpose. Although several cross-sectional studies have validated BICAMS, longitudinal studies evaluating its use as part of a clinical follow-up routine are still lacking.
Objective: : To investigate cognitive function and trajectories of change assessed by the BICAMS test battery in a cohort of newly diagnosed relapsing-remitting MS (RRMS) patients examined at baseline and after 12 and 24 months.
Methods: : BICAMS was used to assess cognitive function in 58 RRMS patients, who also filled in the Hospital Anxiety and Depression Scale (HADS) and the Fatigue Scale for Motor and Cognitive Functions (FSMC), and underwent standard neurological evaluations at baseline and at the two follow-ups.
Results: : A total of 27 patients (46.6%) were defined as cognitively impaired at baseline on at least one test, and 22 (37.9%) were defined as impaired at follow-up after 24 months. Throughout the study, 8 (13.8%) and 4 (6.9%) patients were consistently defined as impaired on two or three tests, respectively. The mean raw scores on two BICAMS subtests (SDMT and CVLT-II) improved significantly from baseline to the first follow-up, and then remained stable the next year, whereas the visual memory test (BVMT-R) were overall unchanged from baseline to the end of the study. The correlations between the scores on HADS, FSMC and the BICAMS subtests were non-significant at baseline, but weak to moderate negative correlations were found at the one- and two-year follow-ups.
Conclusion: : The patients showed improved test results from baseline to the first follow-up examination, indicating that an effect of previous practise should be taken into account when interpreting the results. With results showing both trajectories of stability and change, our study supported the validity of including BICAMS as part of a clinical follow-up routine of RRMS patients. Anxiety, depression, fatigue and cognition should always be assessed at the same time to reveal interaction effects that are expected to affect the daily-life functioning of at least some of the RRMS patients.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system affecting mainly young adults (Thompson et al., 2018). Without therapy, most patients will eventually develop severe disability. Increasingly more effective therapies have become available to reduce disease activity and minimize the neurological symptoms associated with the disease (Dobson and Giovannoni, 2019; Torkildsen et al., 2016). Still, many patients experience impairment of cognitive and emotional functions (Whitehouse et al., 2019).

Cognitive impairment in patients with MS may be present from the early stages of the disease course (Amato et al., 2001, 2006; Bobholz and Rao, 2003; Chiaravalloti and DeLuca, 2008; Cortese et al., 2016), and represents an economic and social burden on the individual as well as the society, mainly due to loss of work capacity and latency of work place customization. An international effort has therefore been put into the work to validate and standardize clinical routines including assessment of cognitive function. The Brief International Cognitive

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Assessment for Multiple Sclerosis (BICAMS) is an outcome from this work (Benedict et al., 2012; Langdon et al., 2012). Several cross-sectional studies have shown that the BICAMS is a reliable and valid test battery to identify cognitive impairment in patients with MS (Corfield and Langdon, 2018), and we have recently reported that almost 50% of newly diagnosed patients with MS had some degree of cognitive impairment measured by the BICAMS (Skorve et al., 2019).

The aim of the current study was to investigate cognitive performance in a sample of newly diagnosed patients with MS using the BICAMS test battery in a two-year longitudinal study. Although some recent studies present longitudinal data on cognitive impairment in MS-patients (Barbu et al., 2018; Berard et al., 2018; Damasceno et al., 2019; Healy et al., 2020; Katsari et al., 2020), few studies have presented results from repeated assessment with the BICAMS subtests over longer intervals (Frau et al., 2018; Jakimovski et al., 2019), and none with cognitive evaluation as primary focus. Therefore, this study is probably the first longitudinal study to evaluate the results on the BICAMS subtests in a sample of newly diagnosed patients, and will by this contribute to evaluate if the test battery should be included in a clinical follow-up routine of patients with MS from an early stage of the disease.

2. Methods

2.1. Study population

BICAMS was used to evaluate cognitive function in a sample of 58 patients with relapsing-remitting MS (RRMS) and less than two years mean disease duration. Baseline data were recently published (Skorve et al., 2019) and in this paper we present follow-up data from evaluations after 12 and 24 months.

2.2. Procedures

Participation in the study was based on written informed consent, and the study was approved by the Regional Ethics Committee of Western Norway (registration number 2016/31/REK Vest)

The patients did not receive any economic compensation for their participation other than follow-up appointments free of charge during the study. All clinical and cognitive tests were performed by a clinical neurologist (E.S).

2.2.1. Questionnaires (Norwegian translations)

Symptoms of depression and anxiety were assessed at each test session by self-reports on the Hospital Anxiety and Depression Scale (HADS) (Pais-Ribeiro et al., 2018; Zigmond and Snaith, 1983). A score of ≥ 8 on each of the HADS sub scores were used to define a clinically meaningful anxiety or depression disorder (Bjelland et al., 2002; Dahl et al., 2009). Prevalence of fatigue were assessed by self-reports on the Fatigue Scale for Motor and Cognitive Functions (FSMC), and the combined score of ≥ 43 was used as the cut-off to define MS-related fatigue (Penner et al., 2009). A self-report questionnaire listing their education and employment status were also completed at each test session.

2.2.2. Clinical evaluations

All participants underwent a standard neurological status examination, including scoring of the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

2.2.3. Neuropsychological tests: BICAMS

The oral version of the Symbol Digit Modalities Test (SDMT) (Smith, 1982) was included as a measure of information processing speed both at baseline and the follow-up sessions. No alternative stimuli was included, as studies have shown only minor learning effects and a high test-retest reliability of SDMT (Strober et al., 2009). The initial learning trials of the official Norwegian translation of the 2nd edition of the California Verbal Learning Test (CVLT-II) (Delis et al., 1987) was included as a measure of verbal memory function. To reduce the risk of a learning effect, known to be significant from baseline to the first follow-up session (Lundervold et al., 2014), an alternative list of 16 words was included in the second assessment procedure. This alternative list included the words from the interference list of the standard format of CVLT-II (List B) as this list was not presented as part of the first test session and have a similar construction as the original list. The word list (List A) from the baseline session was then reintroduced as part of the second follow-up session at 24 months. The initial learning trials of the BVMT-R (Benedict, 1997) were included as a measure of visual memory function. Due to a potential learning effect, the test stimuli were different at baseline and the follow-up sessions (Form 1, Form 2 and Form 3, respectively). A test score was defined as abnormal if the score was ≥ 1.5 standard deviation below the mean in a control group examined in a previous study (Skorve et al., 2019).

2.3. Statistical analyses

Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY), and figures were made using StataSE version 16 (StataCorp LLC, College Station, Texas). Statistical significance was set at alpha level <0.05. Within-group differences were examined with student's paired samples *t*-test and McNemar test for continuous and categorical variables, respectively. Effect sizes were calculated and defined according to Cohen's *d* statistic (0.2 = small, 0.5 = medium, 0.8 = large).

3. Results

3.1. Demographic characteristics

The sample included 58 RRMS patients (18 men, 44 women) with mean age of 37.6 (± 10.6) years at baseline and mean disease duration of 1.9 (± 1.3) years since onset of the first symptom (range 0.3–5.3) and 1.2 (± 0.8) years since diagnosis (range 0.2–2.7). Most (89.5%) of the patients were employed at baseline, and 83.9% were still employed at the last follow-up ($p = 0.39$).

3.2. Clinical characteristics

Median EDSS was 1.5 and remained stable throughout the study duration. No significant changes were observed for the EDSS ($p = 0.11$) or the mean HADS ($p = 0.78$) scores from baseline to 24 months (Table 1). Both fatigue sub-scores (motor and cognitive) showed a significant worsening from baseline to 12 months ($p = 0.021$, and $p = 0.025$, respectively), but only the motor score showed significant overall worsening from baseline to 24 months ($p = 0.028$) (Table 1).

At baseline, 93.1% of the patients received disease modifying therapy (DMT), and 98.3% were on active treatment at the end of the study. From baseline to 24 months 34.5% of the patients changed DMT due to intolerable adverse effects (13.8%) or disease activity revealed by clinical and/or radiological examinations (20.7%). 45% ($n = 9$) of the patients who changed therapy had a deterioration in EDSS score (mean change +1.06 points, range 0.5–2.0 points), 20% ($n = 4$) showed an improvement (mean change −0.63 points, range 0.5–1.0 points), and 35% ($n = 7$) were clinically stable (Table 1). 65% ($n = 13$) escalated therapy from “active” to “highly-active”, 15% ($n = 3$) were treatment naïve at the start of the study, and 20% ($n = 4$) changed to another “highly-active” therapy.

3.3. Cognitive performance (BICAMS) from baseline to follow-up examinations

A total of 27 patients (46.6%) were defined as cognitively impaired at baseline (i.e. more than one abnormal test score (Dusankova et al.,

Table 1
Clinical characteristics at baseline, 12 months and 24 months follow-up.

	Baseline (N = 58)	12 months (N = 58)	24 months (N = 57)
EDSS, mean (median)	1.35 (1.50)	1.50 (1.50)	1.53 (1.50)
EDSS, change from baseline			
Stable,% (N)	–	41.4 (24)	40.4 (23)
Worsening,% (N)	–	36.2 (21)	40.4 (23)
mean score Δ	–	−0.77 points	−0.95 points
Improvement,% (N)	–	22.4 (13)	19.3 (11)
mean score Δ	–	+0.88 points	+1.05 points
HADS total score, mean ± SD	7.8 ± 5.9	7.4 ± 5.5	7.5 ± 5.5
Anxiety, mean ± SD	5.1 ± 3.7	4.9 ± 3.6	4.8 ± 3.6
Depression, mean ± SD	2.7 ± 2.9	2.5 ± 2.5	2.7 ± 2.6
FSMC total score, mean ± SD	26.8 ± 19.3	31.5 ± 21.0*	30.6 ± 20.3*
Cognitive, mean ± SD	13.6 ± 10.1	15.8 ± 10.9*	15.3 ± 10.1
Motor, mean ± SD	13.2 ± 9.8	15.7 ± 10.4*	15.3 ± 10.7*

SD = standard deviation; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; FSMC = Fatigue Scale for Motor and Cognitive Functions.

* Statistically significant change from baseline ($p < 0.05$).

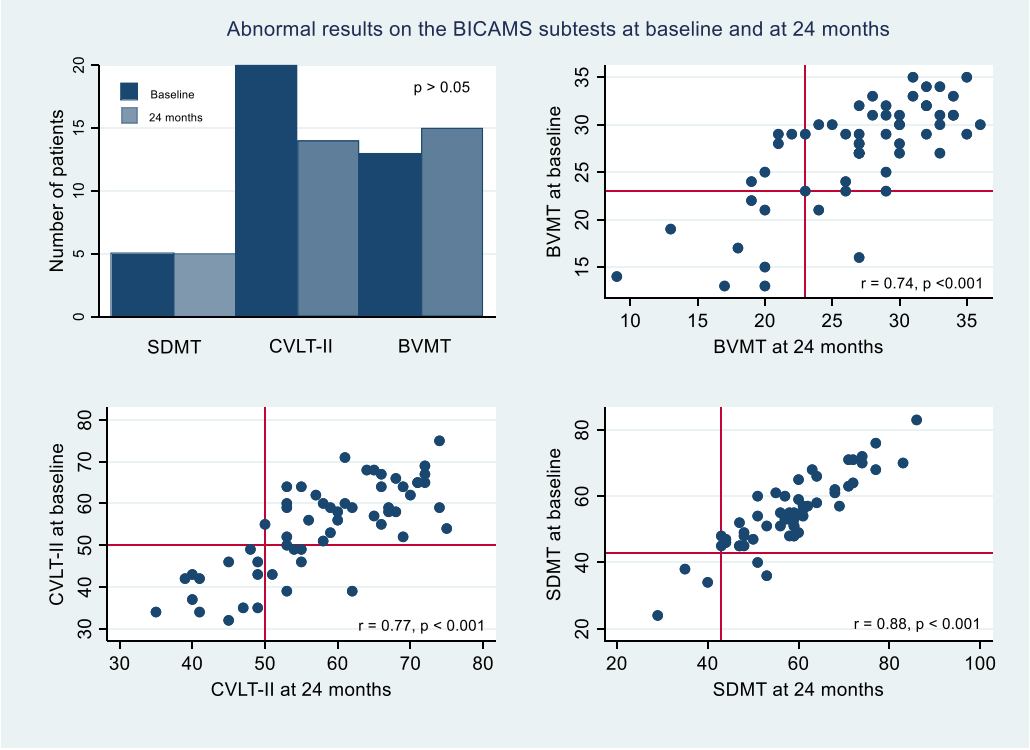

Fig. 1. Number of patients performing below the cut-off scores on the BICAMS subtests (SDMT 43; CVLT-II 50; BVMT 23) at baseline and at the 24-months follow-up, and correlations between the test performances at the two time points.

Table 2
Mean raw scores on BICAMS subtests at baseline, 12 months and 24 months.

	Baseline	12 months				24 months		
	Mean	SD	Mean	SD	Cohens d**	Mean	SD	Cohens d**
SDMT	54.84	10.83	57.28*	11.40	0.41	58.24*	11.34	0.62
CVLT-II	54.29	10.85	57.47*	8.00	0.39	58.10*	10.34	0.53
BVMT-R	27.16	5.59	28.26	5.77	0.20	26.90	5.74	0.06

SD = Standard deviation; SDMT = Symbols Digit Modalities Test; CVLT-II = California Verbal Learning Test, 2nd edition; BVMT-*R* = Brief Visuospatial Memory Test, revised.

* Statistically significant change from baseline ($p < 0.05$).

** Effect size for dependent samples, compared to baseline results.

2012; Skorve et al., 2019)). 19 patients (32.8%) were impaired on only one BICAMS test, and 4 patients (6.9%) scored below the cut-off for impairment on two tests and 4 on all three tests. At the 12 months follow-up assessment, the number of patients with abnormal test results was significantly reduced to 16 patients (27.6%, $p = 0.01$), while 22 patients (37.9%, $p = 0.27$) were defined as cognitively impaired at the end of the study (14 patients showed impairment on one subtest, 4 patients on two tests and 4 patients on three tests) There were no significant changes in number of patients who showed impairment on either of the three BICAMS subtests from baseline to 24 months (see Fig. 1). The mean raw scores for the subtests at baseline, 12 and 24 months are presented in Table 2. Both the SDMT and the CVLT-II scores were significantly improved from baseline to 12 months ($p = 0.003$ and $p = 0.004$, respectively) and from baseline to 24 months ($p < 0.001$ for both tests). The BVMT-R results were overall unchanged from baseline to the end of the study.

The test-retest correlations between test performances at the different time points were significant at $p < 0.001$ for all three tests, with a gradual strengthening of the correlations from baseline through the first to the second follow-up session, reaching $r > 0.75$ by 24 months (Fig. 1).

3.4. Anxiety, depression and fatigue – correlations with cognitive performances

The prevalence of clinically meaningful anxiety and depression at baseline (HADS sub-score ≥8) were 14 (24.1%) and 4 (6.9%), respectively, and these numbers remained unchanged at the 24 months follow-up. Only 13 (22.4%) patients reported some degree of fatigue (i.e., FSMC total score ≥43) at baseline, and this number increased to 19 patients (32.8%) at 24 months. The corresponding changes in prevalence on the cognitive and motor subscales from baseline to the last follow-up were 22.4% to 29.3%, and 20.7% to 25.9%, respectively. All changes in the prevalence of anxiety, depression and fatigue at were statistically non-significant. Correlations between the BICAMS subtests and the mean HADS and FSMC scores are shown in Tables 3a – 3c. No correlations were statistically significant at baseline, but there was a weak to moderate, significant negative correlation between depression, SDMT and CVLT-II, and between the cognitive fatigue subscale, SDMT and CVLT-II at 12 months. At 24 months, only the correlations between depression and CVLT-II, and between the cognitive fatigue subscale and SDMT remained significant. There were no statistically significant correlations between BVMT-R and the HADS and FSMC subscales at any time point.

4. Discussion

To the authors' knowledge, this is the first longitudinal study where cognitive performance is measured by repeated testing with the BICAMS in a sample of newly diagnosed RRMS patients. We found that the group of MS-patients improved significantly from baseline to the first follow-up examination, indicating that the effect of being part of a previous BICAMS assessment is substantial even after 12 months. Furthermore, large variability in detection of impairment between the subtests support that all three subtests should be included when BICAMS is used as a clinical screening tool for cognitive impairment in patients with MS.

Table 3a
Correlations between BICAMS and HADS and FSMC at baseline.

BICAMS subtest	HADS sub scores				FSMC sub scores			
	Anxiety		*Depression*		*Motor*		*Cognitive*	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SDMT	−0.02	0.86	−0.02	0.87	−0.01	0.95	−0.08	0.55
CVLT-II	−0.05	0.74	−0.11	0.44	−0.13	0.34	−0.18	0.18
BVMT-R	−0.06	0.68	−0.06	0.69	−0.13	0.34	−0.10	0.48

Table 3b
Correlations between BICAMS subtests and HADS- and FSMC sub scores at 12 months.

BICAMS subtest	HADS sub scores				FSMC sub scores			
	Anxiety		*Depression*		*Motor*		*Cognitive*	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SDMT	−0.16	0.23	−0.29*	0.03	−0.2	0.15	−0.35*	0.01
CVLT-II	−0.12	0.40	−0.33*	0.02	−0.17	0.22	−0.27*	0.05
BVMT-R	0.09	0.54	−0.15	0.29	−0.09	0.51	−0.2	0.15

Table 3c
Correlations between BICAMS subtests and HADS- and FSMC sub scores at 24 months.

BICAMS subtest	HADS sub scores				FSMC sub scores			
	Anxiety		*Depression*		*Motor*		*Cognitive*	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SDMT	−0.03	0.82	−0.2	0.16	−0.26	0.05	−0.35*	0.01
CVLT-II	−0.03	0.83	−0.27*	0.05	−0.18	0.18	−0.24	0.08
BVMT-R	0.16	025	−0.10	0.5	−0.04	0.75	−0.11	0.41

BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis. SDMT = Symbol Digit Modalities Test. CVLT-II = California Verbal Learning Test, 2nd edition. BVMT-*R* = Brief Visuospatial Memory Test, Revised. HADS = Hospital Anxiety and Depression Scale. FSMC = Fatigue Score for Motor and Cognitive Function.

* Statistically significant correlation.

The BICAMS test battery has been validated in several countries and has become widely accepted as a robust and effective screening tool for cognitive impairment in MS patients (Corfield and Langdon, 2018). The aforementioned validation studies have retested healthy controls and patient samples within the 1–3 week interval recommended to ascertain test-retest reliability (Benedict et al., 2012). Of the few longitudinal studies using the BICAMS specifically for evaluation of cognitive function, one is comparable to the present study regarding sample size, retest interval and level of physical disability (Frau et al., 2018). Our patient sample, however, differed by including patients at a younger age and with a shorter disease duration. Furthermore, our study had a stronger focus on detection and monitoring of cognitive impairment within the sample. By this, our longitudinal study presents data that can be used to evaluate the usability of BICAMS in a routine, clinical practice.

The mean raw scores on the SDMT and the CVLT-II improved significantly from baseline to 12 months and remained stable to the end of the study, whereas the BVMT-R score showed a mild improvement at 12 months but were overall essentially unchanged from baseline to the end of the study. Initial improvement in test performance on a first re-test assessment is known as the practice effect (Ferrer et al., 2004), 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 a reduced test anxiety. The duration of this effect is, however, not established. A recent meta-analysis on this effect on performance on tests of working memory capacity found that at least 16 months interval was necessary to eliminate the effect of having performed the same test at an earlier time point (Scharfen, 2018). Others have shown that this effect is dependent on the cognitive domain tested (Ferrer et al., 2004). Therefore, despite the test interval of 12 months, practice effects cannot be excluded. Studies investigating the practice effects of BICAMS are needed for better interpretation of the results.

Even patients with impaired BICAMS results at baseline showed some improvement at follow-up examinations. While almost 50% of the sample were defined as cognitively impaired at baseline (i.e. abnormal results on at least on one test), the proportion was reduced to below 30% after 12 months and to below 40% by the end of the study. Most of

these patients showed impairment on only one test. By this, the numbers of patients with a mild impairment at baseline were somewhat higher than the number reported in a Danish BICAMS validation study (Marstrand et al., 2020), where approximately 30% of the patients were classified as cognitively impaired on more than one test. The percentages of patients showing impairment on two or more tests were more similar across the two studies and the present study contributed by showing that the patients with a more extended impairment at baseline remained impaired throughout the study. We suggest that this finding support previous studies reporting that cognitive impairment shown in early stages of the disease tends to persist over time (Barbu et al., 2018; Berard et al., 2018). Among patients with impairment on only one cognitive test, however, we confirm that the trajectories of change are much more fluctuating (Katsari et al., 2020). This illustrates the challenge met by clinicians both regarding identification of patients with cognitive impairment and when estimating their prognosis and needs for treatment. Still, we will argue that the quality of the BICAMS gives the clinician a valid screening instrument. We also suggest that patients showing impairment on only one subtest should be invited to annual follow-up assessments to evaluate the risk of a developing a more severe impairment. Patients with impairment on more than one test, on the other hand, should be considered for a more extensive neuropsychological assessment and rehabilitation. With this routine, results on the BICAMS subtests may serve as a gatekeeper for the referral of patients to more extensive examinations with lower capacity and availability than in most Neurological departments.

The psychometric properties of each of the BICAMS tests is also worth a comment. A total of 34.5% of the sample showed abnormal test results on the CVLT-II, while the percentages for BVMT-R and SDMT were 22.4% and 8.6%, respectively (Skorve et al., 2019). The low proportion of impairment detected by the SDMT is in contrast to findings presented in other validation studies of BICAMS (Marstrand et al., 2020; Polychroniadou et al., 2016; Sandi et al., 2015; Sousa et al., 2018), in which the SDMT was found to be the most sensitive test of cognitive changes in patients with MS. The Canadian (Walker et al., 2016) and German (Filser et al., 2018) validation study, however, found that the BVMT-R identified more patients with cognitive impairment than the other tests, while the Irish study reported results similar to ours with the CVLT-II identifying impairment in 40% of the sample (O'Connell et al., 2015). International cut-off scores for the subtests has been proposed (Beier et al., 2017), but given the large variability and lack of consensus across studies from different countries (Smerbeck et al., 2018), national rather than international norms should be developed. It should be noted that SDMT is often used as a stand-alone cognitive test in clinical trials and studies of patients with MS (Benedict et al., 2017; Strober et al., 2019). Recent recommendations for screening and management of cognitive impairment in clinical practice also underline the importance of results on the SDMT (Kalb et al., 2018) as a minimum requirement for cognitive screening. Our findings do not support this practice because most of the newly diagnosed MS patients with mild cognitive impairment in our sample would not have been detected if SDMT was included as the only test of cognitive function. We therefore strongly argue for the implementation of the complete BICAMS test battery into clinical practice. Still, it is important to remember that BICAMS is a screening instrument. Whenever a clinician is uncertain about the results, the patient should be referred to a more extensive neuropsychological examination.

The prevalence of clinically meaningful anxiety in this sample was found to be at the level of the national average reported for MS patients (Dahl et al., 2009), whereas the prevalence of depression was relatively low (Korostil and Feinstein, 2007; Patten and Metz, 1997). About 70% of the participants did not report any fatigue, which is a higher proportion than reported in previous studies (Weiland et al., 2015; Wood et al., 2013). Similar findings have been reported in the Danish validation study, which included a sample of patients with similar age distribution and disease duration as our study (Marstrand et al., 2020). The lack of significant correlations between results on the BICAMS subtests and symptoms of anxiety, depression and fatigue at baseline is also worth a comment. It corresponds to results reported by Golan and colleagues indicating that mild depression and fatigue do not appear to impede cognition (Golan et al., 2018). However, when re-assessed after 12 and 24 months, significant negative correlations emerged between the scores on two of the three BICAMS subtests (SDMT and CVLT-II) and the depression sub score from HADS and the cognitive subscale from the FSMC. Thus, our results indicate that HADS and FSMC should be included as part of the cognitive assessment in follow-up routines of patients with MS (Portaccio, 2016), and that future longitudinal studies investigating modulators of associations between emotional and cognitive function are warranted.

More than 95% of the patients in our study received DMT, of whom approximately 35% changed therapy during the study, 14% did so because of disease activity. Additional analyses of patients who changed therapy versus those who did not, revealed similar findings as the sample as a whole. Given the small number of patients who changed therapy due to disease activity between test sessions, we do not have enough power to state whether or not performance on the BICAMS is influenced by disease activity. In the future, cognitive testing during a relapse could yield interesting insight into fluctuations in cognitive performance over the disease course and its response to disease modifying therapy.

Almost 90% of the patients were employed at the start of the follow-up, and more than 80% were still employed after two years. These uplifting numbers may, in part, be due to the relatively low mean age of the participants, their short disease duration, and low level of physical disability, combined with the use of DMT. Increased focus on cognitive impairment in MS may also have led the patients to request work place customization, promoting an increase or at least a stable work capacity at the individual level. Data was not collected to investigate this important issue, and further studies on the effect of participation in clinical studies on the patients' self-awareness, coping strategies and motivation should be performed.

A limitation of the study is the lack of control for demographic variables, but we considered the cohort to be too small in the present study to yield sufficient statistical power. Furthermore, we did not intend to make predictions on an individual level, but rather investigate overall projections over time for a group of individuals with newly diagnosed MS. A group of healthy controls followed over the same time period would have improved the impact of our results, but longitudinal data from the control group was not available for the present study. Although our cohort is relatively small, it is well-defined with almost no loss of follow-ups so far. Hopefully, we will be able to run 5 and 10 year follow-up studies to determine how well their performances on cognitive tests correspond with results shown in other cohorts.

5. Conclusions

The BICAMS identified almost 50% of a newly diagnosed sample of patients with MS as cognitively impaired on at least one test measure at baseline. Abnormal results on more than one test seemed to predict persistent cognitive impairment, while a more fluctuating developmental pathway was shown by the patients with mild symptoms at baseline, i.e., impairment on only one of the three BICAMS tests. Both this within-subject variability in cognitive function and the significant improvement from baseline to the first follow-up due to practice effects, illustrates the importance of including repeated assessments of cognitive function in patients with MS. The rather large differences in the detection rate on the three subtests also highlights the value of including all three subtests when using the BICAMS as a screening instrument. The symptoms of depression, anxiety and fatigue were mild in the present sample, and although this did not seem to impede cognition in the present study, we still will recommend including assessment of anxiety, depression and fatigue when screening for cognitive

impairment in patients with MS.

Author declerations

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Astri J. Lundervold has no declarations relevant to the field of multiple sclerosis.

Øivind Torkildsen has received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis.

Kjell-Morten Myhr has received unrestricted research grants to his institution and scientific advisory board, and speaker honoraria from Almirall, Biogen, Genzyme, Merck, Novartis, Roche and Teva; and has participated in clinical trials organized by Biogen, Merck, Novartis, and Roche.

CRediT authorship contribution statement

Ellen Skorve: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Project administration, Writing - original draft, Visualization, Funding acquisition. **Astri J. Lundervold:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Supervision. **Øivind Torkildsen:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Kjell-Morten Myhr:** Conceptualization, Methodology, Project administration, Writing - review & editing, Supervision, Funding acquisition.

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