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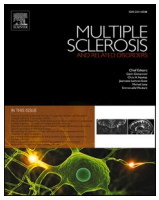

Brief international cognitive assessment for MS (BICAMS) and global brain volumes in early stages of MS – A longitudinal correlation study

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ABSTRACT

Background: Cognitive impairment is common in patients with multiple sclerosis, even in the early stages of the disease. The Brief International Cognitive Assessment for multiple sclerosis (BICAMS) is a short screening tool developed to assess cognitive function in everyday clinical practice.
Objective: To investigate associations between volumetric brain measures derived from a magnetic resonance imaging (MRI) examination and performance on BICAMS subtests in early stages of multiple sclerosis (MS).
Methods: BICAMS was used to assess cognitive function in 49 MS patients at baseline and after one and two years. The patients were separated into two groups (with or without cognitive impairment) based on their performances on BICAMSs subtests. MRI data were analysed by a software tool (MSMetrix), yielding normalized measures of global brain volumes and lesion volumes. Associations between cognitive tests and brain MRI measures were analysed by running correlation analyses, and differences between subgroups and changes over time with independent and paired samples tests, respectively.
Results: The strongest baseline correlations were found between the BICAMS subtests and normalized whole brain volume (NBV) and grey matter volume (NGV); processing speed $r = 0.54/r = 0.48$, verbal memory $r = 0.49/ r = 0.42$, visual memory $r = 0.48 /r = 0.39$. Only the verbal memory test had significant correlations with T2 and T1 lesion volumes (LV) at both time points; T2LV $r = 0.39$, T1LV $r = 0.38$. There were significant loss of grey matter and white matter volume overall (NGV $p<0.001$, NWV $p = 0.003$), as well as an increase in T1LV ($p = 0.013$). The longitudinally defined confirmed cognitively impaired (CCI) and preserved (CCP) patients showed significant group differences on all MRI volume measures at both time points, except for NWV. Only the CCI subgroup showed significant white matter atrophy ($p = 0.006$) and increase in T2LV ($p = 0.029$).
Conclusions: The present study found strong correlations between whole brain and grey matter volumes and performance on the BICAMS subtests as well as significant changes in global volumes from baseline to follow-up with clear differences between patients defined as cognitively impaired and preserved at both baseline and follow-up.

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system, primarily manifesting in early adulthood. Symptoms of MS are widespread and include motor and sensory disturbances, as well as symptoms like fatigue, mood disorders and cognitive impairment (Thompson et al., 2018b).

Cognitive impairment in MS can be present from the very beginning of the disease (Amato et al., 2006; Bobholz and Rao, 2003; Chiaravalloti and DeLuca, 2008; Rao et al., 1991). It has been found in the preclinical phase, and even before characteristic lesions are identified by a magnetic resonance imaging (MRI) examination (Cortese et al., 2016; Hyncicova et al., 2017). Cognitive impairment causes considerable individual disease burden and socioeconomic costs by contributing to poor

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vocational status and early retirement due to disability (Ruet et al., 2013). Increased awareness of the negative effects of impaired cognition has highlighted the need for an easily administered screening tool to identify MS patients with manifest or incipient cognitive impairment. This motivated development of the Brief International Cognitive Assessment for MS (BICAMS) (Benedict et al., 2012; Langdon et al., 2012). It has been shown that the BICAMS provides results corresponding well with those obtained by other, more comprehensive neuropsychological test batteries commonly used in today's clinical practice (Gromisch et al., 2018; Maltby et al., 2020; Niccolai et al., 2015).

MRI is a well-established tool for diagnosing and monitoring treatment outcomes in MS patients (Thompson et al., 2018a), and neurodegenerative changes in general (De Stefano et al., 2014; Lanz et al., 2007). Brain atrophy has been identified in all phenotypes and all stages of MS, even before the disease manifests itself clinically (Amato et al., 2012; De Stefano et al., 2010; Giovannoni, 2017). A recent consensus report recommended the use of global brain atrophy measures rather than regional measures in clinical practice for more accurate predictions of disability across phenotypes and stages of disease (Sastre-Garriga et al., 2020), and that this is particularly important when the follow-up period is short (van Munster and Uitdehaag, 2017).

A few studies have investigated associations between MRI measures and performance on the BICAMS tests (Artemiadis et al., 2018; Fenu et al., 2018; Toth et al., 2018). Only one study included longitudinal data, but the sample was limited to patients without any disease activity identified by MRI during follow-up. Furthermore, all previous studies included patients with more than 10 years of disease duration. Thus, longitudinal studies investigating associations between performance on the BICAMS tests and MRI volume measures in the earliest stages of MS are called for.

We have previously reported the presence of cognitive impairment in this sample of patients in the earliest stages of relapsing remitting MS (RRMS) over a period of two years by using the BICAMS screening tool (Skorve et al., 2019, 2020). We found cognitive impairment on at least one of the BICAMS subtests in about 50% of the sample at baseline, which is in line with the established prevalence of cognitive impairment in MS (Amato et al., 2006; Chiaravalloti and DeLuca, 2008). Thereby, the results supported inclusion of the test battery as part of a clinical follow-up routine.

The aim of the present study was to investigate associations between cognitive function and global volumetric MRI measures in newly diagnosed patients with RRMS. We used both a cross-sectional and longitudinal design by including results from the BICAMS tests and MRI examinations at baseline and at a 2-year follow-up. Expecting deterioration over time, we examined if correlations between performances on the BICAMS subtests and brain volume measures would be stronger at the 2-year follow-up than at baseline. By defining the sample into subgroups with and without cognitive impairment, we expected to find pronounced MRI changes in patients with cognitive impairment persisting from baseline to the follow-up examination.

2. Methods and materials

2.1. Study population

A total of 49 RRMS patients with baseline and 2-year follow-up data available were included. Inclusion criteria were age $\geq$18 years, a definite RRMS diagnosis during the time-period 2014–2016, and onset of MS-symptoms no more than three years prior to diagnosis, and no comorbid conditions associated with cognitive impairment. The patients were followed with clinical, neuropsychological and MRI assessment for two years, and we included cross-sectional data from the baseline evaluation and longitudinal data from the two-year follow-up evaluation in the current study. The study was approved by the Regional Ethics Committee of Western Norway (registration number 2016/31/REK Vest), and inclusion was based on written informed consent

2.2. Procedures

2.2.1. Physical assessment

All patients were assessed by a full neurological examination including scoring of the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) at inclusion and all follow-ups.

2.2.2. Cognitive assessment: brief international cognitive assessment for MS (BICAMS)

Patients were assessed using BICAMS at baseline, after 12 and 24 months, but only data from baseline and the two-year follow-up were included in the current study. Cognitive data from the first year of follow-up were presented in a previous publication (Skorve et al., 2020). Processing speed and memory function are described as the cognitive domains most commonly affected in patients with MS (Chiaravalloti and DeLuca, 2008; Grzegorski and Losy, 2017). Therefore, the BICAMS (Benedict et al., 2012; Langdon et al., 2012) includes three subtests designed to assess performance within these domains. The oral version of the Symbols Digit Modalities Test (SDMT) (Benedict et al., 2017; Smith, 1982) is included as a measure of processing speed. The initial learning trials from the California Verbal Learning Test, 2nd edition (CVLT-II) (Delis et al., 1987) and the Brief Visuospatial Memory Test Revised (BVMT-R) (Benedict, 1997) are included as measures of verbal and visuospatial working memory function, respectively. The restriction of the memory function tests to the learning trials is due to studies showing that the primary memory deficit in MS patients affects memory acquisition rather than recall and recognition (DeLuca et al., 1994). To distinguish these shortened versions of the memory tests from the original full versions, these subtests will hereafter be referred to as CVLT-Learning Trials (CVLT-LT) and BVMT-Learning Trials (BVMT-LT).

Expecting minor learning effects of repeated testing, no alternative stimuli were provided for the follow-up evaluations of SDMT performance (Strober et al., 2009). Expecting short-term effect of previous testing on the CVLT-LT (Lundervold et al., 2014), an alternative word list from the original version of CVLT-II (List B) was included at the one-year follow-up, while the original word list used at baseline was repeated at the follow-up after two years. Different forms of BVMT-R (Forms 1 – 3) figures were included at baseline and the two follow-up sessions.

Information from a control sample examined as part of a previous study (Skorve et al., 2019) was used to define a cut-off value for impairment on each of the BICAMS subtests. A test score was defined as impaired if it was at least 1.5 standard deviations (SD) below the mean score in the control sample (SDMT $\leq$43 points; CVLT-II $\leq$50 points; BVMT-$R \leq$ 23 points). Patients with impaired test scores on at least one of the subtests were classified as cognitively impaired (CI), and the rest of the sample was defined as cognitively preserved (CP) (Dusankova et al., 2012). A longitudinal classification was added for patients classified as CI or CP at both baseline and the two-year follow-up, defined as confirmed cognitively impaired (CCI) and confirmed cognitively preserved (CCP), respectively.

2.2.3. Magnetic resonance imaging (MRI) acquisition and analysis

MRI was conducted on a 3T Magnetom Prisma MR scanner (Siemens Healthcare, Germany) within one month of BICAMS testing. Detailed information about the MRI acquisition protocol is available in a supplementary file (Appendix A). The scans were processed by Icometrix (Leuven, Belgium) for supervised digital image analyses yielding cross-sectional data on global and regional brain volumes and lesion assessment, as well as longitudinal volumetric changes. The icobrain MS tool (MSMetrix, version 4.3.3) (Beadnall et al., 2019; Fragoso et al., 2017; Jain et al., 2015; Smeets et al., 2016), an FDA-approved and CE-marked tool for clinical use, was used to analyse the MRI data. The brain volume measurements were normalized for intracranial volume through the scaling parameter obtained from registration with a reference brain (Evans et al., 1993) and corrected for age and gender. Volume per time

point of normalized whole brain (NBV), normalized grey matter (NGV), normalized white matter (NWM) and normalized lateral ventricle (NVV) are included as measures in the present study, as well as total hyperintense T2-weighted (FLAIR) lesion volumes (T2LV) and hypointense T1-weighted lesion volumes (T1LV) per time point.

2.3. Statistical analyses

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY). Statistical significance level was set to <0.05. Pearson's correlation coefficients were considered strong when $r \geq \pm 0.5$, moderate when $r = \pm 0.30$ - ± 0.49, and weak when $r \leq \pm 0.29$. Group differences were examined with independent samples student's *t*-test and McNemar test for continuous and categorical variables, respectively. Longitudinal changes within groups were examined with paired samples student's *t*-test. Within-subjects effect sizes were calculated according to Cohen's *d*, and between-subject effect sizes according to Hedges *g* to account for small and unequal sample sizes.

3. Results

3.1. Sample characteristics

Baseline demographic and clinical characteristics are listed in Table 1. All patients had less than six years since onset of the first MS symptom and less than three years since diagnosis. All patients had an EDSS scores less than 3.0 at baseline, a level which remained low throughout the study.

3.2. Cognitive performance (BICAMS)

We found cognitive impairment (CI) on one or more subtests in 22/49 patients (45%) at baseline, with the majority (17/22; 77%) having only one impaired test score. Three patients (14%) showed impairment across two subtests, and two patients (9%) across all three. Separate analyses of the three subtests showed that 6% of the patients obtained an impaired test score on the SDMT, and 33% and 20% on the CVLT-LT and BVMT-LT, respectively. After two years, 17/49 patients (35%) were defined as CI. During the observation time three patients (6%) changed classification from preserved to impaired and eight patients (16%) changed from impaired to preserved. The rest of the sample (78%) showed no change and were longitudinally defined as confirmed cognitively impaired (CCI; $n = 14$) and confirmed cognitively preserved (CCP; $n = 24$).

Overall, the improvements in raw scores from baseline to the two-year follow-up were statistically significant for the performance on SDMT ($d = 0.57$) and CVLT-LT ($d = 0.49$), but not for the BVMT-LT (Table 2). A more detailed analysis of patients classified as CI ($n = 17$) or CP ($n = 32$) at follow-up showed that the improvements were still significant for SDMT ($d = 0.70$) and CVLT-LT ($d = 0.50$) for the CP group, while the change was non-significant on all three tests for the CI group (Table 2).

Table 1
Demographic and clinical characteristics at baseline ($N = 49$).

Gender m/f, n (%)	15/34 (31/69)
Age, mean (±SD)	38.7 ± 10.7
EDSS	
mean ±SD	1.3 ± 0.9*
median (range)	1.5 (0.0–3.0)
Disease duration (years)	
since first symptom, mean ±SD (range)	2.1 ± 1.3 (0.3–5.3)
since diagnosis, mean ±SD (range)	1.3 ± 0.8 (0.3–2.7)

SD= Standard deviation. EDSS= Expanded Disability Status Scale.
*mean EDSS at follow-up 1.5 ± 0.9 (not statistically significant).

3.3. MRI correlations with BICAMS subtests

Correlations between cognitive performances and MRI brain volume measures at baseline and at the two-year follow-up are shown in Table 3. Results on the SDMT at baseline were strongly correlated with the normalized whole brain (NBV) and grey matter volumes (NGV), and moderately correlated with normalized lateral ventricle volume (NVV). There were no significant correlations between results on SDMT and lesion volumes (T1LV and T2LV) at either time point. Baseline results on the CVLT-LT were moderately correlated with NBV and NGV, weak to moderately with NVV, and to both T1LV and T2LV. We found a moderate to strong correlation between baseline results on the BVMT-LT and NBV, NGV and NVV, and a weak correlation with T1LV and T2LV. After two years, all aforementioned correlations between performances on SDMT, CVLT-LT and the volume measures remained at the same level. For the BVMT-LT only the correlations with NBV and NGV remained statistically significant, whereas all other correlations lost statistical significance at follow-up. None of the BICAMS subtests showed significant correlations with white matter volume (NWV) at either time point.

3.4. MRI volume changes in relation to cognition

Table 4 shows the overall changes in volumes from baseline to follow-up. During the two-year period, both white matter and grey matter volumes were significantly reduced ($d = 0.44$ and $d = 1.08$, respectively), with a corresponding significant increase in lateral ventricle volumes ($d = 0.80$) and a significant reduction in whole brain volume ($d = 0.93$). During this observation time, there was also a significant increase in the total T1LV ($d = 0.34$), but not in the total T2LV. The correlations between all volume measures at the two time points were strong, with *r*-values approaching 1.0 for all included MRI measures.

To evaluate longitudinal changes and differences between the cognitively impaired and preserved patients over the course of two years, we extracted data from patients who were longitudinally classified as CCI ($n = 14$) and CCP ($n = 24$) (Table 5a-b). The CCI group had significantly lower volumes of whole brain, grey matter, and white matter than the CCP group, and larger lateral ventricle volumes and lesion volumes at both time points. All volume measures deteriorated significantly from baseline to follow-up in the CCI group, except for the T1LV (borderline significant). For the CCP group, there were statistically significant changes in whole brain, grey matter, and lateral ventricle volume, but no significant changes in white matter volume, T2LV or T1LV. Mean annualized whole brain volume change (global atrophy rate) from baseline to the two-year follow-up was lower in the CCP group (−0.15%) than in the CCI group (−0.25%), but the differences were not statistically significant.

4. Discussion

We found significant changes in brain volumes in a group of MS patients in an early stage of the disease, and performance on all three BICAMS subtests correlated strongly with the normalized whole brain and grey matter volumes (NBV and NGV). None of the subtests showed significant correlations with white matter volume (NWV), and only CVLT-LT retained significant correlations with hyperintense T2 FLAIR lesion volume (T2LV) and hypointense T1 lesion volume (T1LV) from baseline to follow-up. Changes in brain volume measures were overall most profound in patients defined as cognitively impaired at both baseline and the two-year follow-up. Both the confirmed cognitively impaired (CCI) and preserved (CCP) patients showed significant atrophy of NBV and NGV, as well as an increase in lateral ventricle volume (NVV), but only the CCI group showed significant increase in T2LV and white matter atrophy over the two-year follow-up period.

The strong correlations between scores on the SDMT (processing speed) and NBV and NGV at both time points are in line with previous

Table 2
BICAMS results at baseline and two year follow-up for the sample overall, and for patients defined as cognitively impaired (CI) and cognitively preserved (CP) at the 2-year follow-up.

BICAMS subtest	Group	N	Baseline Mean	SD	2 years Mean	SD	*t*	*p*	Cohen's *d*	Pearson's *r*	*p*
SDMT	All	49	55.2	10.9	58.4	11.6	−3.995	*<0.001*	0.57	0.88	<0.001
	CI	17	47.9	10.3	50.1	10.4	−1.475	0.16	0.36	0.83	<0.001
	CP	32	59.2	9.1	62.8	9.7	−3.968	*<0.001*	0.70	0.84	<0.001
CVLT-LT	All	49	54.9	10.8	58.4	10.3	−3.447	*0.001*	0.49	0.78	<0.001
	CI	17	47.0	11.3	49.7	10.0	−2.046	0.058	0.50	0.88	<0.001
	CP	32	59.1	8.0	63.0	7.0	−2.804	*0.009*	0.50	0.47	0.007
BVMT-LT	All	49	27.4	5.4	27.5	5.6	0.218	0.83	0.02	0.74	<0.001
	CI	17	24.0	6.2	22.2	5.4	1.677	0.113	0.41	0.73	0.001
	CP	32	29.3	3.9	30.0	3.3	−1.228	0.229	0.22	0.55	0.001

BICAMS=Brief International Cognitive Assessment for MS. SDMT=Symbols Digit Modalities Test. CLVT-LT=California Verbal Learning Test, 2nd edition – learning trials. BVMT-LT=Brief Visuospatial Memory Test-Revised – learning trials. CI=Cognitively impaired. CP=Cognitively preserved. SD=Standard Deviation.

Table 3
Correlations between BICAMS-subscores and computerized analyses of MRI brain volumes and lesion volumes at baseline and two-year follow-up.

Time point	BICAMS subtest	Pearson's correlation coefficient NBV	NVV	NGV	NWV	T2LV	T1LV
Baseline	SDMT	*0.54***	*−0.30**	*0.48***	n.s.	n.s.	n.s.
	CVLT-LT	*0.49***	*−0.37***	*0.42***	n.s.	*−0.39***	*−0.38***
	BVMT-LT	*0.48***	*−0.37***	*0.39***	n.s.	*−0.31**	*−0.31**
2 years	SDMT	*0.51***	*−0.29**	*0.50***	n.s.	n.s.	n.s.
	CVLT-LT	*0.51***	*−0.34**	*0.46***	n.s.	*−0.38***	*−0.39***
	BVMT-LT	*0.42***	n.s.	*0.45***	n.s.	n.s.	n.s.

BICAMS=Brief International Cognitive Assessment for MS. MRI=Magnetic Resonance Imaging. SDMT=Symbols Digit Modalities Test. CLVT-LT=California Verbal Learning Test, 2nd edition – learning trials. BVMT-LT=Brief Visuospatial Memory Test-Revised – learning trials. NBV=Normalized Whole Brain Volume. NVV=Normalized Lateral Ventricle Volume. NGV= Normalized Grey Matter Volume. NWV=Normalized White Matter Volume. T2LV= Total Hyperintense T2 FLAIR Lesion Volume. T1LV= Total Hypointense T1 Lesion Volume.
Only significant values are reported. Significant at the *0.05 level; **0.01 level; ***0.001 level; n.s.=not statistically significant.

Table 4
Overall changes in MRI brain and lesion volumes from baseline to 2 years follow-up.

	Baseline Mean	SD	2 years Mean	SD	*t*	*p*	Cohen's *d*	*r*	*p*
NBV	1540.0	48.5	1534.7	50.4	6.346	*<0.001*	0.93	0.994	<0.001
NVV	28.3	12.4	29.3	12.5	−5.824	*<0.001*	0.80	0.995	<0.001
NGV	920.2	44.1	916.4	44.6	7.022	*<0.001*	1.08	0.997	<0.001
NWV	619.8	27.4	618.2	27.3	3.110	*0.003*	0.44	0.991	<0.001
T2LV	2.0	1.9	2.1	1.9	−1.934	0.059	0.26	0.976	<0.001
T1LV	1.6	1.6	1.7	1.6	−2.571	*0.013*	0.34	0.984	<0.001

MRI=Magnetic Resonance Imaging. SD=Standard deviation. NBV=Normalized Whole Brain Volume. NVV=Normalized Lateral Ventricle Volume. NGV= Normalized Grey Matter Volume. NWV=Normalized White Matter Volume. T2LV=Total Hyperintense T2 FLAIR Lesion Volume. T1LV= Total Hypointense T1 Lesion Volume.

reports (Benedict et al., 2009; Calabrese et al., 2009; Vollmer et al., 2016). Findings that grey matter atrophy is primarily important for SDMT results in the early stages of the disease (Fenu et al., 2018) is supported by our results, which on the other hand showed no significant correlations between test performance and NWV at either time point. However, our finding of statistically non-significant correlations between SDMT scores and either T2LV or T1LV contrast previously well documented strong associations between cognition and lesion volume, in particular T2LV (Benedict et al., 2009; Calabrese et al., 2009; Chiaravalloti and DeLuca, 2008; Dong et al., 2015; Papadopoulou et al., 2013; Pinter et al., 2015; Sacco et al., 2015). The CVLT-LT was the only subtest with significant correlations with both T2LV and T1LV after two years. This was also shown in a recent study, reporting lesion volume to be the only significant volumetric factor predictive of cognitive function, especially when measured by the CVLT-LT (Artemiadis et al., 2018). In contrast to a previous study associating visual memory function with lesion volume, we showed only a weak to moderate correlation between BVMT-LT and lesion volumes, and only at baseline (Benedict et al., 2009). Moderate correlations with NBV and NGV at follow-up, however, support reports of a strong association between grey matter atrophy and BVMT-LT results (Sacco et al., 2015).

The overall increase in T1LV, but not in T2LV, may indicate stability in the inflammatory processes of the disease, with little or no new MS plaques occurring during follow-up. This was also supported by the stable disability level assessed by the EDSS scoring throughout the study, indicating that both changes derived from MRI and cognitive tests may appear before more overt neurological symptoms (Cortese et al., 2016). The significantly higher lesion volumes in the CCI group versus the CCP group are in agreement with a recent study, reporting that white matter lesion volumes may be the main propagator of cognitive impairment in the early stage of MS (Engl et al., 2020), and that white matter lesion volumes may be used to separate cognitively impaired from preserved patients (Sacco et al., 2015). However, it contrasts previous reports of no significant differences in lesion volumes amongst impaired and preserved patients (Zivadinov et al., 2001) and by this indicating that disease burden and lesion accumulation plays a less important role.

Zivadinov and colleagues have previously reported a higher decline in brain parenchymal volumes amongst patients with cognitive impairment worsening over time, indicating that global brain tissue loss is the driving force of cognitive decline in early stages of MS (Zivadinov

Table 5a
Comparing MRI volume measures in MS-patients defined as confirmed cognitively impaired (CCI) and preserved (CCP) both at baseline and 2-year follow-up (independent samples *t*-test).

MRI measure	Time point	Group	N	Mean	SD	*t*	*p*	Hedges *g*
NBV	Baseline	CCI	14	1505.0	46.4	−3.939	*<0.0001*	1.30
		CCP	24	1556.2	33.5			
	2 years	CCI	14	1497.6	48.9	−3.962	*<0.0001*	1.31
		CCP	24	1551.6	34.9			
NVV	Baseline	CCI	14	33.7	11.4	2.738	*0.010*	0.90
		CCP	24	24.8	8.7			
	2 years	CCI	14	35.3	11.6	2.964	*0.005*	0.98
		CCP	24	25.5	8.6			
NGV	Baseline	CCI	14	893.9	47.2	−2.935	*0.006*	0.97
		CCP	24	934.0	36.4			
	2 years	CCI	14	889.3	48.9	−2.975	*0.005*	0.98
		CCP	24	930.6	36.4			
NWV	Baseline	CCI	14	611.1	22.8	−1.305	0.200	0.43
		CCP	24	622.2	26.5			
	2 years	CCI	14	608.3	21.9	−1.532	0.134	0.50
		CCP	24	621.0	26.0			
T2LV	Baseline	CCI	14	3.2	2.4	3.047	*0.008*	1.22
		CCP	24	1.2	1.0			
	2 years	CCI	14	3.3	2.4	2.886	*0.010*	1.13
		CCP	24	1.3	1.2			
T1LV	Baseline	CCI	14	2.6	2.1	2.848	*0.012*	1.15
		CCP	24	0.9	0.8			
	2 years	CCI	14	2.7	2.2	2.777	*0.013*	1.10
		CCP	24	1.0	1.0			

MRI=Magnetic Resonance Imaging. MS=multiple sclerosis. SD=Standard deviation. CCI=Confirmed cognitively impaired. CCP=Confirmed cognitively preserved. NBV=Normalized Whole Brain Volume. NVV=Normalized Lateral Ventricle Volume. NGV= Normalized Grey Matter Volume. NWV=Normalized White Matter Volume. T2LV=Total Hyperintense T2 FLAIR Lesion Volume. T1LV= Total Hypointense T1 Lesion Volume.

Table 5b
Changes in MRI measurements from baseline to follow-up for MS-patients longitudinally defined as confirmed cognitively impaired (CCI) and cognitively preserved (CCP) (paired samples *t*-test).

MRI measure	Group	N	Baseline		2 years		*t*	*p*	Cohen's *d*
			Mean	SD	Mean	SD			
NBV	CCI	14	1505.0	46.4	1497.6	48.9	4.707	*<0.0001*	1.27
	CCP	24	1556.2	33.5	1551.6	34.9	3.660	*0.001*	0.75
NVV	CCI	14	33.7	11.4	35.3	11.6	−4.788	*<0.0001*	1.29
	CCP	24	24.8	8.7	25.5	8.6	−2.720	*0.012*	0.56
NGV	CCI	14	893.9	47.2	889.3	48.9	4.359	*0.001*	1.14
	CCP	24	934.0	36.4	930.6	36.4	4.842	*<0.0001*	0.94
NWV	CCI	14	611.1	22.8	608.3	21.9	3.291	*0.006*	0.89
	CCP	24	622.2	26.5	621.0	26.0	1.381	0.180	0.28
T2LV	CCI	14	3.2	2.4	3.3	2.4	−2.447	*0.029*	0.83
	CCP	24	1.2	1.0	1.3	1.2	−1.247	0.225	0.24
T1LV	CCI	14	2.6	2.1	2.7	2.2	−2.141	0.052	0.60
	CCP	24	0.9	0.8	1.0	1.0	−1.399	0.175	0.29

MRI=Magnetic Resonance Imaging. MS=multiple sclerosis. SD=Standard deviation. CCI=Confirmed cognitively impaired. CCP=Confirmed cognitively preserved. NBV=Normalized Whole Brain Volume. NVV=Normalized Lateral Ventricle Volume. NGV= Normalized Grey Matter Volume. NWV=Normalized White Matter Volume. T2LV=Total Hyperintense T2 FLAIR Lesion Volume. T1LV= Total Hypointense T1 Lesion Volume.

et al., 2001). This is further supported by findings suggesting that measures of atrophy are more strongly associated with and predictive of cognitive impairment than lesion volumes (Benedict et al., 2004). A more recent study, however, showed higher risk of obtaining an impaired score on the BICAMS in patients with high T1/T2 lesion load and lower brain parenchymal fraction, suggesting that both volume measures are reliable predictors of cognitive status (Uher et al., 2017).

Overall, the present study found a significant loss of both grey and white matter, as well as a significant increase of ventricle volume, resulting in atrophy of whole brain volume over the two-year follow-up period. Mean global brain atrophy rate in MS has been reported to be between −0.60% and −1.35% per year (Bermel and Bakshi, 2006) and a change of −0.40% per year is proposed as the cut-off for pathological brain atrophy in MS (De Stefano et al., 2016). In our sample the overall annualized rate of atrophy was −0.18% (data not shown), far lower than the pathological cut-off. Several points may explain this, including that the present patient sample was relatively young, newly diagnosed and with a low level of disability. Time from diagnosis to initiation, and type of disease modifying therapy (DMT) had probably also an effect, but these data were not available for the present study.

Interestingly, even though the results showed an overall statistically significant whole brain volume loss, the global atrophy rate was also lower than expected for the CCI subgroup (−0.25%). This implies that the accelerated atrophy accumulation in cognitively impaired patients may not be as pronounced in the earliest stages of the disease and challenges the previously reported relationship between early brain atrophy and cognitive function (Amato et al., 2004, 2007; Chiaravalloti and DeLuca, 2008; Deloire et al., 2011). However, a follow-up period of only two years may have been too short to discern significant difference in rate of decline in the CCI and CCP groups preserved (Uher et al., 2018). Another plausible explanation for the similar atrophy rate in spite of significant differences between the two groups, may be that the patients have different cerebral "starting points" prior to onset of MS, lending support to the cognitive and brain reserve theories (Sumowski

and Leavitt, 2013; Sumowski et al., 2013).

Although we found white matter volume loss to be significant for the whole sample, only the CCI subgroup showed significant white matter atrophy from baseline to follow-up, indicating that the overall white matter atrophy is mainly represented by this subgroup of patients. This implicates that white matter atrophy may contribute to separate cognitively impaired patients from patients with preserved cognitive function over time (Sacco et al., 2015).

A caveat of assessing white matter atrophy is discerning disease related true atrophy from *pseudoatrophy* due to a reduction in inflammation and oedema known to occur in the early stages of the disease after initiation of disease-modifying therapies (DMTs) (Rao et al., 2002) which may persist beyond the first year of treatment (Sastre-Garriga et al., 2015). The significant loss of white matter volume in the CCI group may be due to a larger degree of pseudoatrophy in response to initiation of DMT, but this was not investigated specifically in the present study. This was mainly because of the large variability in the use of DMTs, causing large discrepancies in group sizes and thereby significant loss of statistical power.

Our study has both strengths and weaknesses. Inclusion of a relatively young, newly diagnosed sample of patients who remained clinically stable at a low disability level throughout the study, is considered to be a main strength. Furthermore, all patients were assessed clinically and cognitively by the same neurologist (E.S.) at all time points.

In previous publications from this cohort, we found cognitive impairment amongst approximately 50% of the patients at baseline (i.e. abnormal result on at least one test) (Skorve et al., 2019). Furthermore, we found significant improvements in SDMT and CVLT-II raw score results from baseline to the one-year follow-up, which remained stable to the two-year follow-up (Skorve et al., 2020). This improvement was mainly found amongst patients classified as cognitively preserved (CP), but patients classified as cognitively impaired (CI) at baseline also showed significant improvement on subsequent testing. This points to a substantial practice effect despite the 12 months interval between cognitive evaluations chosen specifically to reduce this effect. Scharfen and collegues indicate that at least 16 months are required to eliminate the practice effects on tests of working memory capacity (Scharfen et al., 2018), while others have reported that the recommended testing interval varies between the cognitive domains (memory, spatial abilities and speed) (Ferrer et al., 2004). The implementation of alternate forms at each test session (AAA for SDMT, ABA for the CVLT-II and ABC for the BVMT-R), was aimed to strengthen the study by reducing the practice effect. However, the impact of different combinations of test stimuli for each session (AAA at baseline, and ABB and AAC at first and second follow-up, respectively) was not accounted for, and may be a limitation of the study design.

Another perceived weakness of the study is the use of stringent cut-off scores, which disregards the degree of impairment on a given test by classifying all levels of impairment into only two classes. However, this was addressed in a recent study showing that the majority of "at-risk" patients (i.e., patients with only one impaired test score) were reconfirmed as cognitively impaired when assessed by a more extensive neuropsychological test battery (Altieri et al., 2020). These results support that the "at least one abnormal score" definition for cognitive impairment measured by BICAMS (Dusankova et al., 2012) may still be relevant and acceptable for clinical practice.

Given that the atrophy rate is relatively low, a longer follow-up period is probably needed to detect pathological changes in more specific regional brain structures. Global volume measures are therefore recommended in studies with relatively short follow-up periods (Sastre-Garriga et al., 2020; van Munster and Uitdehaag, 2017). We therefore reported the lesion volumes as global measures of the total T2LV and T1LV, being aware that analyses of regional (i.e., juxtacortical, paraventricular and infratentorial) lesion volumes may have yielded different results, since lesion localization may have a large impact on clinical presentation of the disease, including cognition. Furthermore, we did not include measures of normal appearing white matter (NAWM), network connectivity or pathway disruption mechanisms which are shown to reflect white matter pathophysiology of importance to cognition (Rovaris et al., 2006).

The brain scans were normalized according to a reference brain adjusted for age and sex, thereby at least reducing the influence of normal ageing and sex differences on our results. No further adjustments were performed on the MRI data. We did not include a sample of healthy controls in our MRI analyses, but rather used the patients as their own controls yielding longitudinal results at both individual and group levels. The use of software providing automated analysis of MRI data is shown to reduce both intra- and interrater variability of the MRI measurements, and the Icometrix tool is increasingly used in the study of brain volumetrics and volume loss in MS (Beadnall et al., 2019; D'Hooghe et al., 2019; Fragoso et al., 2017). However, there are still significant differences in the results between the different software currently in use, making it challenging to directly compare results across different studies (Steenwijk et al., 2017; Storelli et al., 2018).

5. Conclusions

We found a strong association between cognitive impairment, as measured by longitudinal results on the BICAMS, and global MRI brain volume measures in young, newly diagnosed MS-patients. Despite being clinically stable and with a low EDSS score throughout the two-year follow-up, cognitive impairment was found by at least one subtest in approximately half of the sample at baseline. The changes in brain volumes shown in patients defined as impaired at both baseline and follow-up are potentially of great clinical importance and should indeed be investigated in future studies including a larger sample size.

Author declarations

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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.

Frank Riemer has no declarations relevant to the field of multiple sclerosis.

Renate Grüner has no declarations relevant to the field of multiple sclerosis.

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CRediT authorship contribution statement

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

analysis, Resources, Data curation, Writing – review & editing. **Renate Grüner:** Methodology, Formal analysis, Resources, Data curation, Writing – review & editing, Project administration. **Kjell-Morten Myhr:** Conceptualization, Methodology, Project administration, Writing – review & editing, Supervision, Funding acquisition.

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Supplementary materials

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