Cognitive assessment in the early stages of multiple sclerosis

- the importance of screening and management of cognitive impairment

Ellen Danielsen Skorve

Thesis for the degree of Philosophiae Doctor (PhD)
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Abbreviations

1.5T	1.5 Tesla
3T	3 Tesla
ADL	Activity of Daily Living
APC	Antigen-presenting cell
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BRB-N	Brief Repeatable Battery of Neuropsychological tests
BVMT-R	Brief Visuospatial Memory Test - Revised
CCI	Confirmed Cognitively Impaired / Confirmed Cognitive Impairment
CCP	Confirmed Cognitively Preserved / Confirmed Cognitive Preservation
CD20	Cluster of Differentiation 20
CD4+	Cluster of Differentiation 4 positive
CD52	Cluster of Differentiation 52
CD8+	Cluster of Differentiation 8 positive
CDP	Confirmed Disability Progression
CI	Cognitively impaired / Cognitive impairment
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CP	Cognitively Preserved / Cognitive Preservation
CSF	Cerebrospinal fluid
CVLT-II	California Verbal Learning Test, 2nd edition
DIS	Dissemination in space
DIT	Dissemination in time
DMT	Disease-Modifying Therapy
EBNA-1	Epstein-Barr virus Nuclear Antigen-1
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
FSMC	Fatigue Scale for Motor and Cognitive functions

GWAS	Genome-wide association studies
HADS	Hospital Anxiety and Depression Scale
HC	Healthy control
HEFT	High Efficacy Frontline Treatment
HSCT	Hematopoietic Stem Cell Therapy
ICD-10	International Classification of Disease, 10^{th} edition
MACFIMS	Minimal Assessment of Cognitive Function in MS
MLBG	Maximum Lifetime Brain Growth
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
n	Number (sample size)
ns	Non-significant
NAWM	Normal-appearing white matter
NBV	Normalised whole Brain Volume
NEDA	No Evidence of Disease Activity
NGV	Normalised Grey matter Volume
NVV	Normalised lateral Ventricle Volume
NWV	Normalised White matter Volume
OCB	Oligoclonal band
PMS	Progressive Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
QALYs	Quality Adjusted Life Years
RCT	Randomized, controlled trial
REK	Regional Ethics Committee (Regional Etisk Komité)
ROC	Receiver Operating Characteristics
RRMS	Relapsing-Remitting Multiple Sclerosis
S1P	Sphingosine-1-Phosphate
SD	Standard Deviation
SDMT	Symbols Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
T1LV	Total hypointense T1 Lesion Volume

T2LV	Total hyperintense T2 FLAIR Lesion Volume

Abstract in English

Background: Cognitive impairment (CI) is a common symptom in patients with multiple sclerosis (MS) with a potentially large impact on quality of life, employment, and social life. It may occur at any stage and with any subtype of the disease, yet it is often underreported and not routinely investigated. Early identification and treatment of CI therefore represent a considerable potential to reduce the individual and socioeconomic burden of the disease. Screening and monitoring of cognitive function in patients with MS should therefore be incorporated into everyday clinical practice. The Brief International Cognitive Assessment for Multiple Sclerosis (*BICAMS*) is a short and easily administered 15-minute test battery designed to evaluate cognitive function in patients with MS. The test battery consists of the oral version of the Symbols Digit Modalities Test (*SDMT*) and the learning trials included in both the California Verbal Learning Test 2nd edition (*CVLT-II*) and the Brief Visuospatial Memory Test Revised (*BVMT-R*).

Objectives: The main objective of the thesis was to investigate whether the Norwegian version of the BICAMS could be recommended in clinical practice as part of routine follow-up of patients with MS in an early stage of the disease. In a 2-year follow-up study, we used the BICAMS to investigate the prevalence and development of cognitive impairment in a cohort of newly diagnosed patients with relapsing-remitting MS (RRMS). By including brain volume measurements, derived from magnetic resonance imaging (MRI) examinations, we further explored associations between the BICAMS, cognitive impairment, and MRI findings.

Methods: A sample of newly diagnosed patients with RRMS (n=65) and healthy controls (HCs) (n=68) were assessed with the BICAMS test battery at baseline. A subset of randomly selected HCs (n=29) was retested after 1-4 weeks to establish reliability data. The RRMS patients were reassessed annually for two years, and 3 Tesla (3T) MRI scans were performed ±4 weeks of BICAMS evaluations at baseline and the follow-ups. All participants completed questionnaires about general health,

education, and employment status, including mental health screening (Hospital Anxiety and Depression Scale; HADS). The patients also reported on fatigue symptoms (Fatigue Scale for Motor and Cognitive Functions; FSMC).

Results:

I. BICAMS baseline study (*MS; n*=65/*HC; n*=68): We found statistically significant differences between the patients with MS and HCs on all three BICAMS subtests. After adjusting for education, MS patients still obtained significantly lower scores, but only on the CVLT-II and BVMT-R subtests. There were strong test-retest correlations for SDMT and BVMT-R ($r \geq 0.8$), and CVLT-II achieved an adequate value of $r=0.6$. Cognitive impairment, defined as a test score at least 1.5 standard deviations (SD) below the mean in the control group, was observed in 46% (n=30/65) of the MS patients at baseline, where 15% (n=10/65) had two or more impaired test scores. Altogether 31% ($p=0.003$) and 26% ($p=0.008$) of the patients had impaired scores on CVLT-II and BVMT-R, respectively, but the SDMT score was impaired in only 11% of the patients (*not statistically significant*).

II. BICAMS follow-up study (*MS: n*=58): Results on SDMT and CVLT-II demonstrated a statistically significant improvement from baseline to first follow-up, an improvement which remained stable until the end of the study. The BVMT-R remained overall stable, with initial deterioration in the first year followed by improvement to near baseline level at year two. Approximately 30% of the patients were longitudinally defined as cognitively impaired on at least one measure at both baseline and follow-up.

III. MRI-study (*MS; n*=49): We found strong correlations between the BICAMS subtests and the normalised whole brain volume (NBV) and grey matter volume (NGV) measures. Only performance on the CVLT-II was significantly correlated with T2 (T2LV) and T1 lesion volumes (T1LV) at both baseline and two-year follow-up. We also found a statistically significant loss of grey matter and white matter volume, as well as an increase in T1LV for the whole sample. The group of patients

longitudinally defined as “confirmed cognitively impaired” (CCI, i.e, impaired at both baseline and follow-up) and “preserved” (CCP, i.e., no impairment at any time point) also exhibited significant differences on all included MRI volume measures at both time points, except for the measure of white matter volume (NWV). Only the CCI subgroup showed statistically significant white matter atrophy and increase in T2LV.

Conclusions: Taken together, results from these three studies support that the Norwegian version of the BICAMS should be introduced as part of the clinical follow-up routine of patients with MS in clinical practice. The improvement in test scores from baseline to the first follow-up examination, indicates a practice effect that should be kept in mind when interpreting the results. There were 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. A strong role for white matter pathology was indicated by the clear differences between the confirmed cognitively impaired and preserved patients on measures of white matter atrophy and T2 lesion volume in early stages of the disease.

Abstract in Norwegian

Bakgrunn: Kognitiv svekkelse er et vanlig symptom hos pasienter med multippel sklerose (MS), med potentielt stor innvirkning på livskvalitet, yrkesdeltagelse og sosialt liv. Dette kan oppstå i alle stadier og alle subtyper av sykdommen, men er likevel ofte underrapportert og ikke rutinemessig undersøkt. Tidlig identifisering og behandling av kognitiv svekkelse representerer derfor et betydelig potensial for å redusere byrden av sykdommen for den enkelte pasient og den sosioøkonomiske effekten den har for samfunnet. Screening og overvåking av kognitiv funksjon hos MS-pasienter bør derfor inngå i klinisk praksis. Brief International Cognitive Assessment for MS (*BICAMS*) er et kort og lett administrert testbatteri som kan utføres på 15 minutter, utviklet for å evaluere kognitiv funksjon hos pasienter med MS. Testbatteriet består av den muntlige versjonen av Symbols Digit Modalities Test (*SDMT*) og læringsforsøkene som inngår i California Verbal Learning Test 2nd edition (*CVLT-II*) og Brief Visuospatial Memory Test Revised (*BVMT-R*).

Mål: Hovedmålet med studien var å undersøke om den norske versjonen av BICAMS kan anbefales i klinisk praksis som en del av rutinemessig oppfølging av MS-pasienter i en tidlig fase av sykdommen. Ved å bruke BICAMS i en toårig oppfølgingsstudie ønsket vi å undersøke forekomst og utvikling av kognitiv svekkelse i en kohort av nylig diagnostiserte pasienter med attakkpreget MS (relapsing-remitting MS; RRMS). Ved å inkludere hjernevolummålinger, avledet fra magnetisk resonans (MR)-undersøkelser, utforsket vi assosiasjoner mellom BICAMS, kognitiv svekkelse og MR-funn.

Metoder: Nylig diagnostiserte RRMS-pasienter (n=65) og friske kontroller (*HC*s) (n=68) ble undersøkt med BICAMS-testbatteriet ved baseline, og en gruppe tilfeldig utvalgte kontroller (n=29) ble testet på nytt etter 1-4 uker for reliabilitetssjekk. MS-pasientene ble testet årlig i to år og 3 Tesla (3T) MR-undersøkelse ble utført ±4 uker rundt BICAMS-undersøkelsene ved baseline og oppfølging. Alle deltakere fylte ut spørreskjemaer om generell helse, utdanning og yrkesdeltakelse, samt screening av

mental helse (Hospital Anxiety and Depression Scale; HADS). Pasientene rapporterte også om utmattelsessymptomer (Fatigue Scale for Motor and Cognitive Functions; FSMC).

Resultater:

I. BICAMS baseline-studien (*MS; n*=65/*HC; n*=68): Vi fant statistisk signifikante forskjeller mellom MS-pasientene og de friske kontrollene på alle tre subtester som inngår i BICAMS. Etter justering for utdanningsnivå hadde pasientgruppen fortsatt signifikant lavere score, men bare på CVLT-II og BVMT-R. Det var sterke test-retest-korrelasjoner for SDMT og BVMT-R ($r \geq 0.8$), og CVLT-II oppnådde en adekvat verdi på $r=0.6$. Kognitiv svekkelse, definert som en testscore lik eller svakere enn 1.5 standardavvik under gjennomsnittet i kontrollgruppen, ble påvist hos 46% (n=30/65) av pasientene ved baseline, hvorav 15% (n=10/65) hadde to eller flere svekkede testresultater. Til sammen 31% (p=0.003) og 26 % (p=0.008) hadde svekkede testresultater på henholdsvis CVLT-II og BVMT-R, mens SDMT var nedsatt hos bare 11% av pasientene (ikke statistisk signifikant).

II. BICAMS oppfølgingsstudien (*MS; n*=58): Resultatene på SDMT og CVLT-II viste en statistisk signifikant forbedring fra baseline til første oppfølging, en forbedring som forble stabil over to år. BVMT-R resultatene forble generelt stabile, med en initial forverring første året etterfulgt av forbedring til nært baselinenivå etter to år. Om lag 30% av pasientene var definert som kognitivt svekket på minst én av de tre testene både ved baseline og oppfølging etter to år.

III. MR-studien (*MS; n*=49): Vi fant sterke korrelasjoner mellom BICAMS-testene og normalisert helhjernevolum (*NBV*) og gråsubstansvolum (*NGV*). Kun prestasjoner på CVLT-II var statistisk signifikant korrelert med T2- (*T2LV*) og T1- (*T1LV*) lesjonsvolum ved både baseline og to års oppfølging. Vi ble også funnet et statistisk signifikant tap av grå og hvit substans, samt økning i T1 lesjonsvolum. Gruppen av pasienter longitudinelt definert som bekreftet kognitivt svekket (*CCI, dvs. svekket både ved baseline og oppfølging*) og bevarte (*CCP, dvs. ingen svekkelse på noe*

tidspunkt) fremviste statistisk signifikante forskjeller på alle MR-volummål ved begge tidspunkt, bortsett fra hvitsubstansvolum (*NWV*). Kun CCI-gruppen viste statistisk signifikant atrofi av hvitsubstans og økning i T2-lesjonsvolum.

Konklusjoner: Sett under ett, støtter alle tre studiene oppunder at den norske versjonen av BICAMS bør introduseres som en del av den kliniske oppfølgingsrutinen av MS-pasienter i klinisk praksis. Bedring av testresultatene fra baseline til første oppfølging tyder på en læringseffekt som må tas i betraktning ved tolkning av resultatene. Vi fant sterk korrelasjon mellom helhjerne- og gråsubstansvolum og BICAMS test-resultater, samt signifikante endringer i globale hjernevolummål fra baseline til oppfølging. I tillegg antydet resultatene en sterk betydning av hvitsubstanspatologi ved å vise tydelige forskjeller når det gjelder hvitsubstansatrofi og T2-lesjonsvolum mellom de pasienter med en vedvarende kognitiv svekkelse og de med bevart kognitiv funksjon i tidlig fase av sykdommen.

List of publications

I: Skorve E, Lundervold AJ, Torkildsen Ø, Myhr KM.
The Norwegian translation of the brief international cognitive assessment for multiple sclerosis (BICAMS).
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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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1. Introduction

1.1 Multiple Sclerosis (MS)

1.1.1 Epidemiology and burden of disease

Multiple sclerosis (MS) is a chronic immune-mediated disease characterized by demyelination and neurodegeneration in the central nervous system (CNS)[1] affecting more than 2.8 million people worldwide[2]. The overall prevalence has been steadily increasing[2-4] and in 2020 the global prevalence was 36 per 100.000 people, which is an absolute increase of 50% since 2013[2]. Norway has one of the highest prevalence rates of MS in the world, and as of May 2023, there were 255 per 100.000 people, giving almost 14.000 patients living with MS in Norway[5]. Earlier and more precise diagnosis combined with better disease-modifying therapies leading to longer life expectancy, as well as better understanding of the underlying causes and mechanisms of MS are all factors thought to be contributing to the epidemiological changes over the past few decades[6].

The geographical distribution of MS across the world is significantly correlated to latitude with increasing risk further away from equator in both the southern and northern hemispheres[7,8]. This effect is thought to be mediated through gradually lower levels of sun exposure in geographic areas further away from equator, leading to low levels of cutaneous vitamin D early in life[9], even before birth[10-12]. However, there are notable exceptions in Scandinavia, where no clear prevalence gradient has been found despite covering a broad latitudinal range[13]. The lack of a south-to-north gradient within Norway has been attributed to the customary diet rich in vitamin D in the northern regions and frequent outdoor activity[14-16], as well as the admixture of the indigenous Sami population who have a significantly lower prevalence of MS compared to other Norwegians[17,18].

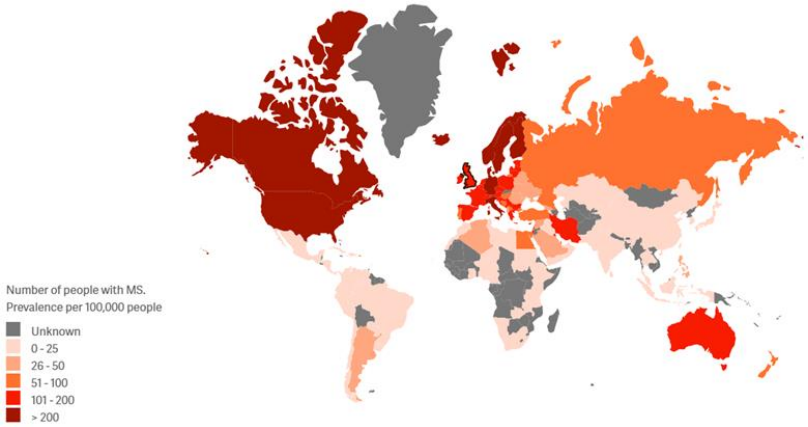

Figure 1. *Illustration of the prevalence of MS in different regions of the world reported per 100.000 people. There are 13.765 people in Norway living with MS (2.9 million people worldwide) as of May 2023. Reproduced with permission from The Multiple Sclerosis International Federation, Atlas of MS*[19]

MS most frequently manifests in early adulthood and is the leading cause of neurological disability in young adults[1]. The disease emerges at a vulnerable period of life when the patients are making decisions related to education, career, and family planning. It causes considerable individual and socioeconomic costs by contributing to loss of work capacity and early retirement due to disability[20]. Even though physical symptoms are the main reason for MS-patients leaving the workforce prematurely, a significant portion of the patients also experience cognitive impairment (CI) that hinders their ability to work[21,22]. Maintaining employment with MS is found to be positively associated with improved quality of life and positive coping strategies[23] and is therefore a treatment goal worth striving for.

1.1.2 Aetiology and pathogenesis

Well known risk factors for MS include childhood obesity[24-26], cigarette smoking[27-29], and low exposure to sunlight[30,31] (i.e., ultraviolet radiation) with subsequent low levels of vitamin D[16,32,33] which is demonstrated by the aforementioned global

latitude gradient. However, there is also a strong genetic basis for MS risk which explains the clustering of MS cases in families[34-36]. Genome-wide association studies (GWAS) have identified over 200 loci involved in MS susceptibility, including both the innate and adaptive immune system, which may explain almost 50% of the hereditability[37].

Historically, MS had been regarded as an organ-specific T-cell mediated disease but increasing evidence from the use and effectiveness of B-cell targeted therapies in later years have shifted this view[38,39]. MS is characterized by a diverse collection of neurological symptoms arising from demyelination, neurodegeneration, and lymphocyte infiltration in localized "plaques" throughout the CNS[40,41]. Neurodegeneration is present along with inflammation from the early stages of the disease[42,43], and has even been demonstrated up to six year prior to the first clinical event[44].

Myelin is an insulating sheath of protein and fatty substances which facilitates rapid nerve transmission and protects the axons from injury[45]. Microglia represent the innate immune cells in the CNS and can act as antigen-presenting cells (APCs) recruiting the adaptive immune cells (T- and B-lymphocytes) to the CNS[46]. Microglia can also act as macrophages – activated by invading immune cells – and contribute to demyelination through phagocytosis[46]. The loss and destabilization of myelin ultimately leads to irreversible axonal damage facilitated by several mechanisms, such as mitochondrial injury through oxidative stress[40,47].

The precise mechanism through which MS is initiated, whether neurodegeneration or inflammation comes first, is still under discussion[48-50]. However, a delayed primary infection with Epstein-Barr virus (EBV) is shown to be essential for the process to initiate[51-55]. EBV is a common lymphotropic human herpesvirus which infects 95% of the population and causes a latent infection to be established in memory B-cells[56]. Most EBV-infections are asymptomatic but may present as infectious mononucleosis in adolescents and young adults. A recent study demonstrated a more than 30-fold

increased risk of MS after adult onset EBV-infection[57,58]. In susceptible people, MS may then be triggered by molecular mimicry[59], promoting an uncontrolled immune response to EBV through pro-inflammatory antigen-presenting B-cells activating pathogenic CD4+ and CD8+ T-cells[60]. CD4+ T-cells specifically reactive to Epstein-Barr nuclear antigen-1 (EBNA-1) are clonally expanded in patients with MS and shown to cross-react with myelin antigens[61,62].

It is believed that an interplay of genetic and modifiable environmental factors determines a person's susceptibility for developing MS[63-66], but an initial infection with EBV is now considered essential[51-55].

1.1.3 Clinical symptoms and signs

Symptoms of MS are widespread and include motor, sensory and autonomic disturbances, as well as so-called "invisible" symptoms like fatigue, mood disorders and cognitive impairment[1]. Depending on the locus of demyelination, a variety of symptoms may occur in MS. Common presenting symptoms of MS include inflammation of the optic nerve (uni- or bilateral painful vision loss/blurring), spinal cord (loss of motor control in one or more of the extremities, altered sensory function, bladder and/or bowel dysfunction), brainstem/cerebellum (diplopia, vertigo, gait ataxia and/or loss of coordination, facial muscle weakness and/or numbness) and/or cerebral hemispheres (loss of motor and/or sensory function in opposite side of the body)[67]. Without therapy, most patients will eventually develop severe disability but there is considerable individual variation in symptomatology and course of the disease.

MS-related disability is usually clinically assessed by the Expanded Disability Status Scale (EDSS)[68], ranging from zero (no clinical symptoms and normal neurological examination) to ten (death by MS). Scores of <4.0 are mainly determined by clinical findings of impairment affecting the following seven neurological domains: *cerebral, visual, brainstem, sensory, motor, cerebellar, and bowel-/bladder functions*. From 4.0

to 6.5, ambulatory function is the major contributor, i.e., how far a patient can walk either unaided or with uni- or bilateral support. From 7.0 to 9.5 a patients' disability status is mainly determined by wheelchair dependence, self-care, and ability to maintain crude survival – eating and/or communicating.

1.1.4 Diagnostic criteria and clinical phenotypes

The McDonald criteria for the diagnosis of MS, most recently revised in 2017[69,70], relies on typical clinical, cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) findings, and is crudely based on multiplicity in time and space, i.e., more than one clinical incident in more than one location in the CNS (DIT = *dissemination in time*; DIS = *dissemination in space*). MRI is the most sensitive tool for detecting MS lesions in the CNS, and is also helpful for differential diagnostics[67] as MS is still considered a diagnosis of exclusion and other possible causes for the patients' presenting symptom therefore must be excluded. The *temporal criterion* is fulfilled when there is anamnestic and clinical evidence of more than one clinical attack, or simultaneous visualisation of enhancing and non-enhancing lesions on MRI, or appearance of new lesions compared to a previous scan. In case of first clinical event (clinically isolated syndrome, CIS), the presence of oligoclonal bands (OCBs) in the CSF serve as an indicator of previous disease as research have shown that CIS patients fulfilling the spatial criterion with CSF-specific OCBs have high risk of conversion to MS within the next few years[71-73]. The *spatial criterion* is fulfilled when there is anamnestic and clinical evidence of more than one attack implicating more than one location in the CNS, or visualisation of typical MS lesions, both symptomatic and asymptomatic, in two or more locations on MRI (periventricular, cortical, juxtacortical, infratentorial or spinal cord)[74,75].

MS is largely divided into two phenotypes, relapsing-remitting and progressive[76]. In 2013, the original MS-classification[77] was revised to include information about disease activity (i.e., new MRI lesions and/or clinical relapses) and progression (i.e., clinical worsening independent of relapse activity). This incorporated a timeline, or

temporal aspect in the clinical course description[78-80] (Figure 2). Most patients have a relapsing-remitting phenotype (RRMS) from onset (85-90%) characterized by episodes of clinical attacks, accompanied by focal inflammation in the CNS and macroscopic lesions visualized on MRI, followed by a stable phase of complete or near-complete remission. Patients who experience a gradual worsening over time without clear episodes or bursts of disease activity are defined as progressive MS (PMS) and when this phenotype is present from onset it is called primary progressive (PPMS). Without treatment most RRMS-patients will eventually convert to a secondary progressive phase (SPMS).

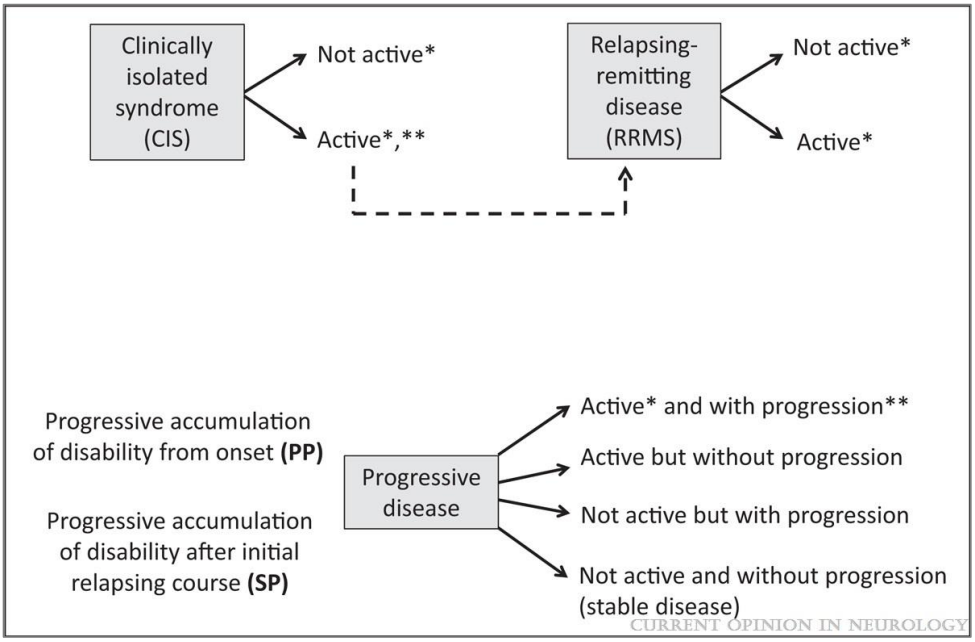

Figure 2. *The 2013 multiple sclerosis phenotype descriptions (adapted from Lublin et al.[76]). *Activity determined by clinical relapses or MRI activity. **CIS, if subsequently active and fulfilling current diagnosis criteria, becomes RRMS. **Progression measured by clinical evaluation of disability worsening independent of relapses during progressive phase (PPMS/SPMS) (Reprinted with permission from Oh et.al., 2018)[67]*

Women are more susceptible to MS than men with a 2-3 times increased risk, but men tend to have worse prognosis regarding relapse-recovery, brain atrophy,

cognitive impairment, and conversion to progressive phase[78-80]. Primary progressive phenotypes seem to be gender equal, and age of onset is also generally a decade later than for relapsing-remitting phenotype[80].

1.1.5 Treatment and prognosis

Due to increasingly effective disease-modifying treatments (DMTs), the overall prognosis of MS has changed dramatically[81]. In Norway, MS is estimated to give a loss of 32 undiscounted quality-adjusted life years (QALYs) compared to the normal, healthy population[82] and a longitudinal population-based study reported a median reduction in life expectancy of 7 years[83].

An emerging treatment target is "No Evidence of Disease Activity" (NEDA) which was originally composed of three parameters (NEDA-3): (1) no relapse, (2) no clinical progression, and (3) no new or enlarging lesions on MRI. However, these factors predominantly reflect the inflammatory processes of MS and not the neurodegenerative, so in recent years it has been proposed to add cerebral atrophy and/or cognitive function as a fourth dimension (NEDA-4)[84-86]. A recent meta-analysis found that NEDA-4 had two times higher odds for no long-term confirmed disability progression (CDP) at 1-2 years, however, there were no advantages over NEDA-3 as an outcome measure in clinical trials[87].

Disease-modifying treatments (DMTs) were introduced in the 1990s and have since become increasingly more effective[81,88,89]. The recently revised Norwegian recommendation is to start all newly diagnosed RRMS patients on high efficacy therapy unless there are medical contraindications, or the patient does not want such therapy[90]. The different DMTs target different sites of the MS pathogenesis – mainly through immune suppression. High efficacy DMTs include anti-CD20-antibodies (rituximab, ocrelizumab, ofatumumab), anti-CD52-antibodies (alemtuzumab), sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ponesimod, ozanimod), cladribine (deoxyadenosine analogue), and natalizumab (anti-α4-integrin

antibody). Moderately effective DMTs include dimethyl fumarate, diroximel fumarate, glatiramer acetate, teriflunomide, and interferon-beta.

Hematopoietic stem cell treatment (HSCT) is also shown to be highly effective, especially for RRMS patients with substantial breakthrough disease activity while receiving DMT. Studies on the safety and efficacy of HSCT show that more than 80% achieve NEDA-3 status within two years, and there is also a 30% increase in employment[91,92].

1.2 Cognitive impairment in MS

1.2.1 Epidemiology and clinical presentation

Cognitive impairment (CI) in MS has been known from the first descriptions of the disease by Charcot in the 19th century[93]. It affects up to 70% of patients and may present in all subtypes and all stages of the disease[94,95]. CI has been listed as one of the most important reasons for leaving the work force prematurely in addition to fatigue and physical disability in upper and lower extremities[22,96] - and is thus an important driving factor of unemployment in young patients with MS, representing a significant socioeconomic burden[21,22,96,97]. Loss of productive years can be substantial given that cognitive impairment has been shown to sometimes manifest before the physical symptoms of MS. Studies have demonstrated signs of CI in patients with clinically isolated syndrome (CIS)[98,99], even preceding clinical onset by up to two years[100]. In addition, cognitive impairment may interfere with social and recreational activities, driving, rehabilitation and treatment outcomes, as well as impacting caregiver strain[101].

Normal cognitive function is dependent on an efficient working of neural networks. CI in MS has been regarded as a consequence of neurodegeneration that over time reaches a threshold leading to *network collapse*[102] (Figure 3). Neural networks can also be disturbed temporarily by factors such as anxiety, depression, and fatigue,

which are shown to impede cognitive domains such as processing speed and executive functioning[103-106].

Cognitive function refers to a variety of mental processes that enable us to acquire, process, store and use information. These functions include learning and memory, reasoning, language and visuospatial skills, the ability to focus attention and stay vigilant[101], as well as executive function, which are crucial for controlling and coordinating other cognitive behaviours and abilities[107]. Processing speed, learning and different aspects of executive functions are most frequently reported as impaired in studies of patients with MS[108-110]. Typically, CI in MS manifests as requiring more time to identify, learn, and retrieve information, as well as solving tasks where focused attention and tempo in task-execution are needed. Severe global decline (i.e., dementia), however, is rare[110].

Several studies have observed a disconnect between the disease burden of MS and clinical disability – also known as a clinico-radiological paradox[111,112] – where there is no consistent association between the extent and development of the lesions visualized on MRI and the clinical and/or cognitive status of the patient. This is clearly demonstrated by the presence of CI in the preclinical phase of MS[98-100]. The *reserve hypothesis*[113,114] has been used to try to explain this paradox. It states that larger brain growth in childhood (*brain reserve*) and higher intellectual enrichment (*cognitive reserve*) in early adulthood promotes a more resilient brain through larger synaptic volume and more complex and efficient neuronal networks. Maximum lifetime brain growth (MLBG) is defined by hereditary factors, but intellectual enrichment is largely a modifiable factor that can be targeted for preventive purposes[112,115]. This hypothesis is supported by studies showing that higher degree of education, intellectual vocation, and participation in cognitively stimulating pastime activities, reduce the risk of dementia[116,117]. Further support of the reserve hypothesis was found in a recent, large genome-wide association study (GWAS). They found strong association between higher education was associated and lesser long-term

disease severity after adjusting for socioeconomic factors (i.e., smoking, income), implicating a potential biological effect of intellectual enrichment[118].

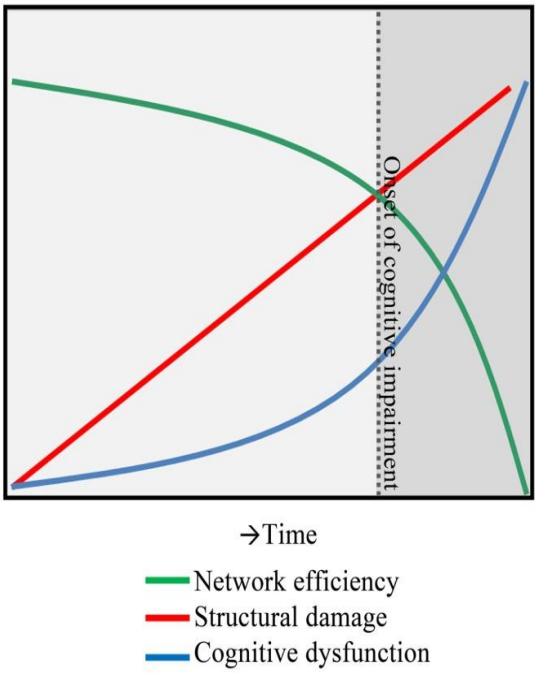

***Figure 3. A hypothesis of network collapse as a cause for developing cognitive impairment in MS**. In early stages of MS, structural damage is low, leaving network efficiency relatively high. As the structural damage accumulates over time, network efficiency levels drop, inducing a network collapse after a critical threshold (indicated by the dotted line) is exceeded. After this, the network is unable to function normally, and cognitive impairment develops. Reprinted with permission (CC BY licence) from Schoonheim et.al, 2015[102]*

1.2.2 Neuropsychological assessment

Reduced information processing speed is reported to be an early sign of CI in patients with MS[119,120], and, together with memory impairment, it constitutes the most prevalent cognitive deficit in MS[94,109,121]. Psychometrically valid measures of these two functions are included in neuropsychological test batteries such as the Brief Repeatable Battery of Neuropsychological tests (BRB-N[95]) and the Minimal Assessment of Cognitive Functions in MS (MACFIMS[122,123]). Given the high prevalence of CI in patients with MS, neuropsychological assessment is recommended. However, time-restrictions may rule out the possibility to prioritize a full neuropsychological examination in an out-patient setting. In addition, these test

batteries require neuropsychologists – commonly not available at the ward – to run, interpret and convey the results to the patients, relatives, and health professionals.

In 2018, recommendations for screening and management of cognitive impairment in MS were proposed[124], including early baseline screening when the patient is clinically stable and subsequent annual reassessments with the same instrument. This will contribute to detection of newly emerging CI, acute disease activity or progression in CI, as well as to assess treatment efficacy. However, adequate access to screening is essential, and implementing such procedures in routine follow-up from the early stages of MS will therefore be very useful in achieving this goal.

1.2.2.1 The Brief International Cognitive Assessment for MS (BICAMS)

The BICAMS was developed in 2011 by a panel of experts in the field of neuropsychology and MS to meet the need for a short and easily administered clinical tool for monitoring cognitive impairment in MS in everyday clinical practice[125]. This test battery comprises the Symbols Digit Modalities Test (SDMT)[126], and the learning trials of the second edition of the California Verbal Learning Test (CVLT-II)[127,128] and the revised Brief Visuospatial Memory Test (BVMT-R)[129]. These tests were included based on an evaluation of psychometric qualities (reliability, validity, and sensitivity) as well as international applicability and feasibility[125], and cover measures of information processing speed, verbal and visual short-term memory, respectively[94,109,110]. Only the learning trials of the CVLT-II and the BVMT-R are included in the BICAMS as immediate recall has been reported as the most sensitive test component in relation to memory deficits in patients with MS[123,130,131]. The remaining subtests (delayed recall, recognition and forced recognition) are therefore not administered, and this contributes to significantly reducing the time spent on testing. BICAMS can thus be completed in 15 minutes and does not require specialized equipment or extensive training.

An international standard for validation was subsequently published[132] and the BICAMS has since been translated and validated in several countries[133,134]. It has been shown to be a reliable and valid test battery for emerging cognitive impairment in MS and has performed well in comparison to other, more comprehensive neuropsychological test batteries in use today[135-137].

The BICAMS is also shown to be a good predictor of employment[136,138-140] and studies implementing the BICAMS as a tool for prediction of performance in activities of daily living (ADL) have found that patients performed significantly worse than healthy controls on both the BICAMS subtests and on everyday tasks, and, conversely, better performance on the BICAMS were positively correlated with independence in ADL[141].

1.2.3 Treatment strategies and prognosis

There are 16 DMTs currently available in Norway today, all with documented effect on relapse rate and progression. However, benefits of DMT on cognition has been reported as small to moderate[142]. Aerobic exercise is widely used in physical rehabilitation and is recommended for maintenance of physical health in MS[143]. As a desirable side effect, it has been found to increase hippocampal volume and connectivity, improving memory function in patients with MS[144]. Along with studies showing that low levels of serum vitamin D and smoking after clinical onset are associated with worse long-term cognitive function[145], these studies show that lifestyle modifications may be beneficial for improving or maintaining cognitive function in patients with MS. Exercise, healthy food, and avoidance of vices like smoking and excessive use of alcohol, as well as participation in cognitively stimulating pastime activities may also help promote cognitive reserve and protect against disease-related cognitive decline[112,115].

Cognitive rehabilitation in MS has amassed a large body of evidence over the last decade. The goals of neuropsychological rehabilitation is to reduce cognitive deficits,

but also to reduce the impact of cognitive impairment by helping the patients to understand and accommodate their disability in daily living through psychoeducation and counselling regarding factors which may affect day-to-day function (i.e., mood, fatigue, sleep, pain, medications etc.) and by learning compensatory strategies[101].

Effective rehabilitation strategies include retrieval practice[146], and the self-generation learning program (self-GEN)[147] either alone or in combination with other techniques like Spaced Learning[148]. There is also compelling evidence for using music mnemonics as a memory aid[149,150] and computerized software (RehaCOM)[151], alone or in combination with physical rehabilitation[152]. Nonetheless, there is only one treatment strategy which can be classified as a *practice standard*, the modified Story Memory Technique (mSMT). This treatment is administered over 10 sessions using imagery and context to improve verbal learning and memory[153,154] and was recently found effective also in patients with progressive MS[155], with effects lasting at least three months.

Overall, there is high-quality evidence for improvement of CI by cognitive training and rehabilitation[156-158], but heterogeneity regarding methods and reporting bias reduces the comparability of the studies. Larger-scale, longitudinal, multi-center RCTs using more sensitive and standardized cognitive outcome measures over a longer follow-up time are indeed needed to strengthen the evidence.

Cognitive impairment (CI) in the early stages of MS has been found to predict disability progression and conversion to secondary progressive phase. Patients with CI were found to physically decline three times faster than cognitively preserved (CP) patients and enter a progressive phase twice as fast[159]. CI is also known to progress over time[160], but the assumption of a linear, inevitable decline is contested by recent research reporting a more fluid and fluctuating functional pattern throughout the course of the disease, especially in the earliest stages[161] Furthermore, the lower-than-expected rate of decline in the first half-decade of the disease indicates a therapeutic

window where intervention may be beneficial to slow down the decline and help obtain optimal cognitive function[99].

1.3 MRI and cognition

Cognitive impairment is largely associated with neurodegeneration and loss of parenchymal brain volume, and CI in the early stages have been shown to be more dependent on brain volume loss than lesion load[162,163]. However, studies have also shown that patients with higher lesion load and lower brain parenchymal fraction demonstrates a higher risk of obtaining abnormal scores on cognitive tests[164], indicating that the predictive ability of lesion load should not be discounted.

Both white and grey matter atrophy are central in MS pathology, but an important caveat when interpreting white matter atrophy is distinguishing disease-related atrophy from *pseudo atrophy* - a reduction of tissue volume due to the receding inflammation and oedema known to occur in the early phase after initiation of DMT[165,166]. Mean global atrophy rate has been proposed to be pathological if it exceeds -0.4% per year[167] and there is an assumption of accelerated atrophy accumulation in patients with CI in the early stages of MS[168-170]. However, given this relatively low rate of annual brain volume loss, longer follow-up periods are needed to detect any meaningful pathological changes, especially in smaller regions of the brain, such as deep grey matter structures like the thalamus and hippocampus[171]. Therefore, a consensus report has recommended that global, rather than regional, volume measures should be used when assessing associations between clinical and radiological outcomes in MS[172].

Grey matter atrophy and widespread tissue damage may arise either directly through localized inflammation or indirectly through interrupted pathways in normal-appearing white matter (NAWM), leading to a “disconnection syndrome” or disruption in functional networks in the brain[173]. Together with widespread cortical

thinning and cortical lesions, these changes are shown to be strong predictors of cognitive impairment[174-176]. Unfortunately, conventional MRI machines with 1.5T field strength, which are most widely used, do not readily allow for clear visualization of cortical lesions. A recent study validating the latest in MRI visualization techniques (both 1.5T and 3T) against histopathologically confirmed cortical lesions, achieved a less than 25% detection rate[177]. Therefore, these lesions are largely underdiagnosed, which may be a possible explanation for the aforementioned cognitive clinico-radiological paradox[111,178]. On the other hand, evidence of cortical reorganization in the early stages of MS suggests that some degree of brain plasticity and cognitive reserve may contribute to the maintenance of a normal level of cognitive function and limit the cognitive deficits despite widespread tissue damage[113,114,173,179].

The notion of functional network disruption[102,180] is increasingly used to address the pathophysiology of CI by implementing graph theory[181]. This generates computerized models of the brain and its functional networks and connections through hubs, pathways, and hierarchical organization. Deficits in global transmission and integration of information is then associated with clinical and structural correlates of MS-related CI[102,182,183]. A large multicentre functional MRI (fMRI) study investigating functional networks in relation to cognition[180] found significant differences between cognitively preserved (CP) and CI patients in terms of centrality (i.e., number of functional connections between each grey matter voxel and the rest of the brain) of primary sensory-motor networks and resting state default mode networks (i.e., specific brain systems activated at passive rest, when engaged in internally focused tasks, mind-wandering, and thinking about oneself or others, etc.[184]). Other fMRI evaluating the efficacy of neuropsychological rehabilitation and exercise, has found increased connectivity and volume in regions involved in memory functions[144,185,186], thus making fMRI studies useful also in monitoring effects of cognitive rehabilitation. However, these examinations are not as readily available as conventional MRI techniques where global and regional atrophy, as well as lesion

assessment, are commonly used as proxies for MS-related physical and cognitive disability[172].

2 Study rationale and objectives

The high prevalence rate and socioeconomic burden of the disease, along with the evidence of early, and even preclinical, cognitive symptoms, highlight the need for a standardized tool for early screening of cognitive function in patients with MS. The Brief International Cognitive Assessment for MS (BICAMS) is meant to be such a tool, used to identify and monitor MS patients with potential CI. This study investigated the feasibility of using the BICAMS in routine follow-up of Norwegian MS patients, from the early phase of the disease.

2.1 Paper I: The Norwegian translation of the brief international cognitive assessment for multiple sclerosis (BICAMS).

The main objectives for paper I was to investigate the Norwegian translation of the BICAMS using the proposed international "validation protocol"[132], and to assess the prevalence of cognitive impairment in the early stages of MS using a sample of healthy controls and newly diagnosed patients with RRMS (≤5 years of disease activity) in a cross-sectional baseline study.

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

The aims of paper II was to evaluate cognitive performance in the early stages of MS and to investigate trajectories of change in cognitive function by annual assessments with the BICAMS for two years, and by this assess feasability of implementing yearly cognitive evaluations in clinical practice.

2.3 Paper III: Brief international cognitive assessment for MS (BICAMS) and global brain volumes in early stages of MS - A longitudinal correlation study.

Paper III was an extension of paper II, including brain volume measures derived from concurrent MRI examinations analysed by the automated Icometrix 'icobrain ms' tool. The main objectives were to investigate associations between cognitive function and global brain volumes at baseline and after two years follow-up, and to evaluate the changes in brain volumes in relation to changes in cognitive function.

3 Methods and materials

3.1 Study design

This thesis is based on observational, quantitative research with both a cross-sectional and a prospective longitudinal design. The patients received standard treatment and care and underwent cognitive testing not widely accessible in everyday clinical practice. Papers I-III were based on different study designs and are therefore described separately below.

3.1.1 Paper I

Paper I was based on a case-control, cross-sectional design where a group of recently diagnosed patients with RRMS and a group of healthy controls (HCs) were compared on cognitive measures assessed with the BICAMS test battery. A subset of randomly chosen HCs were subsequently retested within 4 weeks to establish test-retest data. The study was performed in accordance with the proposed "validation protocol"[132] and patients and controls were matched by age, gender and education.

3.1.2 *Paper II*

Paper II was based on a prospective longitudinal design investigating the prevalence of cognitive impairment and changes in cognitive performance assessed by the BICAMS in recently diagnosed patients with RRMS over a 2-year follow-up period.

3.1.3 *Paper III*

Paper III was based on both a cross-sectional and a prospective longitudinal design. Performances on the BICAMS subtests were correlated with global brain volume measures at baseline and at the 2-year follow-up. The presence of cognitive impairment at the two time points were compared, and the change in both cognitive function and brain volumes over the 2-year follow-up period were evaluated for the whole sample and for subgroups defined as cognitively impaired and preserved, respectively.

3.2 Study population

3.2.1 *Patients*

For this study we established a patient cohort of recently diagnosed patients with MS. Patient selection started in November 2015, and the inclusion phase lasted from September 2016 until September 2017.

3.2.1.1 Inclusion criteria

The inclusion criteria for the study were: 1) Age 18-65; 2) Definite MS- or CIS-diagnosis (2010 McDonald revision)[70] 3) Attending follow-up at Haukeland University Hospital; 4) Year of diagnosis 2014-2017. 5) Clinical disease onset no more than three years prior to diagnosis.

3.2.1.2 Exclusion criteria

The exclusion criteria for the study were: 1) Clinical disease onset more than three years prior to diagnosis. 2) Physical conditions that could interfere with the implementation of tests (i.e., substantial visual or hearing impairment, severe weakness of upper limb, dysarthria and/or aphasia). 3) Comorbidity, including other brain diseases and psychiatric conditions that could preclude participation.

3.2.1.3 Establishing a cohort: selection and recruitment

The patient cohort was established by screening the hospital patient registry for "first time diagnosis" G35 Multiple Sclerosis (ICD-10) from January 1st, 2014, to August 31st, 2017 (n=272). The lists of patients were manually checked against the patients' hospital records and pre-screened for eligibility. The patients who fit the inclusion criteria but were diagnosed with MS as part of a second opinion evaluation, were pre-excluded as they belonged to other health care regions and were not available for routine follow-up locally. The patients who were a preliminary match to the inclusion criteria were sent an invitation letter by mail (n=158), including information about the study. All patients who replied (n=97) were then interviewed over the telephone for final inclusion or exclusion. Graphic rendering of patient inclusion and selection to cohort and publications is shown in Figure 4. The total number of patients at

baseline was 73 (PPMS=2, CIS=5, RRMS=66), but given the large discrepancy in group sizes, the PPMS patients were later excluded from statistical analyses. The CIS-patients were retained in the cohort despite the low number due to the potential for conversion to RRMS but were excluded from statistical analyses as long as the CIS diagnosis remained valid. One patient with RRMS was excluded from the cohort due to completely normalised MRI and clinical findings within the first year of follow-up (i.e., uncertain diagnosis). Thus, a total of 70 patients were included in the cohort for this thesis (RRMS=65, CIS=5) at baseline. During first year of follow-up one CIS patient experienced new clinical symptoms and two CIS patients were reclassified as RRMS due to revisions of the diagnostic criteria in 2017. Therefore the follow-up cohort comprised of 68 patients with RRMS and 2 patients with CIS.

3.2.2 *Controls*

According to recommendations for validation of the BICAMS test battery, a sample size of at least 65 healthy controls should provide enough power for correlation with MS patients[132]. The healthy controls were matched to the patient sample on age, gender, and education.

3.2.2.1 Recruitment and selection

Healthy controls (HCs) between 18 and 65 years of age were asked to participate, recruited by local announcement (posters in the hospital campus buildings) and assessed at the Neuropsychological out-patient clinic at the University of Bergen. None of the participants reported substance abuse or present/previous physical, neurological, or psychiatric illness that could impede cognition or interfere with implementation of the tests. All participants who volunteered (n=61) were tested at baseline, but three participants were subsequently excluded due to non-fluency in Norwegian (German, Senegalese, and Lithuanian, respectively). The remaining 58 HCs were included, but preliminary analyses revealed there was a mismatch with the patient group regarding education (significantly more patients within the lower

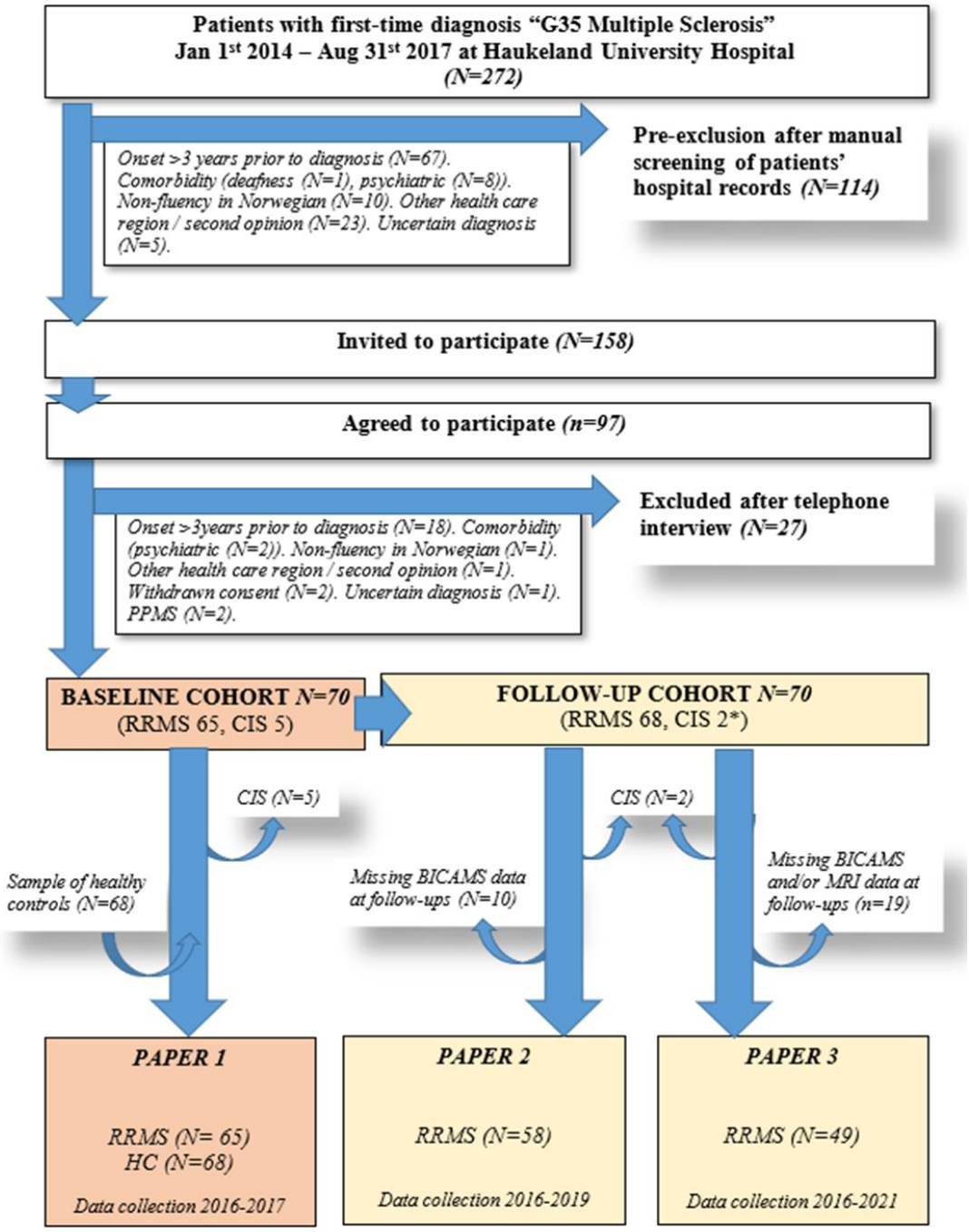

Figure 4. *Graphic rendering of patient selection <to cohort and publication. * 1 CIS patient had clinical progression to RRMS during first year of follow-up and 2 CIS patients were retroactively reclassified as RRMS due to the 2017 revisions to the McDonald criteria.*

brackets of education than in the control group). Therefore, an additional 10 participants with education levels <13 years (high school equivalent) were added to adjust the discrepancy. From the included sample of HCs (n=68), a subset of randomly selected participants was retested within 4 weeks of baseline (n=29) to establish test-retest (reliability) data, aiming for Pearson correlation coefficients of ≥0.7[132].

3.3 Ethics

3.3.1 Ethical approval and consent

The study was approved by the Regional Ethics Committee of Western Norway in February 2016 (registration number 2016/31/REK Vest) and participation was based on written informed consent for both patients and healthy controls.
The sample of healthy controls (HCs) was originally not included in the ethics application and was therefore approved as an addendum to the original approval in May 2016.
Specifically for paper III we had to obtain additional consent from the patients to export MRI data out of the country for automated analyses by Icometrix ® in Leuven, Belgium. This was obtained by passive consent (i.e., the patients were given written information and the opportunity to object). This mode of consent acquisition was approved by REK Vest as an addendum in August 2018.

3.3.2 Compensation and incentives

The HCs were compensated with validated parking and two cinema tickets per testing (i.e., the randomly selected retested controls received four cinema tickets in total). The MS patients did not receive any incentive to participate other than follow-up appointments at the neurology department's out-patient clinic free of charge for the duration of the study (every six months, in total 5 appointments).

3.4 Procedures and data collection

Demographic and clinical data, including screening for mood disorders and fatigue were collected at each test session. Cognitive assessment was performed at baseline (HC and MS) and after 12 and 24 months (MS), and all patients were offered a 3T MRI evaluation in relation to the BICAMS test sessions (±4 weeks).

3.4.1 Demographic data

All participants were asked to complete a questionnaire on general health, education, and employment prior to all BICAMS test sessions. Age, gender, years of education and employment status were registered.

3.4.2 Clinical data (MS patients only)

For the purpose of inclusion, the following clinical parameters pertaining to the diagnosis were collected prior to testing: disease duration (month and year of onset, and month and year of diagnosis), presenting symptom, presence of oligoclonal bands in the cerebrospinal fluid and MRI findings at time of diagnosis.

3.4.3 Neurological assessments

All patients were examined with a complete neurological exam, including scoring with the EDSS[68] at baseline and every six months for 2 years (5 evaluations in total).

3.4.4 Mood disorders

All participants were requested to complete the Hospital Anxiety and Depression Scale (HADS)[187] prior to BICAMS testing. This is a 14-item self-report questionnaire, widely used for screening of anxiety and depression in patients with chronic illness, which is validated for use in MS populations[188]. Clinically meaningful anxiety and depression are shown to have some modulatory effect on cognition, and concurrent assessment of mood disorders are therefore recommended[104-106]. Traditionally, the cut-off scores for the HADS-Anxiety and HADS-Depression subscales are set at ≥8 for clinically meaningful anxiety or depression, respectively. Studies have shown increased specificity and positive predictive value when

increasing the cut-off scores to ≥11 in the MS population[189], but for the purpose of this study the traditional cut-off was used as the optimal balance between sensitivity and specificity in most studies were met with a score of 8 or more on both HADS-A and –D[190]. Patients and HCs with abnormal scores on the HADS were advised to contact their family doctor/GP for further evaluation and treatment.

3.4.5 Fatigue

Fatigue is a highly prevalent symptom in patients with MS (up to 80%)[191] and is known to affect cognitive performance[103,192]. To assess the extent of fatigue in our sample, all patients were therefore asked to complete the Fatigue Scale for Motor and Cognitive Function (FSMC)[193] prior to testing. The FSMC questionnaire comprises 20 questions related to cognitive and motor fatigue which are highly sensitive to MS-related symptoms. The combined score of ≥43 was used as the cut-off for MS-related fatigue (≥22 for either subscale). The most common confounding factor to the FSMC is depression which may be controlled for by the simultaneous use of HADS[193].

3.5 Cognitive assessment

3.5.1 Brief International Cognitive Assessment for MS (BICAMS)

Cognitive assessment was performed using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)[125,132]. This test battery comprises the oral version of the Symbols Digit Modalities Test (SDMT)[126,194], the learning trials from the California Verbal Learning Test 2nd edition (CVLT-II)[127,128] and the learning trials from the Brief Visuospatial Memory Test Revised (BVMT-R)[129]. It is completed in 15 minutes, included allotted time for instructions, and no special training or equipment is needed other than a pencil, an eraser, and a stopwatch.

3.5.1.1 BICAMS "validation protocol" recommendations[132]

I. Test stimuli should be standardized for language and culture.

II. Examiners instructions should be standardized and translated to the language in question, including information from manuals necessary for administration and interpretation.

III. A selection of at least 65 healthy controls should be tested for normative information matched to patient population by age, gender, and education.

IV. Test-retest-reliability is examined by retesting a small sample of the healthy controls 1-3 weeks after baseline.

V. Validity is established by comparing the healthy controls against the MS-patients.

3.5.1.2 Symbols Digit Modalities Test – Information processing speed

An A4 sheet of paper with rows of nine abstract symbols arranged randomly is presented to the subject. A cipher key linking each of these symbols to a single digit (1-9) is located at the top of the page. After a short, written practice session on the first 10 symbols, the test subject must voice the digit corresponding to each symbol as rapidly as possible for 90 seconds. The outcome measure is the number of correctly identified symbols in the 90-second timeframe. The same version of SDMT was presented in the test and retest sessions.

3.5.1.3 California Verbal Learning Test 2nd ed. – Verbal short-term memory

The examiner reads aloud a list of 16 words which are semantically divided into 4 categories, and the test subject is then asked to repeat as many words as possible in no particular order. This is documented by the examiner and the list is repeated four more times. The outcome measure is the number of correct words remembered across the five trials. For the first retest session in the present study, the 16 words from the interference list ("List B") of the standard format of CVLT-II were used. The word list ("List A") from the baseline session was then reintroduced as part of the second follow-up session after two years.

3.5.1.4 Brief Visuospatial Memory Test Revised – Visual short-term memory

A stimulus sheet with six abstract figures arranged 2x3 are presented for 10 seconds, before it is hidden from view. The subject is then asked to draw these figures

correctly and in the same spatial arrangement at it was presented. The score is based on accuracy and location (0-2 points per figure). The stimulus is presented in total three times and the outcome measure is the total number of points across the three trials. For the BVMT-R, we used Forms 1, 2 and 3 at the different test sessions, respectively (for the healthy controls Forms 1 and 2 was used for the test and retest sessions, respectively).

3.5.2 Definition of cognitive impairment and preservation

Cut-off values were calculated for each subtest (≤1.5 standard deviations below the mean score of the control group), and patients were defined as either "cognitively impaired" (CI) or "cognitively preserved" (CP) based on the occurrence of abnormal test scores on at least one subtest[195]. Patients who were classified as cognitively impaired at both baseline and follow-up were termed "confirmed cognitively impaired" (CCI). Conversely, patients were classified as "confirmed cognitively preserved" (CCP) when classified as CP at all time points.

3.6 Magnetic Resonance Imaging (MRI)

All patients were offered MRI examinations conducted on a 3T Magnetom Prisma MR scanner (Siemens Healthcare, Germany), with a specialized protocol (see Table 1) within 4 weeks of BICAMS testing (69, 66 and 60 patients at baseline, 1- and 2-year follow-up, respectively). Reasons for not performing the MRI were mainly that the appointed time did not suit the patient and could not be rescheduled, or in case of pregnancy. If MRI scans at any point revealed probable disease activity (new T2- or enlarging T1-lesions and/or contrast enhancement) the patient was contacted, and the current treatment was reassessed and usually escalated.

3.6.1 Icometrix ®

As part of the study, MRI data material was exported to Icometrix in Leuven, Belgium for supervised digital analysis yielding cross-sectional brain and lesion volumes, and longitudinal atrophy measures by using the Icobrain MS tool (MSMetrix version 4.3.3)[196-199]. The brain volume measurements were normalized for

intracranial volume[200] and corrected for age and gender. Due to technical challenges, we were only able to retrieve 49 linked sets of BICAMS- and MRI data from both baseline and the two-year follow-up. Data from the one-year follow-up was not included as we wanted longest possible follow-up time. A total of 297 measures of volume and volume change (atrophy) were calculated per scan (891 per patient). For this thesis the following measures were extracted per time point; Normalised whole brain volume (NBV), normalised grey matter volume (NGV), normalised white matter volume (NWV), normalised lateral ventricle volume (NVV), total hypointense T1 lesion volume (T1LV), total hyperintense T2 FLAIR lesion volume (T2LV).

	Anatomical T1-weighted volumes	**T2-FLAIR volumes**	**T2 volumes**
	MPRAGE 3D T1-weighted sagittal volume	*SPACE 3D T2-weighted sagittal volume*	*2D TSE T2-weighted axial volume*
TE/TR/TI	2.28 ms/1.8 s/900 ms	386 ms/5 s/1600 ms	100 ms/6000 ms/-
Acquisition matrix	256 × 256 × 192	256 × 256 × 192	512 × 512 × 112
Field of view (FOV)	256 × 256 mm^2	256 × 256 mm^2	220 × 220 mm^2
Slice thickness	1 mm	1 mm	4 mm
Readout bandwith	200 Hz/px	751 Hz/px	723 Hz/px
Total acquisition duration	7.40 min	6.17 min	2.10 min

Table 1. *Detailed MRI acquisition protocol*

3.7 Statistical analyses

Statistical analyses were performed using SPSS version 24 (papers I and II) and version 26 (paper III) (IBM Corp., Armonk, NY), and figures were made using StataSE version 15 (paper I) and version 16 (paper II) (StataCorp LLC, College Station, Texas). Statistical significance was set at alpha level <0.05.

Effect sizes were calculated and defined according to Cohen's *d* statistic (and according to Hedges *g* where applicable, to account for small and unequal sample sizes) (0.2=small, 0.5=medium, 0.8=large). Pearson's correlation coefficients were

considered strong when $r \geq \pm 0.5$, moderate when $r = \pm 0.30$ - ± 0.49, and weak when $r \leq \pm 0.29$. Cross-sectional between-group differences were examined with independent samples student's *t* test and McNemar test for continuous and categorical dichotomous variables, respectively. Longitudinal within-group differences were examined with student's paired samples *t* test and McNemar test for continuous and categorical dichotomous variables, respectively. A stepwise linear regression was performed to assess if BICAMS performance predicted self-reported employment status at baseline. Age, gender, education level, EDSS, disease duration and HADS-scores were entered as predictors in the first step and the BICAMS-scores in the second step.

Missing values were analysed by multiple imputation and pattern analysis. Overall missing values were 0.8% (9/1096) and 1.1% (9/807) for the baseline MS cohort and healthy controls, respectively (paper I). For paper II there were 1.8% (51/2733) missing values, and for paper III there were no missing values. There were no missing BICAMS data for either paper as patient samples were selected based on 100% completeness of BICAMS and/or MRI data.

4 Summary of results

4.1 Paper I: The Norwegian translation of the brief international cognitive assessment for multiple sclerosis (BICAMS).

In paper I, we reported on the psychometric properties of the BICAMS in a healthy control (HC) sample (n=68) and results from the baseline assessment in a sample of newly diagnosed patients with RRMS (n=65).

There were strong test-retest correlations for all three subtests. SDMT and BVMT-R both obtained r-values ≥0.8, and CVLT-II achieved an r=0.6. There was a significant improvement on the SDMT-scores (d=0.44) from baseline to retest, but there was no significant correlation between the improvement in test scores and the time interval between test sessions.

All BICAMS raw scores were significantly lower in the MS group compared to the HCs, but when adjusting for the differences in level of education and anxiety scores, the SDMT-scores were no longer significantly different in the two groups.

Cut-off scores for each of the subtests were calculated and applied throughout the study (score ≤1.5 SD below the mean in the control group) – SDMT 43 points, CVLT-II 49 points, and BVMT-R 23 points. Cognitive impairment (CI), i.e., ≥1 impaired test score[195], was found in almost 50% of the patients and 20% of the HCs. Two or more impaired test scores were found in 15% of the patients and 4% of the HCs, whereas three impaired test scores were found in 6% and 3% of the MS and control groups, respectively (*ns*).

Two thirds (n=21/30) of the impaired MS patients had only one abnormal test score and the majority were impaired on the CVLT-II (n=12/21), followed by the BVMT-R (n=8/21) and the SDMT (n=1/21). Overall, the SDMT identified only 11% of the MS sample as impaired, and the BVMT-R and CVLT-II identified 26% and 31%,

respectively. Corresponding results from the HCs were 8% (*ns*), 9%, and 10% for the SDMT, BVMT-R, and CVLT-II, respectively.

Although mean scores on the anxiety subscale were significantly higher in the MS group, the proportion of clinically meaningful anxiety was not significantly higher in patients with MS compared to the healthy controls. The depression subscale showed similar levels in both groups, and the proportions of clinically meaningful depression were not significantly different between the groups. Fatigue of any degree was reported by 22% of the patient sample (14% mild, 5% moderate and 3% severe fatigue). Neither the FSMC nor HADS sub scores correlated significantly with the BICAMS test scores at baseline.

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

In paper II, we reported on the longitudinal 2-year follow-up of 58 newly diagnosed MS patients using the BICAMS to assess cognitive performance annually as part of routine follow-up.

There were significant overall improvements in performance on the SDMT and CVLT-II from baseline to first year follow-up (d=0.41 and d=0.39, respectively) which remained stable until the end of the study (d>0.5 for both tests,). The results on the BVMT-R showed an initial improvement to year one (*ns*) followed by a significant deterioration at year two but overall change from baseline to the two-year follow-up was not significant.

Test-retest correlations from baseline through the first to the second follow-up were strong for all three subtests (SDMT r=0.88, CVLT-II r=0.77, and BVMT-R r=0.74). In this follow-up study 47% (n=27/58) of the sample was defined as CI at baseline, with a significant reduction to 28% (n=16/58) after one year followed by an increase to 38% (n=22/58) at the end of the study (*ns* change from baseline).

Proportions of clinically meaningful anxiety, depression and fatigue at baseline were 24%, 7% and 22%, respectively, and did not change significantly throughout the study. At baseline we found no significant correlations between the BICAMS subtest scores and the scores on the HADS and FSMC (paper I), but after one year we found significant weak to moderate negative correlations between performances on the SDMT and CVLT-II and the depression- and the cognitive fatigue sub score. At the two-year follow-up there were significant negative correlations between the performance on the SDMT cognitive fatigue sub score, and between performance on the CVLT-II and the depression sub score. Performance on the BVMT-R did not, at any time point, correlate significantly with the HADS or FSMC scores.

4.3 Paper III: Brief international cognitive assessment for MS (BICAMS) and global brain volumes in early stages of MS - A longitudinal correlation study.

Paper III was an extension of paper II with inclusion of MRI data derived from concurrent MRI scans (n=49) which were analysed by artificial intelligence software to yield normalised global brain volumes. The correlations between the two time points for all volume measures were extremely strong, with r-values approaching 1.0 for all included MRI measures.

Normalised whole brain volume (NBV) and grey matter volume (NGV) were strongly correlated with performances on all three BICAMS subtests at both time points. Both lesion volumes (T2LV and T1LV) were moderately correlated with CVLT-II and BVMT-R at baseline, but only the CVLT-II retained significant correlations after two years. Normalised white matter volume (NWV) was not significantly correlated to any of the subtests at any point in the study.

Overall, there was significant whole brain atrophy with loss of both white and grey matter and a corresponding increase in ventricle volume. There was also a significant increase in T1LV, but no increase in T2LV during the two years follow-up.

At baseline 45% (*n*=22/49) of the patients were defined as CI, and during the observation time, almost 80% of the total sample were longitudinally classified as either confirmed cognitively impaired (CCI, *n*=14, 29%) or confirmed cognitively preserved (CCP, *n*=24, 49%).

Data extracted from the patients who were defined as CCI or CCP, showed that 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. Changes in whole brain, grey matter, and ventricle volumes from baseline to follow-up were significant in both groups, but only the CCI patients also had significant white matter atrophy and increased lesion volumes. Mean 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 difference was not statistically significant.

5 Discussion

This study contributes to the international effort of BICAMS validation by providing the first data from a Norwegian cohort of MS patients. We included patients with shorter disease duration than the majority of other BICAMS studies[133,134], yielding insight into cognitive function in the early stages of the disease. Furthermore, this study was one of the first to provide longitudinal data from repeated testing with the BICAMS, including correlations with MRI data, in newly diagnosed patients with RRMS.

5.1 Psychometric properties of the BICAMS in a Norwegian sample – reliability and validity

The overall balance of sensitivity and specificity for the BICAMS is reported to be good[195], and the test battery performs well in comparison to traditional neuropsychological test batteries[135-137]. In this study we also found overall good psychometric properties for the three subtests with strong test-retest correlations in the HC group for the SDMT and BVMT-r ($r \geq 0.8$). The CVLT-II achieved a value of $r=0.6$, which is just short of the recommended $r=0.7$ proposed in the international guidelines[132]. However, when used annually for the MS patients in this study, the CVLT-II achieved an *r*-value approaching 0.8 making the BICAMS test battery a suitable tool for monitoring cognitive function.

Most BICAMS studies have chosen to use the same CVLT-II forms at test and retest[130,201-211] (or this information was not provided)[135,195,212-216]. With no official guidelines for the use of alternative stimuli for the shortened BICAMS-version of the test for the retest session, we found it convenient to use the words from the interference list (List B) as it is constructed similarly to the standard list and is not presented as part of the baseline assessment. Our results gave some support to this choice by showing a statistically significant correlation between the two lists in the control group. Furthermore, two other studies have also chosen to use List B at retest

achieving *r*-values >0.8[217,218]. Still, the validity of including this list for repeated testing with the BICAMS should be further investigated and proper guidelines established. Another interesting point is that several of the studies found that the CVLT-II could not reliably discriminate patients with MS from HCs[130,139,202,213,219], whereas we found the CVLT-II to be the most sensitive indicator of CI with over 30% impaired results at baseline. The considerable heterogeneity in the results achieved by CVLT-II (or equivalents) in the various BICAMS studies[134], has thus raised a question regarding linguistic and cultural differences limiting true international applicability of this test[130,220,221].

Processing speed is reported to be the first cognitive deficit to emerge[119,120,222] and the SDMT is well established as the strongest and most robust indicator of CI in patients with MS[135,222,223]. The SDMT is therefore widely used as a standalone test for cognitive screening both in clinical practice and in clinical trials[124,171]. In the most recent meta-analysis incorporating 26 BICAMS studies[134] (including our study), over 70% of the studies reporting percentage of impairment on the individual tests confirmed the SDMT to be the most sensitive of the three subtests. Contrary to this, our study was the only one reporting both low sensitivity and non-significant results when comparing SDMT performance in the HC group to patients with MS. Before adjusting our results for differences in level of education there was a significant difference in SDMT scores in the patient and control groups. However, the differences in percentage of impairment on the SDMT between the two groups were still non-significant.

The low percentage of CI measured by SDMT was confirmed when used annually in the two-year follow-up study of patients with MS, yielding similar percentages throughout the study. The unexpectedly weak performance of the SDMT may be due to sample characteristics. Our sample included younger patients with shorter disease duration and high employment rate compared to most other studies. However, considering the relatively large percentage of impairment detected by the BVMT-R and CVLT-II (25% and 30%, respectively) this could imply a rather high rate of false

positive abnormal results on these two tests. Therefore, we found these results to be conflicting as to whether the low proportion of impairment on SDMT reflect a poor sensitivity of the test in our sample, or if impairment of processing speed is truly not as evident in the early stages of MS.

Considering our results and the common practice of using SDMT as a standalone test for screening cognitive function, the number of patients defined as cognitively impaired would be greatly underestimated based on SDMT performance alone. This should definitely support the recommendation using the whole test battery for screening and monitoring of CI in patients with MS[224].

5.2 Cognitive impairment in the early stages of MS

At the time paper II was written, there were some recent publications reporting longitudinal data on CI in MS patients[161,225-228], but only a few studies presented results from repeated testing with the BICAMS in a longer time perspective [229,230]. This study was therefore one of the first to report follow-up data on the BICAMS in early stages of MS. Since then, some follow-up studies have been published reporting both stability or improvement[231], and decline[203] with a follow-up period of five years.

At baseline, we observed CI on at least one subtest in almost 50% of the patient sample. However, there was a significant decrease in the proportion of CI from baseline to first follow-up by almost 20%, followed by a subsequent increase of 10% during year two, yielding an overall non-significant decline from baseline. Overall, the majority of the sample exhibited cognitive stability as 80% were longitudinally confirmed as either cognitively impaired (CCI; 30%) or preserved (CCP; 50%) at baseline and 2-year follow-up. Furthermore, 10% of the CCI patients had a temporary improvement at year one. The remaining 20% of the sample showed lasting improvement (14.5%) or deterioration (6.5%) from baseline to the two-year mark. This indicates that cognitive impairment is not always a fixed disability with a

linear decline but can also be flexible and dynamic[161,232,233]. The low incidence of emerging CI during follow-up (6.5%) also supports a slower-than-expected rate of decline in the early stages of the disease[99]. We did not further investigate characteristics of these patients, as the disproportionate groups sizes would lead to significant loss of statistical power.

Improvements in test performance from a baseline evaluation to subsequent evaluations, often due to familiarity with test material procedures, are known as *practice effects*[234]. The improvement we observed in the SDMT-results in the baseline study (paper I) was attributed to a likely practice effect even though there were no significant correlations between improvement in test score and length of test interval (7-32 days). Previous research specifically investigating practice effects for the SDMT had concluded with minimal practice effect when applied monthly[235] and we therefore assumed that a test interval of 12 months in the follow-up study was long enough not to warrant alternate test stimuli for this test. However, in the first year of follow-up (paper II) there were significant improvements in group-level performances on both the SDMT and CVLT-II which remained stable until the end of the study. There has been reported a practice effect on the SDMT in the first 12 months whereby results deteriorated[236], indicating a practice effect beyond one year is less likely. However, a meta-analysis by Scharfen et.al found that at least 16-month intervals might be necessary to completely eliminate this effect, although this will vary between different cognitive tests and domains tested [237].

Taken together, we could not eliminate practice effects as a cause of the initial improvement of the SDMT and CVLT-II scores in our sample, and most likely the improvement in test scores did not reflect an actual gain in cognitive functioning. Some reports indicate that the higher baseline score on the SDMT, the higher probability of improvement on subsequent testing and more benefit from practice[225]. Indeed, when analysed separately, it emerged that this improvement in test scores was mainly represented by the CP patients. However, there was no clear tendency in our sample indicating that high scorers improved more than low scorers. In the end, the

mere fact that the patients were made aware of CI as a potential symptom may have inadvertently treated the patients through psychoeducational feedback[238]. This underlines the need of a re-baseline assessment to ascertain a patient's "true" level of cognitive functioning after test familiarity, test anxiety and the effect of psychoeducation is established.

5.3 Global brain volumes and cognitive impairment

In the MRI study, we found that performances on all three BICAMS subtests were strongly correlated with normalised whole brain volume (NBV) and grey matter volume (NGV), but we found no significant correlations between normalised white matter volume (NWV) and performances on either of the subtests at any time point. Performance on the CVLT-II was the only measure of CI to consistently show significant correlations with lesion volumes (T1LV and T2LV) was CVLT-II, A similar result was also found in a recent study highlighting lesion volume as a significant predictor of CI when assessed by the shortened BICAMS-version of the CVLT-II[239]. We found no correlations between SDMT and lesion volumes, and only a weak to moderate baseline correlation between BVMT-R and lesion volumes, contrasting findings associating visual memory function and processing speed with lesion volume[94,175,240-244].

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. These findings are in accordance with results in a recent study, reporting that white matter lesion volumes may be the main propagator of cognitive impairment in the early stage of MS[245]. Given the high percentage of CI defined by the CVLT-II and the strong correlations performance on this test and lesion volumes, this supports the role of disease burden, measured by lesion load, as a contributor to CI in the early stages of MS[175,241-243]. However, the overall increase in T1LV, but not in T2LV, indicate a stability in the inflammatory processes, with little or no new lesions appearing during

follow-up. Together with the clinical stability measured by the EDSS, this lends support to subclinical development of CI demonstrating the clinico-radiological paradox and disconnect between lesion load, physical disability and cognition, especially in the early stages of the disease[112].

We also found a significant overall white matter atrophy from baseline to follow-up, but when analysed separately, this was only significant for the patients defined as CCI and not for those defined as CCP, implicating white matter volume loss in the pathology of CI in the early stages of MS and, furthermore, that white matter atrophy may contribute to separate cognitively impaired patients from patients with preserved cognitive function over time[240]. However, the reduction of white matter volume may also be due to some degree of pseudoatrophy[165] since this effect may persist beyond the first year of treatment[166] and this current sample of patients were newly diagnosed and thus recently started disease modifying treatment (DMT). We did collect information regarding use of DMT, but when stratifying the patients by treatment, the groups become too small (*n* ranging from 2 to 20) to be included in statistical analyses without significant loss of power. Therefore, we could not assess whether stability or change in cognitive function, EDSS, or MRI findings were associated to type of DMT.

Even though the overall loss of whole brain volume was significant in the study, the mean annualized whole brain atrophy rate was unexpectedly low (-0.18%). The proposed threshold for pathological volume loss is proposed to be -0.4% per year[167], and even when analysing the CCI and CCP patients separately, the threshold was still not met and the difference between the groups was not statistically significant. This implies that the accelerated atrophy accumulation in cognitively impaired patients may not be pronounced in the earliest stages of the disease and challenges the previously reported relationship between early brain atrophy and cognitive function[94,168-170]. However, several points may explain our findings, 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) was probably also a contributing factor, but these data were not available for the present study. Another plausible explanation for the similar atrophy rate despite significant volumetric 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[113,114]. These differences may prove to be more pronounced later in the disease course and it would be especially interesting to investigate the differences in patients classified as impaired around time of diagnosis and those developing CI at a later stage.

5.4 Methodological considerations and limitations

5.4.1 General limitations and strenghts of the present study

This study was based on the BICAMS initiative and the "international standards for validation"[132]. However, it was not a *true* validation as we did not validate the BICAMS definition of impairment against a definition based on established and more extensive neuropsychological evaluations. We also did not perform Receiver Operating Characteristics (ROC)-analyses to ascertain the accuracy, sensitivity, and specificity of the tests in our sample. In addition, we did not time our sessions to assess whether the Norwegian version of the BICAMS does in fact adhere to the 15-minute timeframe. A main strength of the present study lies in the inclusion of a relatively young sample of newly diagnosed patients with low degree of accumulated physical disability and the concurrent collection of data regarding fatigue, mood disorders and MRI. Furthermore, all patients were assessed by the same neurologist (EDS), at approximately the same time of day for repeated testing (±1 hour) to circumvent the potential effect of diurnal variation in fatigue and alertness. The healthy controls were tested at the Department of Biological and Medical Psychology by trained test technicians supervised by one of the co-supervisors (AJL). A limitation of the longitudinal study is the lack of control for demographic variables (age, gender, education, employment), 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.

Strengths of the BICAMS as a screening instrument in general include its brevity and easy administration in addition to being very well tolerated by the patients. On the other hand, a perceived weakness of the BICAMS is the use of strict cut-off scores which reduces cognitive impairment to a dichotomous variable, disregarding the degree of impairment on a given test. However, this was addressed in a recent study showing that the majority of patients with only one impaired test score were reconfirmed as cognitively impaired when assessed by a more extensive neuropsychological test battery[246] lending support to the "one-or-more abnormal test score" as a reliable definition of CI.

Brain scans from healthy controls were not available for this study, so our scans were normalised according to a reference brain and adjusted for age and gender. Thus, the influence of normal ageing and gender differences on our results were reduced, and no further adjustments had to be made to the MRI data. The patients acted as their own controls gauging changes over time at both individual and group levels.
The use of artificial intelligence (AI) to analyse MRI data is considered a strength as it reduces both intra- and interrater variability. The Icometrix tool is a validated and increasingly utilized software in MRI-studies investigating MS patients[197,199,247], but the significant differences in the results yielded from various software currently in use poses a challenge when comparing results across different studies[248,249].

Finally, we reported the lesion volumes as global measures of the total T2LV and T1LV, even though analyses of regional lesion volumes could have yielded different results, given the impact of lesion localization 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[176,180,250] as this was beyond the scope of the study, requiring functional MRI examinations.

5.4.2 Selection bias and sample size

All patients who were diagnosed with MS at Haukeland University Hospital between January 2014 and September 2017 were considered for participation in this study. The hospital records were then pre-screened for preliminary matches to the inclusion criteria and almost 60% were eligible for participation and formally invited (44% of all invitees were ultimately included). Selection bias was therefore probably low, although self-selection bias or volunteer bias cannot be excluded.

For the control sample there may be a participation bias introduced in the recruitment method (flyers/posters in the hospital buildings) which led mainly hospital staff to volunteer (nurses, orderlies, physical therapists, doctors, bioengineers etc.). The mismatch in education level may also be a consequence of this recruitment strategy, and efforts to equalize by selectively recruiting participants with only high school/vocational school education in the same manner, may have selected certain occupational groups commonly found in the hospital area and further homogenized the sample. Despite this addition to the sample, we were not able to eliminate the group differences altogether, so we performed adjustments to the analyses to account for the discrepancies (linear regression with group and level of education as predictors of BICAMS test scores).

The establishment of national norms for BICAMS was beyond the scope of this study in regards to time and resources, as it would require samples of 150 or more volunteers[132]. We applied the minimum demand of 65 healthy controls to achieve enough statistical power to make comparisons to our patient sample. The cut-off scores this study yielded may therefore not be representative to the MS-population nationwide. Also, the tendency of higher educational level in the control group compared to the MS group may have inflated the cut-off scores leading to an overestimation of CI in the patients group.

We did not retain the control sample for longitudinal follow-up and realize that it would have improved the impact of the study to see the average cognitive decline in non-MS patients over the same follow-up period. Although our cohort was relatively small, it was well-defined with low loss-to-follow-up (4% first year and 10% second year (14% total). To achieve complete BICAMS and/or MRI data for the publications we had to extract different sample sizes from the cohort (65/58/49), but overall prevalence of impairment on the BICAMS tests was the same for all three publications.

5.4.3 Confounders

The exact nature of how anxiety, depression and fatigue may confound the performances on the cognitive tests remains unclear. Even though the anxiety sub scores were significantly higher in the MS group than in the control group, the prevalence of clinically meaningful anxiety and depression was low[105,251,252]. Correlations between cognitive performance and mood disorders were non-significant at baseline, and at follow-up, weak but significant correlations emerged between SDMT/CVLT-II and depression corresponding to the current literature stating that mild anxiety and depression do not seem to impede cognition, but stronger associations emerges with increased severity of mood disturbances[103,106]. The prevalence of fatigue in the sample was also lower than expected[251,253] and showed no significant correlation with BICAMS at baseline similarly to another study with similar sample characteristics regarding clinical and vocational variables[212]. Like the HADS-scores, weak but significant negative correlations emerged at follow-up between the SDMT and CVLT sub scores and results on the FSMC, again in line with current research reporting a stronger association with stronger severity of fatigue[103,106,191,192,227,254]. The emergence of significant correlations during follow-up strengthens the importance of concurrent assessment of mood and fatigue when evaluating cognitive impairment. The exact nature and extent to which these factors impact one another needs further investigation so that more reliable assessments can be made.

6 Concluding remarks and future perspectives

The BICAMS test battery is proven to be a reliable screening tool for cognitive impairment across cultures and languages[133,134], and provides a platform of international comparability in the field of *MS and cognition*. In this thesis we have shown that the Norwegian translation of the BICAMS is feasible to use and well-accepted by patients in an out-patient setting. We can therefore recommend that the BICAMS is included as a screening instrument in routine follow-up of patients with MS. A proposed algorithm for implementation is presented in Figure 5.

To achieve optimal clinical applicability, there is a need for studies investigating practice effects for the BICAMS subtests, establishing optimal assessment intervals and proper guidelines for the use of alternative stimuli. A certain practice effect from baseline to first follow-up is unavoidable as the patients are unlikely to completely forget everything about the baseline testing. Thus, a re-baseline assessment is recommended to ascertain the "true" level of cognitive function, accounting for this effect of "situational test familiarity". Furthermore, the interpretation of test scores needs to be standardized, i.e., generating and applying "reliable change" methodology to the individual tests to define clinically meaningful improvement or deterioration[255,256], thus limiting the risk of overloading the local neuropsychological services with "false positives", and referrals based on the clinicians discretion.

However, exactly how to use the BICAMS results on an individual level needs further investigation. In our study, we found cognitive impairment in almost half the sample of patients, but also in 20% of the healthy controls. Although this was statistically significant, the effect sizes for the tests were small to medium, and therefore, our results may only be relevant on a group-level. Population-based national norms based on studies of larger samples controlled for demographic variables like age, gender, and education, are therefore needed to reliably evaluate individual performances in a clinical setting. Given the heterogeneity of results

reported in the various BICAMS studies, especially on the verbal memory test, these guidelines should be developed nationally, rather than internationally[221].

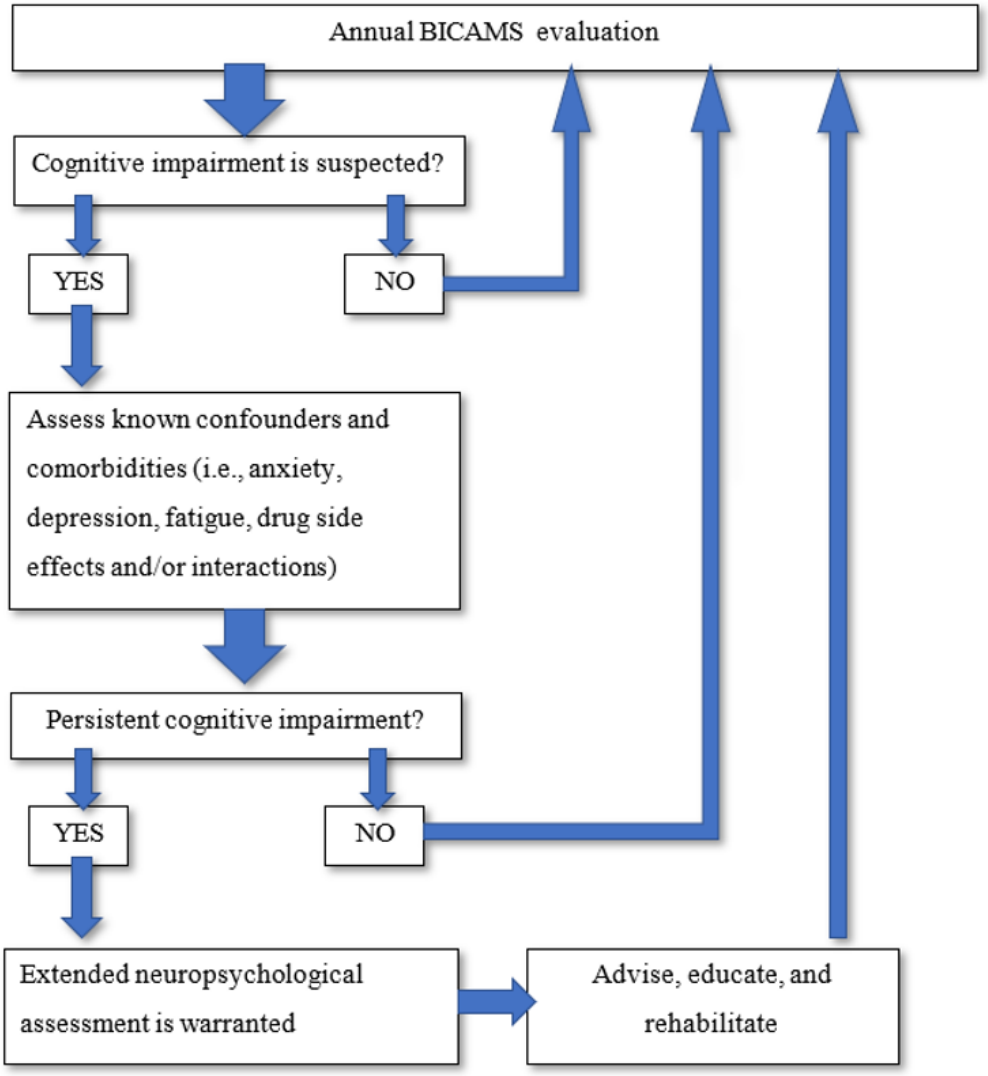

Figure 5. *Proposed algorithm for screening and management of cognitive impairment using the BICAMS in clinical practice. Adapted from Bakirtzis et al., 2018*[257]

7 Appendix – BICAMS test battery – examples of stimuli

Figure 6. *Example of stimuli of the* ***SDMT*** *type. Reprinted with permission (Creative Commons Attribution Licence) from Langdon et.al 2012*[125]

	1.	2.	3.	4.	5
Apple					
Bear					
Piano					
Hammer					
Banana					
Chisel					
Trumpet					
Orange					
Lion					
Wrench					
Peach					
Saw					
Drum					
Tiger					
Violin					
Giraffe					

***Figure** 7. Example of stimuli of the **CVLT** type. Reprinted with permission (Creative Commons Attribution Licence) from Langdon et.al 2012*[125]

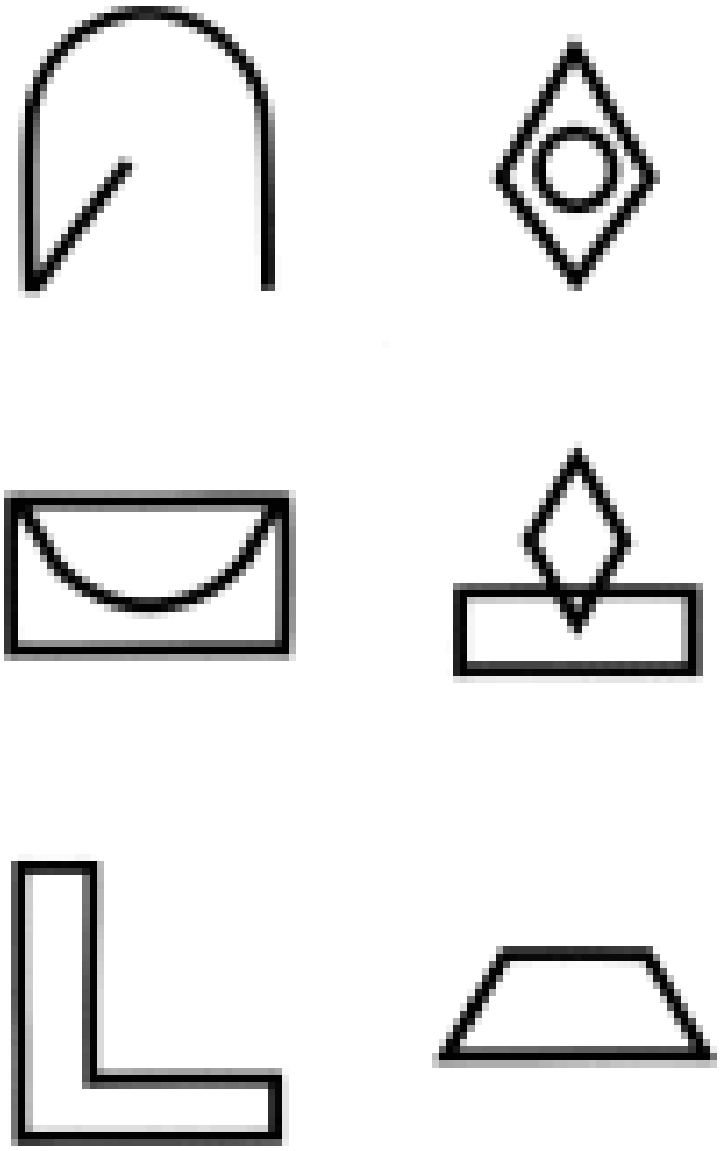

***Figure 8**. Example of stimuli of the **BVMT** type. Reprinted with permission (Creative Commons Attribution Licence) from Langdon et.al 2012*[125]

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The Norwegian translation of the brief international cognitive assessment for multiple sclerosis (BICAMS)

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ABSTRACT

Background: Cognitive impairment is a common symptom in all stages of multiple sclerosis (MS), yet it is underreported and not routinely evaluated. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a short and easily administered test battery for screening of cognitive impairment in MS that can be completed within 15 min and incorporated into routine clinical practice. The test battery consists of the oral version of the Symbols Digit Modalities Test (SDMT) and the initial learning trials of the California Verbal Learning Test 2nd edition (CVLT-II) and the Brief Visuospatial Memory Test Revised (BVMT-R).

Objective: To investigate if the Norwegian version of the BICAMS could identify cognitive impairment in early stages of MS and be used as part of routine follow-up procedures.

Methods: A total of 65 relapsing-remitting MS (RRMS) patients and 68 healthy controls were examined with the BICAMS test battery. A randomly selected subset of 29 controls were retested 1–4 weeks after baseline. All participants were screened for anxiety and depression using the Hospital Anxiety and Depression Scale (HADS).

Results: There were statistically significant differences between the patients with MS and the healthy controls on all three subtests, and the differences remained significant for the CVLT-II ($p = 0.003$) and BVMT-R ($p = 0.011$) after adjusting for education. There were no statistically significant correlations between BICAMS scores and anxiety and depression. SDMT and BVMT-R results in the control group at baseline and re-test were strongly correlated ($r \geq 0.70$, $p < 0.001$), and CVLT-II achieved an adequate value of $r = 0.60$ ($p = 0.001$). On the SDMT, there was a statistically significant improvement between the two test-sessions. Cognitive impairment, defined as an abnormal test score on ≥ 1 subtest, was identified in 46.2% of the patient sample, whereas 15.4% were considered cognitively impaired on ≥ 2 subtests.

Conclusion: This study supports that the Norwegian version of the BICAMS should be included as a screening procedure for cognitive impairment in Norwegian MS patients.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, affecting approximately 2.3 million people worldwide (Thompson et al., 2018). Cognitive impairment is a well-documented symptom in MS, and affects up to 65% of the patients (Amato et al., 2006; Bobholz and Rao, 2003; Chiaravalloti and DeLuca, 2008; Rao et al., 1991). It is present in all subtypes and at all stages of the disease, and it is known to progress over time (Amato et al., 2001, 2006; Patti et al., 2009; Rao et al., 1991). Many patients with MS exhibit signs of cognitive impairment even before the first physical symptom of the disease manifests (Cortese et al., 2016), which implies a preclinical disease activity affecting cognition. The high prevalence rate, along with the evidence of preclinical cognitive symptoms, highlight the need for a standardized tool for screening of cognitive function in patients with MS.

Awareness of cognitive symptoms associated with MS has improved during the recent years. Traditionally, the cognitive assessment of patients with MS has been performed by trained neuropsychologists in specialized centers, and involves time-consuming comprehensive test batteries, such as the Brief Repeatable Battery of Neuropsychological tests (BRB-N) and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006; Strober et al., 2009). Such evaluations have been reserved for patients who already have an apparent degree of cognitive impairment, and is not routinely offered to young or employed patients with MS. In order to detect the

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early, subtle changes in cognition, there has been a call for a short, sensitive and easily administered test battery; one that can be incorporated into standard routines when diagnosing and following up patients with MS. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed for this purpose (Langdon et al., 2012).

The BICAMS can be completed in 15 min without requiring any special equipment or extensive assessor training, and is shown to be sensitive to cognitive changes associated with MS (Langdon et al., 2012). Subtests are included based on psychometric qualities (reliability, validity and sensitivity) and international applicability and feasibility. The BICAMS evaluates (1) information processing speed by the Symbol Digit Modalities Test (SDMT), (2) verbal memory function by the learning trials of the California Verbal Learning test, 2nd edition (CVLT-II) and (3) visual memory function by the learning trials of the revised Brief Visuospatial Memory Test (BVMT-R) (Langdon et al., 2012). The test battery thereby includes measures of the cognitive functions that are most commonly affected in MS (Chiaravalloti and DeLuca, 2008; Langdon, 2011). An international standard for validation has been developed (Benedict et al., 2012) and the BICAMS has been translated and validated in several countries (Corfield and Langdon, 2018; Costers et al., 2017; Dusankova et al., 2012; Filser et al., 2018; O'Connell et al., 2015; Polychroniadou et al., 2016; Sandi et al., 2015; Sousa et al., 2018; Walker et al., 2016).

This paper presents results on the Norwegian version of the BICAMS in a cohort of newly diagnosed MS patients with disease duration of less than 6 years. From previous studies we expected that the tests would discriminate well between the patients and the controls and that a significant proportion of the MS patients would be defined as impaired on at least one of the tests. The BICAMS tests were used in accordance with the proposed international validation protocol (Benedict et al., 2012).

2. Methods

2.1. Study population

2.1.1. Patients

All relapsing-remitting MS (RRMS) patients between 18 and 65 years of age, with first-time diagnosis (Polman et al., 2011) between January 1st 2014 and September 1st 2017, were screened using hospital records at Haukeland University Hospital, Western Norway. A total of 158 patients with less than three years of documented disease activity prior to diagnosis were invited to participate in the study, and 98 (62%) agreed to participate. Following a telephone interview, 33 patients were excluded, leaving 65 RRMS patients for inclusion. Reasons for exclusion were: self-reported MS-related symptoms more than three years prior to diagnosis ($n = 18$), primary language not Norwegian ($n = 1$), neurological or psychiatric comorbidities that could impede cognition ($n = 2$), affiliation to other health care region ($n = 1$), unresponsive to contact ($n = 1$), withdrawal of consent ($n = 2$), clinically isolated syndrome or progressive subtype ($n = 8$).

2.1.2. Controls

We recruited 68 healthy controls from the community through posters in the Hospital buildings and advertisements on the Norwegian MS Society web site. The controls were between 18 and 65 years of age with Norwegian as their primary language. None of the participants reported present or previous neurological or psychiatric illnesses that could impede cognition.

2.2. Procedures

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

The controls received two cinema tickets and free parking as compensation for their participation, and the patients with MS were compensated for their deductible related to the study examinations.

2.2.1. Questionnaires

To assess whether depression or anxiety influenced cognitive performance, both the patients with MS and the healthy controls were asked to complete the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) which has been translated into Norwegian and validated for use in the MS population (Pais-Ribeiro et al., 2018). In addition, all participants completed a self-report questionnaire listing their education, employment status and general health status.

2.2.2. Physical examination

All patients with MS were examined with a full neurological evaluation, 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) is included as a measure of information processing speed. An A4 sheet of paper with rows of nine abstract symbols arranged pseudo-randomly is presented to the subject. A cipher key linking each of these symbols to a single digit is located at the top of the page. After a short written practice session on the first 10 symbols, the test subject has to voice the digit corresponding to each symbol as rapidly as possible for 90 s. The outcome measure is the number of correctly identified symbols in the 90-second timeframe. No translation is required as the symbols have no semantic meaning. A previous study has reported high sensitivity, a good test-retest reliability and only a minor learning effect on this version of the SDMT (Strober et al., 2009). The same version of SDMT was therefore presented in the test and re-test session.

The first five learning trials of the official Norwegian translation (Lundervold, 2004) of the 2nd edition of the California Verbal Learning Test (CVLT-II) (Delis et al., 1987) are included to obtain a measure of verbal memory function. The restriction to the learning trials is based on results from previous studies (Stegen et al., 2010). The examiner reads aloud a list of 16 words (List A) and the test subject is then asked to repeat as many words as possible. The list is repeated five times, and the number of correct words remembered across the five trials is used as the outcome measure. To reduce the risk of a learning effect, an alternate list of 16 words is included in the re-test session. The use of such an alternate form is highly recommended during the short-interval repeated assessment of memory function in patients with MS (Benedict, 2005), but studies validating alternate forms of the shortened version of CVLT-II included in the BICAMS are still missing. For the re-test session in the present study, the 16 words from the interference list of the standard format of CVLT-II (List B) were selected, as they were not presented as part of the first test session and is constructed similarly to the original list.

The first three learning trials of the BVMT-R (Benedict, 1997) are included to obtain a measure of visual memory function. The restriction to the learning trials is based results from previous studies (Benedict et al., 2006; Costers et al., 2017). A stimulus sheet showing an array of 2×3 abstract designs is presented to the test subject for 10 s. When the stimulus is then hidden from view, the test subject is asked to draw from memory the same abstract designs in the same spatial arrangement as presented on the stimulus sheet. This is repeated three times and the outcome measure is the total score achieved over all three trials. There is a potential learning effect with repeated testing. The test stimuli are therefore different at baseline and re-test (Form 1 and Form 2, respectively).

2.3. Statistical analyses

Statistical analyses were performed using SPSS version 24 (IBM

Corp., Armonk, NY), and figures were made using StataSE version 15 (StataCorp LLC, College Station, Texas). Statistical significance was set at alpha level < 0.05. Between-group differences were examined with student's *t*-test and chi-square for continuous and categorical variables, respectively. Effect sizes were calculated according to Cohen's *d* statistic (0.2 = small, 0.5 = medium, 0.8 = large). The relationship between the BICAMS scores and anxiety/depression (HADS-scores) was calculated by running a Pearson's correlational analysis. Correlation analysis was also used to assess the test-retest reliability of the BICAMS subtests and paired *t* tests were calculated to evaluate improvement from baseline to re-test in the control group. Cut-off values were calculated for each subtest (≤1.5 standard deviations below the mean of the control group), and participants were defined as cognitively impaired or cognitively preserved based on the occurrence of abnormal test scores on one, two and three subtests, respectively. A stepwise linear regression was performed to assess if BICAMS performance predicted self-reported employment status. Age, gender, education level, EDSS, disease duration and HADS-scores were entered as predictors on the first step and the BICAMS-scores on the second step.

3. Results

3.1. Demographic characteristics

We included 65 patients with RRMS and 68 healthy controls in the study. Baseline demographic characteristics are outlined in Table 1. There were no statistically significant differences between the groups regarding age or gender, but the number of participants with the lowest level of education was significantly higher in the MS than the control group, with a corresponding higher number of controls at the two highest levels. Almost all participants in both groups were employed, and more than two thirds were employed full time

All participants in the MS group had a relapsing-remitting subtype, with an EDSS score ranging from 0 to 3 (mean 1.28 ± 0.88), and an average disease duration (time from first documented clinical symptom to BICAMS testing) ranging from 0.25 to 5.33 (mean 1.81 ± 1.23) years.

3.2. Impact of anxiety and depression on BICAMS performance

The scores on the Hospital Anxiety and Depression Scale (HADS) showed that the patients with MS reported significantly higher levels of anxiety compared to the controls (Table 2), with a non-significant difference in level of depression. The combined anxiety and depression score (HADS-total) was significantly higher in the MS than the control group ($p = 0.041$). The level of anxiety and depression did not, however, correlate significantly to the BICAMS scores in either group (Table 3).

Table 1
Baseline demographic characteristics in the MS group (MS) and the healthy control group (HC).

	MS (*N* = 65)	HC (*N* = 68)	*p*-value
Gender male/female, N (% female)	23/42 (64.6)	23/45 (66.2)	0.850
Age (years), mean ± SD	37.02 ± 10.40	38.13 ± 11.40	0.556
Education, N			
< 14 years	23	11	*0.038*
14–16 years	24	31	
> 16 years	18	26	
Employed,%	89.2	97.0	0.080
Fulltime,%	70.3	76.6	0.423
Disease duration (years), mean ± SD			
Since first symptom	1.81 ± 1.23	–	–
Since diagnosis	1.08 ± 0.74	–	–
EDSS, mean ± SD	1.28 ± 0.88	–	–

SD = Standard deviation. EDSS = Expanded Disability Status Scale.

Table 2
Group differences on measures of anxiety and depression among patients with MS and healthy controls (HC).

	MS Mean (± SD)	HC Mean (± SD)	*t*	*p*-value
HADS-Anxiety	5.64 (± 4.00)	4.29 (± 3.16)	2.145	0.034
HADS-Depression	2.95 (± 3.23)	2.20 (± 2.48	1.494	0.138
HADS-Total	8.59 (± 6.49)	6.48 (± 5.11)	2.062	0.041

SD = Standard deviation. HADS = Hospital Anxiety and Depression Scale.

Table 3
Correlations between the BICAMS subtests and anxiety/depression.

Test	**Group**	**HADS-total**	
		Pearson's *r*	*p*-value
SDMT	*MS*	−0.018	0.888
	HC	−0.034	0.787
CVLT-II	*MS*	−0.135	0.288
	HC	0.024	0.846
BVMT-R	*MS*	−0.080	0.532
	HC	0.006	0.962

MS = (patients with) Multiple Sclerosis. HC = Healthy controls. HADS = Hospital Anxiety and Depression Scale. **SDMT** = Symbols Digit Modalities Test. **CVLT-II** = California Verbal Learning Test, 2nd edition. **BVMT-*R*** = Brief Visuospatial Memory Test, Revised.

3.3. Group differences on BICAMS measures

The mean scores on the SDMT, CVLT-II and BVMT-R were all significantly lower in the MS group than in the control group (Table 4), with differences of small to medium effect sizes. When adjusting for group mismatch in education and anxiety/depression, the scores remained significantly lower in the MS group on the CVLT-II and the BVMT-R, but not for the SDMT.

3.4. Test-retest data in the control group

We retested the healthy controls 7 to 32 (mean 19.63 ± 7.87) days after the baseline assessment and the test-retest data are shown in Table 5 and Fig. 1. Strong correlations between the results at baseline and retest were found for all subtests; the SDMT and BVMT-R both achieved excellent *r*-values of ~ 0.80 ($p < 0.001$) whereas the CVLT-II obtained an *r*-value of ~ 0.60 ($p = 0.001$). There was a statistically significant improvement on the SDMT between the two sessions (~ 3.5 points, $p = 0.024$).

3.5. Cognitive impairment in the MS group

A score ≤1.5 standard deviations below the mean score of the control group defined the cut-off value for cognitive impairment on each of the three BICAMS tests. Following the criteria of ≥1 abnormal test score (Dusankova et al., 2012), 46.2% of the patient sample were considered cognitively impaired (Table 6). They were most likely to be impaired on the CVLT-II, with 30.8% of the patients scoring below the cut-off value. On the BVMT-R and SDMT, 26.2% and 10.8% were considered cognitively impaired, respectively. When the definition of cognitive impairment was defined as ≥ 2 abnormal tests, only 15.4% of the patients with MS were considered cognitively impaired, and a small subset of 6.2% scored below the cut-off value on all three tests.

3.6. BICAMS and employment

There was no significant difference between the groups in regards to overall employment status (Table 1). When entered into a stepwise regression model, only age ($F = 5.077$, $p = 0.028$) was retained in the

Table 4
Group differences on BICAMS measures, independent samples *t*-test.

Test	*MS* (mean ± SD)	*HC* (mean ± SD)	Mean Δ	*t*	*p*-value	Adjusted *p*-value*	Cohen's *d*
SDMT	54.65 ± 10.79	58.52 ± 10.53	3.87	−2.09	0.039	0.201	0.37
CVLT-II	54.55 ± 10.86	60.32 ± 7.75	5.77	−3.51	0.001	0.008	0.62
BVMT-R	26.55 ± 5.76	29.03 ± 4.01	2.48	−2.89	0.005	0.027	0.51

HC = Healthy controls. Δ = difference. **SD** = Standard deviation. **SDMT** = Symbols Digit Modalities Test. **CVLT-II** = California Verbal Learning Test, 2nd edition. **BVMT-*R*** = Brief Visuospatial Memory Test, Revised.
* Adjusted for level of education and anxiety/depression.

model as a significant predictor (variables entered: age, gender, disease duration (from onset and from diagnosis), level of education, EDSS, HADS-scores and raw scores on the BICAMS subtests).

4. Discussion

The present study found that the BICAMS subtests discriminated well between the MS and the control group, a finding that was retained for CVLT-II and BMVT-R when accounting for level of education and anxiety/depression. Almost half of the MS patients were identified with cognitive impairment on at least one subtest, and results at baseline and re-test were significantly correlated on all BICAMS tests in the control group, with a weak improvement on the SDMT.

Most other published BICAMS-studies present data from patient groups with mean disease duration of ~10 years (Corfield and Langdon, 2018). To our knowledge, this is the first BICAMS-study to investigate newly diagnosed patients with a specific criterion of less than three years from first clinical symptom to diagnosis. This provides an insight into the development of cognitive impairment in the earliest stages of the disease, but may also limit the value of direct comparisons to other BICAMS-studies.

With cognitive impairment defined as at least one abnormal test score (Dusankova et al., 2012), the BICAMS battery identified 46.2% of the current patient sample as cognitively impaired. This is lower than the prevalence found in Canada (57.9%) (Walker et al., 2016), Ireland (57%) (O'Connell et al., 2015) and Hungary (52.3%) (Sandi et al., 2015), which were all in line with the prevalence documented by the Czech study comparing BICAMS and MACFIMS (55% and 58% respectively) (Dusankova et al., 2012). It was, however, significantly higher than the prevalence reported from the Portuguese (24.8%) (Sousa et al., 2018) and German (32.6%) (Filser et al., 2018) studies. When cognitive impairment was defined as at least two abnormal test scores, the number of patients with impairment was cut to a third of the original estimate (15.4%), indicating that the cognitive impairment should be characterized as mild in most of the affected patients.

Separate analyses of the subtests showed, in contrast to other BICAMS-publications, that CVLT-II identified impairment in a higher number of patients (30.8%) than the other subtests (BVMT-R 26.4% and SDMT 10.8%) (Costers et al., 2017; Filser et al., 2018; Polychroniadou et al., 2016; Sandi et al., 2015; Sousa et al., 2018; Walker et al., 2016). The low rate of impaired SDMT scores was surprising especially since low scores on this subtest has been reported to be a strong indicator of cognitive impairment in patients with MS (Benedict et al., 2017). The non-significant proportion of patients identified as impaired by the SDMT in our sample may be explained by the inclusion of only RRMS patients in an early stage of the disease.

The SDMT showed a statistically significant improvement from baseline to retest at a group-level, suggesting that at least some of the participants may have remembered symbol-number associations over the short time-period between the two test sessions. However, the lack of significant correlations between test intervals and SDMT score change in the present study did not support this (data not shown). In any case, such a learning effect will probably be milder with the longer time-frame planned for the re-test of MS patients (≥ 12 months). For the CVLT-II and BVMT-R we found non-significant differences between performances at the two time points and significant correlations between performances a baseline and re-test. Although results for the alternate word lists in CVLT-II fell short of the requested goal from the validation standards of $r \geq 0.70$ (Benedict et al., 2012), we conclude that our results support the use of all three tests as part of follow-up procedures in Norwegian MS patients. However, the validity of the re-test list for the CVLT-II included in the present study should be further investigated.

Despite the relatively high prevalence of cognitive impairment in this sample, there was a low degree of unemployment (10.8%) and only age was found to be a statistically significant predictor of employment status at this early stage of the disease. This indicates that most patients continue to work in spite of mild signs of cognitive impairment. With early identification of cognitive impairment we may optimize treatment, implement coping strategies and work place customization, as well as cognitive rehabilitation (Goverover et al., 2018; Hamalainen and Rosti-Otajarvi, 2016), and therefore hopefully postpone or prevent early retirement due to MS. Exactly how to define a "positive" screening result on the BICAMS in clinical practice, however, remains unclear. Using the one-or-more criterion as a threshold for referral to further evaluation may overload the local neuropsychological services and classify normal variation as pathology. Restriction to the two-or-more criterion may, on the other hand, overlook patients in real need of help, with the risk of giving treatment options too late to be effective. Further investigation into the optimal scoring and follow-up of a positive screening result on the BICAMS is therefore required.

5. Conclusions

Used in accordance with the proposed international validation protocol (Benedict et al., 2012), the Norwegian version of the BICAMS

Table 5
Test-retest means and correlations for control group.

	Paired samples *t*-test					**Pearson's correlation**	
	Test Mean ± SD	Retest Mean ± SD	Mean Δ	t	*p*-value	Pearson's r	*p*-value
SDMT	60.21 ± 12.13	63.69 ± 12.90	−3.48	−2.378	0.024	0.803	< 0.001
CVLT-II	59.24 ± 7.44	61.07 ± 6.68	−1.83	−1.532	0.137	0.590	0.001
BVMT-R	28.86 ± 4.23	29.07 ± 4.68	−0.21	−0.375	0.710	0.783	< 0.001

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

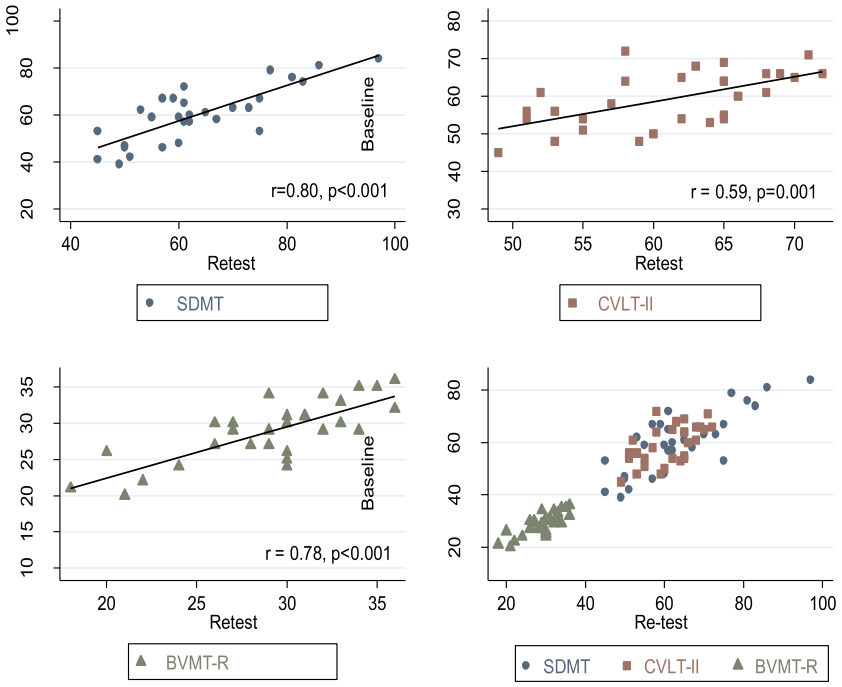

Fig. 1. Scatterplots and test-retest correlation data for SDMT, CVLT-II and BVMT-R in the control group.

Table 6
Estimation of cognitive impairment in the MS group.

	Cutoff-value (≤ 1.5 SD)	**MS-group**	
		N	%
Abnormal test score on SDMT	≤ *43*	7	10.8
Abnormal test score on CVLT-II	≤ 49	20	30.8*
Abnormal test score on BVMT-R	≤ *23*	17	26.2*
≥ 1 abnormal test scores		30	46.2*
≥ 2 abnormal test scores		10	15.4*
3 abnormal test scores		4	6.2
No abnormal test scores		35	53.8*
Abnormal SDMT *and* CVLT-II		5	7.7
Abnormal SDMT *and* BVMT-R		5	7.7
Abnormal CVLT-II *and* BVMT-R		8	12.3*

SDMT = Symbols Digit Modalities Test. CVLT-II = California Verbal Learning Test, 2nd edition. BVMT-*R* = Brief Visuospatial Memory Test, Revised.
* Pearson's Chi-square $p < 0.05$.

was found to discriminate well between MS patients and controls and identify individuals with suspect cognitive impairment in an early stage of the disease. We therefore recommend implementation of the BICAMS into clinical practice and routine evaluation of Norwegian MS patients.

CRediT authorship contribution statement

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

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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 ($p < 0.05$).

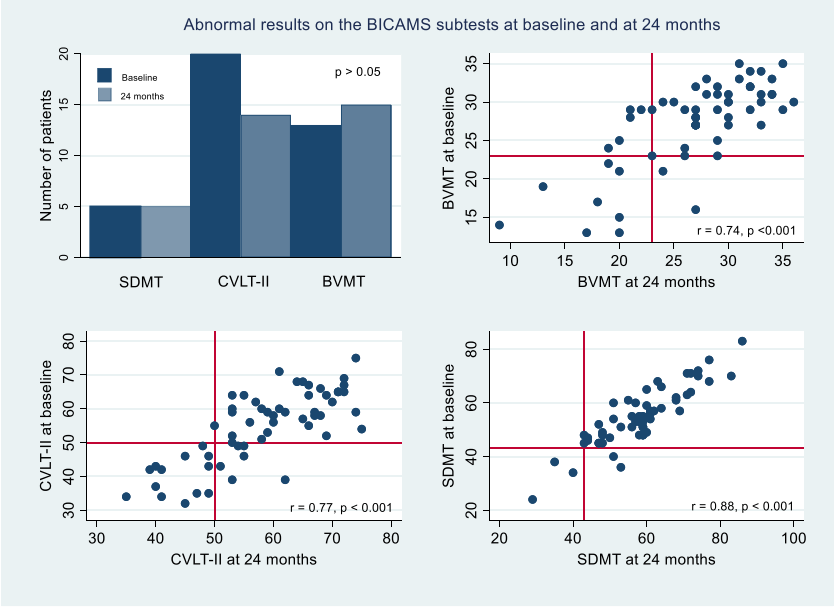

Fig. 1. Number of patients performing below the cut-off scores on the BICAMS subtests (SDMT 43; CVLT-II 50; BVMT 23) at baseline and at the 24-months follow-up, and correlations between the test performances at the two time points.

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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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		2 years		*t*	*p*	Cohen's *d*	Pearson's *r*	*p*
			Mean	SD	Mean	SD					
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		2 years		*t*	*p*	Cohen's *d*	*r*	*p*
	Mean	SD	Mean	SD					
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.

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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.

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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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