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CEREBRAL SYMPTOMS AND THEIR TRAJECTORY IN DIFFERENT MULTIPLE SCLEROSIS TYPES: A 1-YEAR LONGITUDINAL OBSERVATIONAL STUDY OF COGNITIVE IMPAIRMENT, PSYCHOPATHOLOGY, AND FATIGUE

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List of abbreviations

ANCOVA	**Analysis of Covariance**
ANOVA	**Analysis of Variance**
BICAMS	**Brief International Cognitive Assessment in Multiple Sclerosis**
BRB-N	**Brief Repeatable Battery of Neuropsychological Tests**
BVMT-R	**Brief Visuo-Spatial Memory Test-Revised**
CI	**Confidence Intervall**
COWAT	**Controlled Oral Word Association Test**
CSF	**Cerebrospinal Fluid**
BDT	**Block Design Test**
DMT	**Disease Modyfing Therapies**
EBV	**Epstein Barr Virus**
EF	**Executive Functions**
EDSS	**Expanded Disability Status Scale**
FSMC	**Fatigue Scala for Motor and Cognitive Functions**
HADS	**Hospital Anxiety and Depression Scale**
HC	**Healthy Controls**
ICD	**International Statistical Classification of Diseases and Related Health Problems**
IPS	**Information Processing Speed**
MACFIMS	**Minimal Assessment of Cognitive Function in MS**
MRI	**Magnetic Resonance Imaging**
MS	**Multiple Sclerosis**

MSFC	**Multiple Sclerosis Functional Composite**
PASAT	**Paced Auditory Serial Addition Test**
PPMS	**Primary Progredient Multiple Sclerosis**
RRMS	**Relapsing Remitting Multiple Sclerosis**
SD	**Standard Deviation**
SDMT	**Symbol Digit Modalities Test**
SPMS	**Secondary progredient Multiple Sclerosis**
VLMT	**Verbal Learning Modal Test**

1 Introduction

1.1 Criteria for MS diagnosis and Epidemiology

Multiple sclerosis (MS) is a complex disease and its clinical and radiological heterogeneity often make it difficult to diagnose. There are no sensitive and specific biomarkers and many diseases can present with a similar clinical picture [65].
The development of diagnostic criteria for MS began 50 years ago. The criteria have been revised regularly, so that the diagnosis of multiple sclerosis can be made earlier and earlier. Starting with the Schumacher criteria in 1965, the diagnosis is based on the following five findings:

1- A typical syndrome for MS demyelination
2- Objective evidence of central nervous system impairment
3- Confirmation of temporal dissemination
4- Confirmation of spatial dissemination
5- No better explanation than MS

Worldwide, about 2.5 million patients suffer from MS. Thus, multiple sclerosis is the most common inflammatory disease of the central nervous system and the most common disease that leads to permanent disability in young adults[43]. MS prevalence shows clear geographical differences. Generally, the prevalence of MS increases with the distance from the equator.

In the northern hemisphere, MS is the most common neurological disorder in young adults and the prevalence is higher in women than in men. The highest prevalence rates are between 35-64 years for both genders. The estimated annual incidence for Europe is 4.3 cases per 100.000 people [43].

Prevalence and incidence estimates for Germany vary depending on year, region and dataset, with more recent studies showing a prevalence of about 252,000 persons and an incidence rate of 18/100,000 persons [12].(see Figure 1)

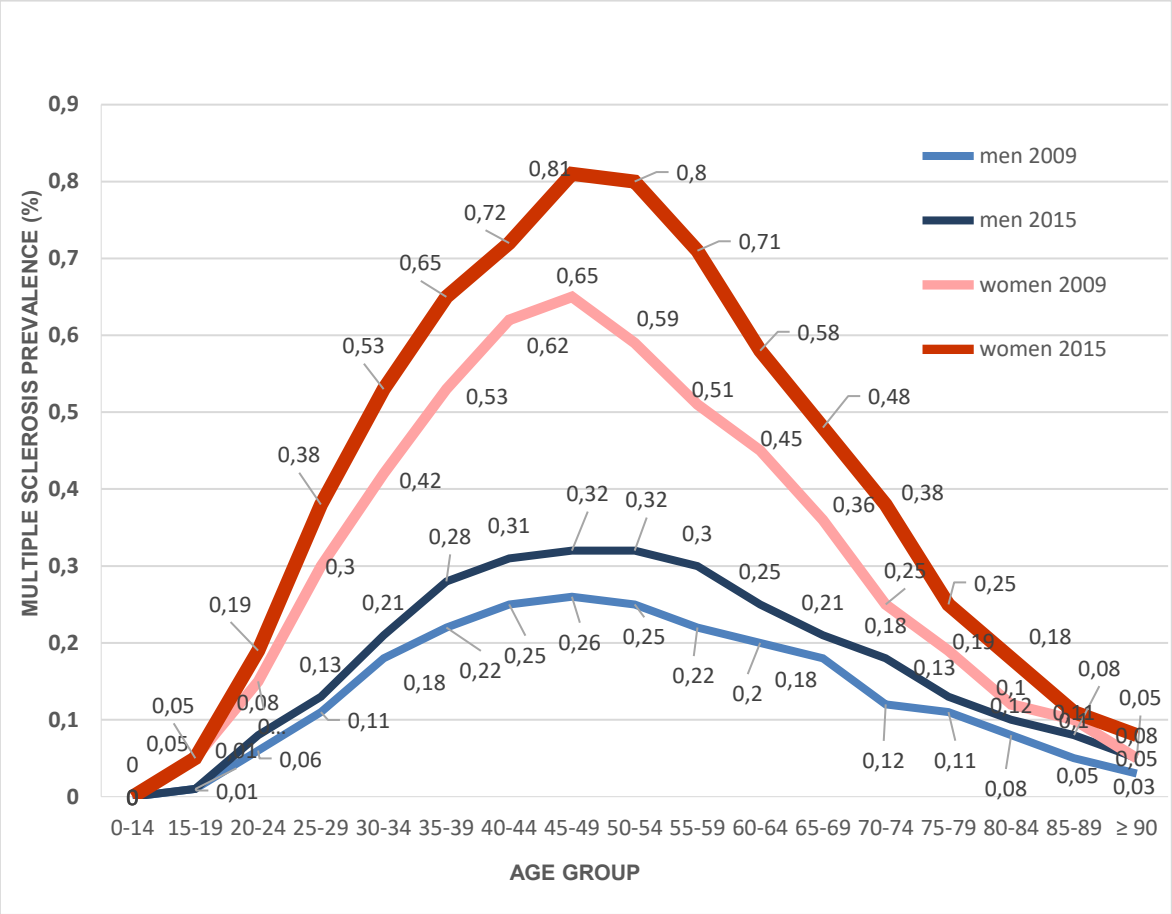

Figure 1: Diagnosis prevalence of multiple sclerosis according to 5-year age groups and gender in comparison of the years 2009 and 2015 (based on [35], KM6-statistics [57] and nationwide cross-statutory health insurance billing data, so called VDX data)

1.2 MS Symptoms

Sensory symptoms are the most common symptoms in MS (21-55%) and eventually develop in all MS patients. The impairment of touch (hypoaesthesia) and tingling feeling (dysaesthesia) are the most common sensory symptoms. Motor deficits can have a sudden onset or develop gradually. They manifest with paralysis in one or more extremities and spasticity (increased tone of the extremities), which worsen the ability to walk and coordination. Motor symptoms occur in 32% to 41% of patients, and in the course of the disease, the prevalence of these deficits may be higher than 60% [41].

In 14% to 23% of patients the first symptom of MS is optic neuritis (inflammation of the optic nerve). More than 50% of MS patients suffer from optic neuritis during their lifetime[40].

Cerebellar symptoms such as tremor, chanting language (slow and slurred speech) and balance problems (ataxia) develop during the course of the disease, but are very rarely present at disease onset.

Spinal injury resulting from MS lesions also cause bladder disorders such as urinary urgency and urinary incontinence. Up to 70% of MS patients have both bladder and bowel dysfunction [78].

Today it is known that in addition to physical function, cognitive function is also impaired. Between 40% and 70% of patients suffer from cognitive problems [58]. Age, duration of illness, and disability do not predict the extent of cognitive deficits, nor does the lesion load detected in MRI. Cognitive symptoms are often overlooked in the standardized neurological examination. Episodic memory, processing speed, verbal fluency and abstract thinking may be impaired. Further exploration of cognitive deficits in the context of MS is provided in chapter 1.10.

Affective disorders, such as depression and anxiety disorders, also occur significantly more frequently in MS patients than in healthy individuals. In long-term studies, the incidence of depression was up to 50% [20]. Both depression and anxiety disorders do not correlate with physical or cognitive impairment, nor with the MRI lesions[31] .

1.3 MS disease course

The majority of patients diagnosed with MS (80-85%) have a relapsing-remitting form (RRMS). This type of MS is characterized by episodes of sudden onset of new or worsening symptoms followed by full, partial, or no recovery. The typical onset of relapsing-remitting MS is between 20 to 40 years of age with a significantly higher proportion of women affected. Many studies have shown that 25% to 40% of patients with RRMS go into a secondary progressive MS form (SPMS) after 20 years of disease duration. There may be superimposed relapses during the progressive phase, but the patients show disease progression over a period of at least 6 months [51].

Typical is a gradual worsening of walking ability, coordination, spasticity, and bladder emptying disorders. Often an increase in cognitive deficits is reported in the progressive phase.

About 10% to 15% of patients have a progressive disease course from onset, and are classified as having PPMS. This form of MS is characterized by gradual disability progression. It is clinically characterized by myelopathy symptoms, rarely by brainstem or cerebellar symptoms. Patients have worsening of walking ability, balance problems, spasticity, paralysis of the extremities, and bladder dysfunction. PPMS occurs less frequently than the relapsing-remitting form [59]. Patients with PPMS tend to be older (mean age of 40 years compared with 30 years for RRMS patients) and there is no gender difference. MRI lesions look similar to those in RRMS, but especially in cerebral regions they are significantly fewer in number and are not enhanced after the administration of gadolinium.

1.4 Neuropathology

For MS, focal lesions with demyelination and astrocytic scars result specifically from the inflammatory process. These lesions are found in the white matter of the brain and spinal cord but also in the gray matter of the cortex, in the brainstem, and in the spinal cord[27]. Demyelination is defined as destruction of the myelin sheath and olygodendrocytes; axons remain partially intact. These lesions can be partially or completely repaired by remyelination, the efficiency of which varies from patient to patient [62]. In addition, diffuse neurodegeneration takes place, causing global atrophy.

MS patients may have several distinct lesions: active lesions with pronounced blood-brain barrier disruption, chronic active lesions that slowly spread with low demyelinating activity at the edge of the lesion and no disruption of the blood-brain barrier, inactive lesions, and remyelinating shadow plaques[45]. The active lesions are found in the early stages of the disease and are less common in patients in the progressive phase. Large neuropathological studies showed no differences between SPMS and PPMS patients with respect to the type and spread of lesions [53].

The cortical lesions can be easily seen with imaging and are localized in the cortical, subcortical or intracortical regions of the brain, while abundant subpial lesions are difficult to detect with imaging[28]. Cortical lesions occur in the early stage of the disease, but the size and number increase in the course of MS and the lesions are very pronounced in progressive MS, with no distinction between primary and

secondary progressive MS[48]. The subpial cortical lesions are associated with meningeal inflammation. The meningeal inflammation consists of aggregates of T cells, B cells and plasma cells [74]. The severity of meningeal inflammation correlates with the spread of subpial cortical demyelination and neurodegeneration. These aggregates are typical for SPMS patients and are absent in most PPMS patients, but they are also present in PPMS patients with rapid progression [16].

1.5 Immunology

Many immunological studies have been conducted to find MS-specific biomarkers and to elucidate the mechanisms of the disease. Up until now, the biomarker with highest clinical relevance appears to be the IgG index and the presence of oligoclonal bands, reflecting the intrathecal synthesis of immunoglobulins. These biomarkers are very sensitive for MS, but they may also occur in other inflammatory diseases of the CNS. With respect to PPMS, the presence of oligoclonal bands is important for the diagnosis and is included in the new diagnostic criteria [77].

In MS two inflammatory processes take place; they happen in parallel and independently from each other. The first is the invasion of B and T cells through the damaged blood-brain barrier. These cells attack the white matter and create the classic active lesions. The second process consists of a slow accumulation of T and B cells in the meninges and perivascular spaces [15]. These cells initiate cerebral and cerebellar cortical lesions and the resulting diffuse neurodegeneration of the white and gray matter. The first process is found in acute and relapsing MS. The second type of inflammation is already present at the onset of the disease, but the amount increases with the duration and age of the patients. CD8+ T cells promote neuroinflammation, and B lymphocytes promote demyelination and neurodegeneration as a result of production of neurotoxic factors. However, plasma cells and plasma blasts also express IL-10, and it is possible that these cells may actually reduce inflammation [56]. The role of B cells is dependent of the stage of differentiation and the activity status of the lesions. These two types of inflammation occur in both RRMS and in progressive MS. It remains unclear whether these two different processes reflect immune responses to different antigens or to a single antigen [34].

1.6 Aetiology

It is often reported that the cause of MS is unknown; however, risk factors have certainly been identified. Epstein-Barr virus infection, sun exposure, smoking, and vitamin D concentrations combined with a genetic background play an important role in the development of MS. Migration studies have shown that emigrants migrating from high risk to low risk countries in adolescence have a low risk, while those relocating from low risk to high risk acquire a higher risk of developing MS[1]. This observation supports the theory that exposure to specific environmental factors in the first two decades of life may influence the risk of disease development.

Elevated vitamin D levels before age twenty are associated with a low risk for MS. UV radiation protects against MS, both by increasing vitamin D concentrations and also by influencing the immune system[52]. Vitamin D suppresses B- and T-cell proliferation, switching the T cells from inflammatory effects to regulatory responses [6].

Smoking is a well-known risk factor for development of MS, and also increases disease activity by altering the response of T-helper 17 cells in the lungs[82]. Oral tobacco does not have this effect on the T cells [32].

Although it has long been thought that the major risk factor for development of MS is a viral infection, no single causatory virus has been identified so far. There is a link between increased risk of MS and mononucleosis infectiosa or increased antibodies to EBVNA1. It is not clear how EBV infection leads to MS [29]. The postulated link between viral infection and MS led to use of interferons as an anti-MS therapy.

No specific diet is associated with MS. The role of dietary factors is complex and many dietary components such as vitamin D, A, salt, omega-3 and polyphenols can alter immune modulation [67].

The microbiome-which contains trillions of microorganisms in the gut alone-have the capability to alter lymphoid tissues. The microbiome plays a role in the development of diseases, infections, atherosclerosis, cancer, and autoimmune diseases [55]. Recent studies show that the microbiome participates in many immunmodulatory processes and can protect from or induce disease.

In the microbiome of MS patients, it has been shown that bacterial species Methanobrevibacter and Akkermansia are increased in number and Butyricimonas are decreased [37]. This clinical significance of these observations is not yet elucidated.

1.7 Diagnosis

The diagnostic criteria for MS include the occurrence of at least two symptomatic episodes and at least two symptoms that reflect the involvement of two non-adjacent white matter pathways. Symptoms must last for at least 24 hours, with a minimum interval of one month between episodes. At least one of the two required disease symptoms must be verified by clinical neurological examination, the other can be assessed by paraclinical procedures such as MRI or evoked potentials.

More than 95% of MS cases have characteristic pathology visible on MRI. MRI lesions correspond to the pathological pattern of perivenular demyelination perpendicular to the ventricular surface (Dawson's finger). The lesions are multifocal in the cerebrum, brainstem and spinal cord. Lesions of the anterior corpus callosum are of diagnostic value, as this region is usually spared in cerebrovascular diseases. Mononuclear pleocytosis and increased intrathecal IgG production are typical CSF changes in MS. The CSF protein is usually normal or slightly increased [77].

No single clinical sign or single diagnostic test can prove or rule out MS. Alternative diagnoses should always be considered. This is especially true if the symptoms are limited exclusively to the posterior fossa, the craniocervical junction, or the spinal cord; if the patient is younger than 15 or older than 60 years old; the disease is continuous from the beginning; the patient has never had visual, sensory or bladder dysfunction; or paraclinical findings appear atypical [39].

The McDonald criteria provide an internationally recognized summary of standardized clinical criteria for diagnosis (Table 1).

Table 1 McDonald Criteria for MS Diagnosis

Clinical Presentation	Additional Data Needed for Diagnosis
≥2 clinical attacks and objective evidence of ≥2 lesions	None
≥2 clinical attacks and objective evidence of 1 lesion	DIS: an additional attack implicating a different CNS site OR by MRI[a]
1 clinical attack and objective clinical evidence of ≥ 2 lesions	DIT: an additional clinical attack OR by MRI[b] OR CSF-specific oligoclonal bands
1 clinical attack and objective evidence of 1 lesion	DIS: an additional clinical attack implicating a different CNS site OR by MRI[a] OR DIT:an additional clinical attack OR by MRI[b] OR CSF-specific oligoclonal bands

Based on Thomson AJ, Banwell BL, Barkhof F. et. al. Diagnosis of multiple sclerosis:2017 revisions of the McDonald Criteria. Lancet Neurol.2018; 17:162-73
[a]DIS by MRI: new lesions on follow-up imaging or both gadolinium-enhancing and non-enhancing lesions on single MRI
[b]DIS by MRI: ≥1 symptomatic or asymptomatic lesion in ≥2 areas including cortical/juxtacortical, periventricular, infratentorial or spinal

1.8 Assessment of MS disease course

For the clinical evaluation and quantification of the symptoms in patients diagnosed with MS, the Expanded Disability Status Scale (EDSS) is the scale that is most often used [46]. The scale was created in 1983 and has been used since then. It evaluates 8 functional systems that are affected in MS and summarizes the clinical status as a number between 0 at 10 (0=normal neurological examination, 10=death due to MS). These 8 functional systems are: pyramidal, cerebellar, brain stem, sensory, bladder-bowel, visual, cerebral and ambulation (Table 2).

The scale provides a simple index of disease progress over time, which is a major advantage.

The EDSS scale has also many disadvantages. The definition of a 1 point deterioration is different for each functional system and level. The time a patient stays at a certain score also varies, for example a patient may have an EDSS of 4 for one year and of 6 for four years. The higher steps of EDSS are not sensitive enough when it comes to deterioration of neurological symptoms. Also, cognitive

deficits are not well-captured with EDSS and these are a significant cause of disability at all score levels [3]. For lower scores, the changes in EDSS are well represented, higher scores are less sensitive to changes. The pyramidal and cerebellar functions contribute significantly to the EDSS score, the brainstem and sensory functional systems contribute moderately, while the cerebral has a limited contribution, especially for higher scores.

Also, the EDSS score does not represent walking ability properly (for example it shows no changes at distances over 500 m). Additionally, the same EDSS score can mean very different things functionally; for example, an EDSS of 4,5 can mean that the patient can walk 300 m without aid, or alternatively, the patient has 4 points in two functional systems [2].

Nevertheless, the EDSS remains the most widely used scale for measuring the disability of patients with MS.

Table 2 Expanded Disability Status Scale for MS as defined by Kurtzke[47]

0	Normal neurological examination (all grade 0 in FS; Cerebral grade 1 acceptable)
1.0	No disability, minimal signs in one FS (i.e., grade 1 excluding Cerebral grade 1)
1.5	No disability; minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, other 0 and 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability is severe enough to impair full daily activities (e.g., to work without special provision). (Usual FS equivalents are one grade 5 alone others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or a combination of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or a chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of the arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of the day; has some effective use of arms(s); retains some self-care functions. (Usual FS equivalents are combinations, generally grade 4+ in several systems)
9.0	Helpless bed patient can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10	Death due to MS

Another scale for assessing the degree of impairment in MS patients is the Multiple Sclerosis Functional Composite (MSFC). The following tests are used: Timed 25-Foot Walk (T25W) for leg function and ambulation, 9-hole Peg Test (9HPT) for arm and hand function, and Paced Auditory Serial Addition Test (PASAT) for cognition function.

1.9 Treatment of MS

Although there is no cure for multiple sclerosis, a suitable regimen can slow disease progression, improve symptoms, and help improve quality of life. MS medications can be divided in three categories: therapy for acute relapses, therapy for slowing disease progression, and symptomatic therapies. The therapy for acute relapses consists of short-term administration of anti-inflammatory agents such as corticosteroids [23]. These do not affect the course of the disease, but improve the symptoms and shorten the time for recovery from acute attacks.

Disease-Modifying Therapies (DMTs) are used to reduce clinical and subclinical disease activity and prevent disability accumulation [19]. Treatment should begin as soon as possible after diagnosis in order to prevent disease progression and a high rate of relapses [30]. Unfortunately, these therapies have little effect in the progressive forms of MS [24].

The currently approved DMTs that slow disease progression and prevent the development of new inflammatory lesions are listed in Tables 3, 4 and 5.

Table 3 Treatment Chart MS, Self-injected Medications

Self-injected Medications for MS		
Medication Name	**Type of Drug**	**How administered**
Avonex® (Interferon beta-1a)	Immune system modulator with antiviral properties	30 micrograms taken via weekly intermuscular injection
Betaferon® (Interferon beta-1b)	Immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day
Copaxone® (glatiramer acetate)	Synthetic chain of four amino acids found in myelin	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection
Extavia® (interferon beta-1b)	Immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day
Plegridy® (interferon beta-1a)	Immune system modulator with antiviral properties	125 micrograms taken via subcutaneous injection once every two weeks
Rebif® (Interferon beta-1a)	Immune system modulator with antiviral properties	44micrograms taken via subcutaneous injection three times weekly

Table 4 Treatment Chart MS, Oral Medications

Oral Medications for MS		
Medication Name	**Type of Drug**	**How administered**
Aubagio® (teriflunomide)	Immunmodulator	14 milligram tablet taken orally, once per day
Tecfidera® (dimethyl fumarate)	Immunmodulator	240 milligram tablet taken twice daily
Gilenya® (fingolimod)	S1P-receptor modulator	0,5 milligram capsule taken orally once per day
Mavenclad® (cladribine)	Purine antimetabolite, Selective immune reconstitution therapy	Cumulative dosage of 3,5 mg/kg administered orally and divided into 2 treatment courses. Each treatment course is divided into 2 treatment cycles.

Table 5 Treatment Chart MS, Infused Medications

Infused Medications for MS		
Medication Name	**Type of drug**	**How administered**
Lemtrada® (alemtuzumab)	Humanized monoclonal antibody	Course of five days via intravenous infusion followed one year later by a second three-day course
Ralenova® (mitoxantrone)	Antineoplastic agent	Intravenous infusion once every three months
Tysabri® (natalizumab)	Humanized monoclonal antibody	Intravenous infusion every four weeks
Ocrevus® (ocrelizumab)	Humanized monoclonal antibody	Intravenous infusion every six months

The third component of MS therapy is symptomatic therapy. MS symptoms such as spasticity, pain, paraesthesia, fatigue, mood changes, cognitive impairment, bowel and bladder dysfunction occur as a direct consequence of nerve damage [33]. Symptomatic therapy can be both nonpharmacologic and pharmacologic. Physical and occupational therapy can significantly improve spasticity, associated pain and fatigue.

1.10 Cognition in MS

Cognition represents the function of various neural pathways involved in information processing by the brain. These pathways are inclusive of both correlated and interdependent higher-level cognitive skills such as: executive functions, learning and memory, complex attention, perceptual-motor function and social cognition, as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)[22]. Impairment of one or more of these domains may cause dysfunction of the global cognitive performance[84].

Jean-Martin Charcot was first to describe cognitive problems in MS, but it was not until 1991 when S. Rao brought renewed attention on the topic, aiming to reveal the precise mechanisms, in order to develop effective treatments[66].

Although all cognitive domains may be altered in MS, the most affected ones are the episodic memory and information processing speed. The most frequent cognitive domains of interest are described in Table 6.

Table 6 Frequency of cognitive impairment in patients with multiple sclerosis (MS) by cognitive domain

Cognitive Domain	Frequency
Learning Memory	40-65%
Visual Episodic Memory	20-75%
Verbal Episodic Memory	15-80%
Complex Attention	5-25%
Information processing Speed	15-50%
Executive Functions	15-25%
Working Memory	15-60%
Inhibitory control	15-30%
Language	20-58%
Verbal Fluency	15-25%
Social Cognition	20-40%

Based on Rao et al. 1991, Benedict et al. 2006, Chiaravaloti et al. 2008, Dulau 2017, Cotter et al.2018, Ciampi et al. 2018, Ntoskou et al. 2018.

The relationship between cognitive impairment in MS patients and the natural progression of the disease remains poorly described. When studying the prevalence of cognitive deficits in different forms of MS, one has to consider not only the pathomechanism but also the duration of the disease and the age of the patient [4]. This is sometimes difficult to achieve, as relapsing MS and secondary progressive MS occur successively. Furthermore, current available studies are still facing challenges like the use of different neuropsychological tests and different cognitive areas that were studied [3].

Cognitive Impairment and Disease Duration

The influence of disease duration on cognition has been investigated in a clinical study by Amato et al, in which 50 patients with short-term disease duration and 70 healthy controls were examined. After 10 years, cognitive impairment was observed in short-term verbal memory, abstract reasoning and linguistic abilities; attention and short-term spatial memory were also involved [5]. At the start of the study, 74% of the patients had no cognitive problems; this proportion had decreased to 44% after 10 years. Nevertheless, after adjusting the duration of the illness and clinical course with respect to age and disability, the association with cognitive impairment was no longer significant, so that it is clear that age and duration of illness are very strongly associated [70].

Cognitive Impairment according to clinical phenotype

Relapsing-remitting MS

The frequency of cognitive deficits has been measured in many studies, but most of these studies had no control group. The frequencies of deficits varied from 21% to 45%. The cognitive profile in RRMS showed deficits mainly in information processing speed, verbal and visuospatial memory, and executive functions [63].

Secondary progressive MS

The epidemiology of secondary progressive MS has changed considerably in the last 15 years due to the development of new disease modifying therapies. Studies conducted in the 1980s showed that almost 75% of RRMS patients had converted to SPMS after 30 years [79]. In more recent studies, however, the number of patients converting from RRMS to SPMS was lower [76]. However, the frequency of

cognitive impairment in patients with SPMS seems to be very high, up to 80% [61]. Patients with SPMS are more frequently cognitively impaired than patients with RRMS in information processing speed (IPS), verbal fluency, verbal episodic memory, working memory, visuospatial construction and executive functions (EF)[65].

Primary progressive MS

For a long time, cognitive impairment in PPMS was considered very rare, due to the fact that PPMS appears to affect the spinal cord more than the brain [18]. However, recent studies showed cognitive impairment in 56% to 91% of PPMS patients. Cognitive deficits were seen in attention, IPS, working memory, EF and verbal episodic memory. Unfortunately, though, these studies did not have control groups and the increasing mean age of the patients could potentially explain the cognitive deficits [71].

1.11 Objectives

Cerebral symptoms such as cognitive impairment, fatigue, and psychopathology are commonly observed in multiple sclerosis (MS). However, there is no clear understanding of these cerebral symptoms and their progression in different types of MS.

Moreover, the connection between cerebral symptoms and the occurence of relapses (or a progressive course) has not been sufficiently investigated. Our study aims to fill this gap by investigating a wide range of cerebral symptoms and their course over a 1-year period within different types of MS. We compared MS types with healthy controls, as well as MS types with each other. In addition, we looked at individuals with and without history of relapses or a progressive course.

Moreover, MS-related disability is linked with cognitive impairment, but associations with psychopathology and fatigue are still unclear. Here, the study aims to clarify these relationships.

Current available studies indicate that a short cognitive test battery (BICAMS) is sufficient to detect cognitive impairment in MS. However, it is not clear whether other cognitive tests may be more adequate in detecting MS-related cognitive impairment. Our study extends the BICAMS battery in order to provide evidence for the use of even more valid and less time-consuming tests.

The following questions were posed:

1.1a) Do all MS types have more cerebral symptoms (cognitive impairment, fatigue and psychopathology) compared with healthy controls?

1.1b) Do MS types differ in cerebral symptoms (cognitive impairment, fatigue and psychopathology)?

1.1c) Are cerebral symptoms (cognitive impairment, fatigue and psychopathology) related to the existence of a relapse or progressive disease course?

1.2a) Do MS types deteriorate more in cerebral symptoms (cognitive impairment, fatigue and psychopathology) compared with healthy controls?

1.2b) Do MS types deteriorate differentially in cerebral symptoms (cognitive impairment, fatigue and psychopathology) over one year?

1.2c) Are relapse and progression of MS symptoms in the history associated with changes in cerebral symptoms (cognitive impairment, fatigue and psychopathology) over one year?

2a) Is MS disability measured with EDSS related to cerebral symptoms (cognitive impairment, fatigue, or psychopathology)?

2b) Is MS disability measured with EDSS related to cognitive test results?

3a) Which cognitive tests are most valid in detecting cognitive impairment related to relapse and progression?

3b) Which cognitive tests are most valid in detecting cognitive impairment in different MS types?

3c) Which cognitive tests are most valid in detecting patients with MS versus healthy controls cognitive deficits?

2 Methods

2.1 Study Design

The study was carried out at the Ulm University Hospital from 2017 to 2019. The subjects were followed for a year and regularly examined clinically and tested neuropsychologically. After admission to the study, the baseline examination was carried out at time 0 and the follow-up after 12 months. In addition to the clinical examination, EDSS and neuropsychological parameters were collected; all of the collected values are explained in detail in the following sections. The study protocol was submitted to and approved by the responsible ethics committee in Ulm before the study began. (File number 157/16)

Probands

Subjects were recruited from the MS outpatient clinic in Ulm for the study and largely came from Ulm and the surrounding area. The following groups were recruited: 22 subjects with RRMS, 22 subjects with SPMS, 22 subjects with PPMS and 22 healthy subjects.

A two-factor analysis of variance (ANOVA) model with repeated measurements was applied, using the intrasubject factor “time of examination” (T0, T1) and the intersubject factor “course type” (4 groups). In order to account for interaction effects in addition to main effects, according to Cohen's conventions, an effect size of $f = 0.4$ should be applied (small effect: $f = 0.1$; medium effect: $f = 0.25$). Assuming an error probability of $\alpha = 0.05$ and a test power of $1-\beta = 0.95$, this results in a total sample size of $n = 88$ required for the detection of a group difference.

The healthy control subjects were recruited for the most part from the caregivers of the MS patients and were therefore largely a convenience sample. Age and sex were matched to study patients as far as possible. An overview of the demographic data of the entire collective and the subgroups are shown in the results section.

The author of this study explained to the participants in detail about the purpose, the objective and the duration of this investigation. This was followed by the signature of the written informed consent. Informed consent could have been revoked at any time by the patients as well as by the healthy controls without any disadvantages. The currently valid data protection regulations were taken into account when

collecting and processing the data. The author carried out the investigations, evaluated the test forms and handled the data.

A requirement for participation was the fulfillment of the following criteria:

2.2 Inclusion and exclusion criteria

Inclusion criteria

- Age between 18 and 85
- Clinically proven MS
- The patients must have been able to understand the purpose of the examination and have been able to communicate with the examiner so that it was possible to carry out all planned study measures properly
- Patients must have been able to give their consent to participate in the study

Exclusion criteria

- Patients suffering from another illness, if the other illness was expected to impair the clinical assessment of MS symptoms
- Patients with a history of severe depression or severe psychiatric illness

2.3 Assessments

At baseline (time 0) and at 12 months, all subjects underwent a comprehensive neurological examination, neuropsychological test battery, and disability questionnaires.

For the neuropsychological examination, we included tests that asses the cognitive domains affected by MS- COWAT for verbal fluency, VLMT for verbal memory, BVMT-R for visual memory, SDMT for sustained attention, PASAT for sustained attention and working memory, BDT for spatial visual ability and motor skill.

The sequence of the individual assessments was carried out according to a uniformly defined scheme. The assessments were performed in the same order for

all test participants in order to keep the influence of fatigue effects on the participants constant. The following tests and parameters were carried out and recorded in the order listed at both examination times:

Table 7 Study Design with test parameters and survey times, Ulm University Hospital (2017-2019)

Study Design		
Parameter	**Baseline**	**Follow-up at 12 months**
Neurological examination	X	X
Expanded Disability Status Scale	X	X
Controlled Oral Word Association Test	X	X
Verbal Learning and Awareness Test	X	X
Brief Visuo-Spatial Memory Test-revised	X	X
Symbol Digit Modalities Test	X	X
Paced Auditory Serial Addition Test	X	X
Block design Test	X	X
Hospital Anxiety and Depression Scale	X	X
Fatigue Scala for Motor and Cognitive Functions	X	X

MS-related disability

The EDSS has been described in Chapter 1.8

Cognition

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT, letters F-A-S) has been used to measure both language and executive function domains.

In this test, the subject should say as many words as possible that begin with the letters F, A, or S (German language). For every letter, the subject has 60 seconds of time. Proper names, numbers or words with different tenses or endings once the root word has been given are excluded from the rating. The letters F, A, and S differ in their frequency in spoken German and thus allow the level of difficulty to be graded. The result is a raw score comprised of the total number of said words.

VLMT- Verbal learning and memory test

The VLMT is used to assess memory functions (learning performance, consolidation into long-term memory and recognition performance of verbal material). After the test subject receives instructions on how the test is carried out, the test begins with a learning phase. The subject is read a word list consisting of 15 words five times; after each presentation the test subject is to say as many words as possible from memory. The word list is queried again after an interference list with 15 other words has been read and queried. This concludes the first part of the test.

A second part takes place after approximatively 30 minutes. In the meantime, the subject is to take other neuropsychological tests that are non- linguistic (the tests BVMT-R, SDMT, PASAT and BDT were administered at this point). The first list of words is then queried again without being presented again. Finally, a recognizable list consisting of the 30 words from the two lists, as well as 20 additional words is read, and the subject must indicate whether each word came from the initial word list.

The following values are used to assess the verbal memory performance of the test subjects: the reproduced words from the first five rounds are summarized as an overall learning performance value; subjects were able to achieve a maximum score of 75. For the number of correctly reproduced words according to the interference list after a delay, test values between 0 and 15 are possible: 0 would indicate that no words were correctly recognized and 15 that every word was correctly recognized.

BVMT-R- Brief visuo-spatial memory test-revised

The brief visuo-spatial memory test is used to assess visual memory capacity and spatial memory. The test material consists of a stimulus sheet on which six independent geometric figures are arranged, and a total of three answer sheets.

The examiner presents the subject the sheet with the 6 figures for ten seconds. Then the sheet is covered. The subject must draw the figures as correctly as possible in the original position. The subject has no maximum time for this task, and decides when the test ends. The answer sheet is collected and the subject receives the second answer sheet in exchange. Another iteration follows in which the stimulus is presented again for 10 seconds and then covered. A total of three iterations are performed. The second part of the test follows after 30 minutes, when the subject has to draw the 6 figures without the stimulus being presented.

Two points are awarded for a figure reproduced in the correct place on the answer sheet and in the correct form. A point is awarded for a correctly reproduced figure in the wrong position. A point is also awarded for a figure with errors that is drawn in the correct position.

SDMT- Symbol digit modalities test

The SDMT records the speed of information processing and appears to be the most sensitive test for this capability. Working memory influences the test result to only small extent and the test-retest learning effect is very low. It is therefore particularly well suited for follow-ups. In this test, a series of geometric figures in a legend is assigned a numerical value from one to nine.

The subject assigns the corresponding numerical values to the figures depicted in the legend and has exactly 90 seconds to complete the task. The final test score corresponds to the number of correctly displayed numerical values. To make sure that the test person has correctly understood the test instructions, a short practice session is carried out before the actual test in that the first ten symbols on the test sheet are assigned under the supervision of the examiner. If necessary, the examiner should correct the test person at this time. After this short test phase, the actual test begins.

PASAT- Paced Auditory Serial Addition Test

The PASAT is intended to provide a rough assessment of cognitive function. During the test, the patient receives a new number from a tape every 3 seconds. It is the patient's task to add the last two numbers together. To cope with the task, the last named number must be kept in mind during addition in order to prepare for the next addition. Therefore, arithmetic skills and above all working memory and attention (in particular shared attention) are required to perform the test. The patient receives one point for each correct calculation, and a maximum of 60 points can be achieved.

For the VLMT, BVMT-R, SDMT, and PASAT, several versions of the test are provided, which can be used alternately in the course of studies to counteract the effects of test repetition.

Block design Test

This test is part of several test batteries for intelligence measurement, and assesses spatial perception, visuomotor coordination, and distinction between parts and the whole in abstract visual patterns. The Block design test includes nine similar red and white patterned cubes and nine different printed sample templates as well as a test protocol for the examiner. The task for the test person is to recreate specified patterns using the cubes. The different patterns consist of two, four, or nine dice, and there are varying time limits allowed for replication. Up to sample number 4, the test subject receives two points on the first correct attempt and one point on the second correct attempt. From sample number 5 to 8, the subject receives 4 points on the first correct attempt. From sample number 9 to 14, the subject receives 4, 5, 6 or 7 points. If the subject solves the puzzle quickly, time bonus points are awarded. Without time bonus points, every correct reproduction from sample 1 to 4 receives 2 points, and from 5 to 14 receives 4 points.

In order to show the test subjects how to proceed, the first sample (sample number 5, the starting pattern) is shown by the examiner. The subject should then reproduce the pattern. The subject then shown a second pattern (number 6) based on a template. If the subject scored zero or one point in questions 5 and 6, four easier

patterns are presented in descending order (patterns 1 through 4) until two consecutive patterns were scored with two points. If this happens, the test continues with pattern 7 and two points are credited for the remaining easier tasks. Subjects who solve patterns 5 and 6 with 2 or more points are not presented the easier patters 1 to 4 and are simply credited with the highest score for them. The test is terminated when the subject scores zero points on two successive tasks. A maximum of 66 points (with time bonuses) can be achieved.

Psychopathology

HADS- Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale is a self-assessment sheet developed by Snaith and Zigmond (1983) to measure anxiety and depression in routine medical care. The validity of the scale, its instrumental usability, and patient acceptance was documented in over 100 publications including a total of 15000 patients.

The HADS was specially designed for use in “non-psychiatric hospital departments” and thus has a stronger emphasis on milder forms of anxiety and depression and their quantification. Therefore, the questionnaire is well suited as a descriptive screening method for the detection of symptoms of anxiety and depression by somatic illness such as in MS patients.

The HADS contains 14 items (7 each per subscale in an alternating sequence) with four-step answer options (0-3). Adding the subscales results in a possible range of values from 0 to 21. Values of <7 on each subscale were originally regarded as unremarkable. Values from 8 to 10 are considered borderline and those >11 as conspicuous. The cutoff values given by Zigmond and Snaith are to be understood as “orientation marks” and not as absolute determinations.

The anxiety subscale

The symptoms of the anxiety scale correspond to the guidelines of generalized anxiety disorder according to ICD10. General fears, worries and nervousness are discussed as well as aspects of motor tension or deficits in relaxation. These contain a body reference, but according to the construction there is no statement about physical complaints. An item takes into account the prevalence of panic symptoms, which can often be found in the context of somatoform complaints.

Table 8 shows the different categories of fear and the associated items on the subscale.

Table 8 Anxiety Subscale of the HADS

Anxiety Subscale of the HADS	
Anxiety Items	**Category**
I feel tense or “wound up”	Nervousness
I get a sort of frightened feeling as if something awful is about to happen	General fears and concerns
Worrying thoughts go through my mind	General fears and concerns
I can sit at ease and feel relaxed	Aspects of motor relaxation and relaxation deficits
I get a sort of frightened feeling like butterflies in the stomach	Aspects of motor relaxation and relaxation deficits
I feel restless as I have to be on the move	Aspects of motor relaxation and relaxation deficits
I get sudden feelings of panic	Panic attacks

Hermann et al. 1995, Anxiety Subscale of the Hamilton Anxiety and Depression Scale (HADS)

The depression subscale

The items on the depression subscale (Table 9) ask about symptoms such as loss of motivation and zest for life, loss of interest, joylessness and reduced drive. In the ICD classification, these are key symptoms of a depressive episode.

Table 9 Depression subscale of the HADS

Depression subscale of the HADS	
Depression Items	Category
I still enjoy the things I used to enjoy	Joylessness
I can laugh and see the funny side of things	Joylessness
I feel cheerful	Joylessness
I feel as if I am slowed down	Reduced drive
I have lost interest in my appearance	Loss of interest
I look forward with enjoyment to things	Joylessness
I can enjoy a good book or radio or TV program	Loss of interest

Hermann et al. 1995, Depression subscale of the Hamilton Anxiety and Depression Scale (HADS)

According to the recommendation of Snaith and Zigmond (1983), a cut-off value of >11 was chosen as the pathological value when using the two subscales.

Fatigue

FSMC- The Fatigue Scale for motor and cognitive functions

The FSMC as a standardized self-assessment procedure for recording subjectively experienced motor and cognitive fatigue was developed for use by MS patients[64]. Using 20 items, the scale records the extent of the perceived cognitive and motor fatigue with the help of a five level Likert scale, which ranges from not at all=1 to completely true=5. The evaluation can be done separately for each subscale or as an aggregated score. A maximum value of 50 points per subscale can be achieved, or 100 points for the entire scale. A patient who has neither motor nor cognitive fatigue would score a total of 20 points. In addition, cut-off values have been defined which make it possible to grade fatigue from mild to moderate to severe. To differentiate between normal and pathological fatigue, the limit of the overall scale is 43 points, for the cognitive scale at 22 and for the motor scale also at 22.

Composite scores – primary outcomes

The global cognition score was calculated by averaging all eight *z*-standardized cognitive test scores [73]. It was multiplied by -1 in order to transform it to a cognitive impairment score. Based on theoretical consideration, an executive function subscore was built by averaging z-standardized SDMT, COWAT, BDT, and PASAT scores (see Figure 3a).

An episodic memory subscore was constructed from VLMT total score, VLMT delayed recall score, BVMT-R total score, and BVMT-R delayed recall score (see Figure 3b).

A visual cognition subscore was built from BVMT-R total score, BVMT-R delayed recall score, SDMT, and BDT test (see Figure 3c).

A verbal cognition subscore was constructed from VLMT total score, VLMT delayed recall score, PASAT, and COWAT (see Figure 3d).

Psychopathology score was calculated by averaging z-standardized anxiety and depression scores from the HADS. Fatigue score was built by averaging z-standardized motor and cognitive fatigue scores from the FSMC. The cerebral symptoms score was built by averaging z-standardized cognitive impairment score, fatigue score and psychopathology score (see Figure 2).

2.4 Statistical analyses

For group comparisons, analysis of covariance (ANCOVA) was used. Factors included group [HC vs RRMS, PPMS, SPMS], MS type [RRMS, PPMS, SPMS], history of a progressive course [yes, no], history of relapses [yes, no]). Covariates included age and education for cerebral symptoms and cognitive impairment as well as age for psychopathology and fatigue as outcomes. The Tukey significance difference test was used for *post-hoc* pairwise comparisons following ANCOVAs. When the homogeneity of variances was violated, Games-Howell *post-hoc* tests were used. In additional analyses, disease duration was included as a covariate. *Post-hoc* analysis was performed with Bonferroni adjustment.

Additionally, effect sizes (ES) for group comparisons were defined as group differences (at baseline and change from baseline to 1-year FU) divided by baseline

standard deviation (z-standardization). Partial η^2 was calculated as effect size for the factors history of relapses and history of a progressive course.

Multiple regression analyses were performed to assess the relation of MS-related disability with all outcome variables. For cerebral symptoms and cognitive impairment as outcome variables age and education was accounted for. For fatigue and psychopathology only age was accounted for. Standardized beta (β) was reported as effect size measure.

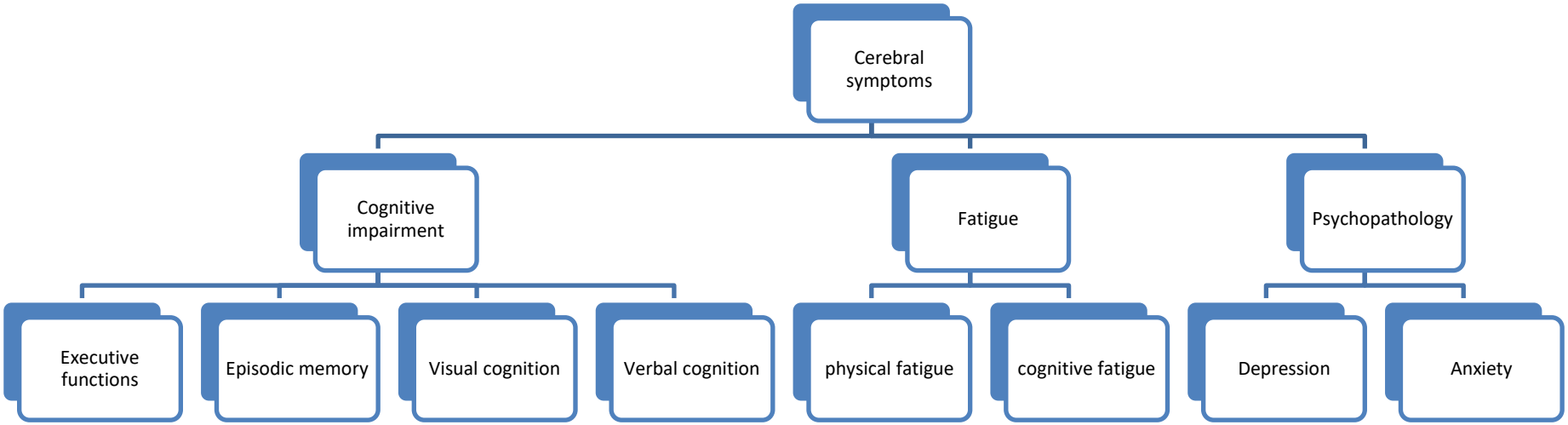

Figure 2 Schematic diagram for building the cerebral symptoms score

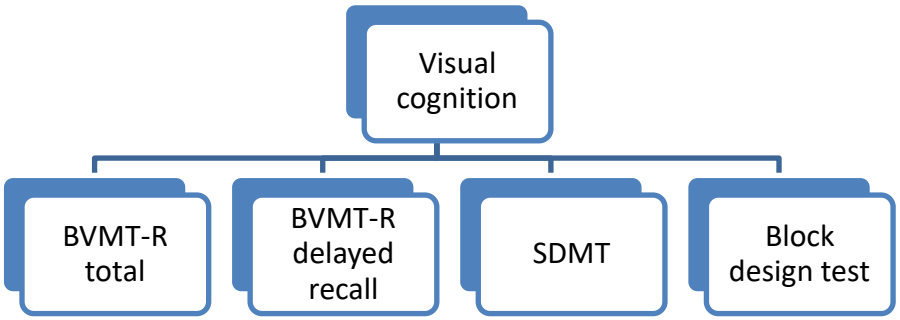

Figure 3 a

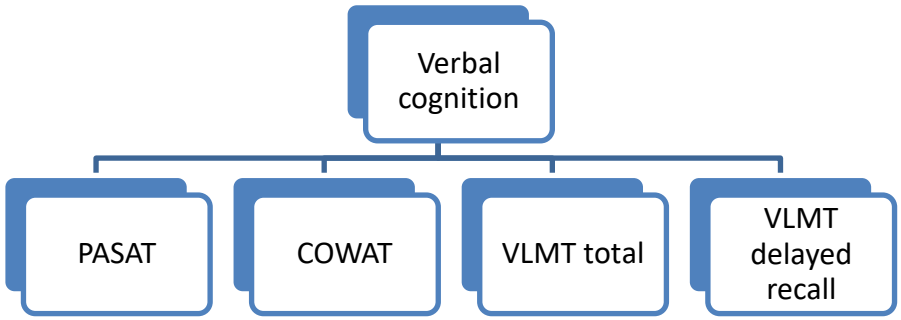

Figure 3 b

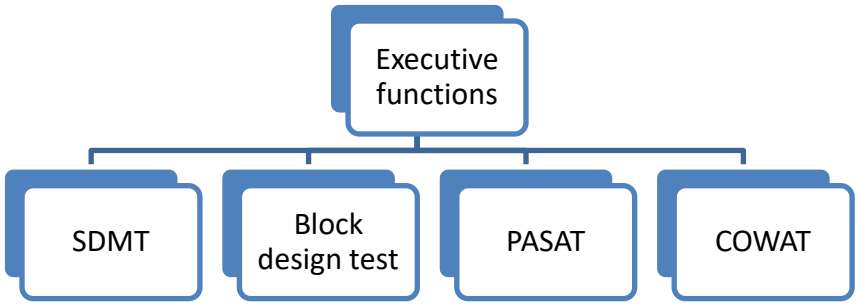

Figure 3 c

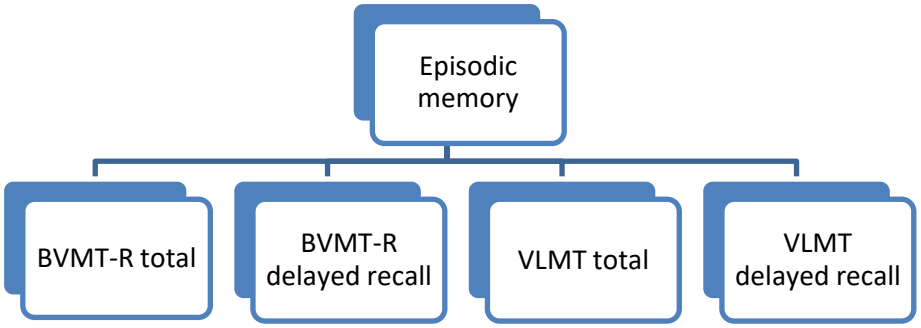

Figure 3 d

Figure 3 Schematic diagram for building cognitive subscores

VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-Paced Auditory Serial Addition Test

3 Results

3.1 Demographics and baseline characteristics

A total of 88 people were included in this study. This collective was composed of 4 groups: 22 patients with relapsing-remitting MS, 22 patients with secondary progressive MS, 22 patients with primary progressive MS, and 22 healthy subjects. Demographic and baseline values are presented in Table 10.

Table 10 Demographic and clinical characteristics of MS patients and healthy controls, Ulm University Hospital (2017-2019)

Descriptive variables	RRMS	SPMS	PPMS	Healthy controls	p[a]
N	22	22	22	22	
Demographics					
Age in years Mean(SD)	40.2 (10)	51.4 (8.8)	53.3 (6.6)	49.8 (14.8)	**<0.001**
Sex female/male	15/7	12/10	14/8	11/11	0.6[b]
Education Mean years (SD)	10.3 (2.5)	10.1 (2.7)	11.2 (1.9)	11.8 (2.2)	0.064
Clinical disability					
EDSS N (%)					
0-3	18 (82)	0	4 (18)		
>3-6.0	3 (13.5)	10 (45.5)	11 (49.5)		
>6.5	1 (4.5)	12 (54.5)	7 (31.5)		
Years since first symptom	11.8(8.7)	18.2(8.3)	10.8(7.2)		**0.008**
Years since MS diagnosis	8.2 (6.2)	14.6 (8.1)	6.1 (4.5)		**0.001**
Current therapy N (%)					
No therapy	5 (22.7)	9 (40.9)	12 (54.6)		
First line	13 (59.1)	5 (22.7)	-		
Second line	4 (18.2)	3 (13.6)	-		
Third line		2 (9.1)	7 (31.8)		
Biotin		3 (13.6)	3 (13.6)		

[a]one-Way ANOVA for comparing several independent means
[b] chi-square test of independence
SD-Standard Deviation, N-Number, EDSS-Expanded Disability Status Scale,MS-Multiple Sclerosis, RRMS-Relapsing-Remitting Multiple Sclerosis. SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis
First line therapies:interferons, glatiramer acetate, teriflunomide, dimethyl fumarate
Second line therapies:fingolimod,siponimod, cladribine
Third line therapies:natalizumab, ocrelizumab

3.2 Distribution of MS

Age distribution

The mean age in the relapsing-remitting MS group was 40.2±10 years, in the secondary progressive MS group was 51.4±8.8 years, in the primary progressive MS group was 53.3±6.6 years and in the healthy control group was 49.8±14.8 years (Table 10). A one-way ANOVA indicated that the mean ages were significantly different between the groups. Tukey *post hoc* analysis revealed that the mean age of the RRMS group was significantly less than that of the other groups, as would be expected given that RRMS patients are generally early in the course of the disease. In comparison with the other groups, the RRMS group was a mean of 11.18 years younger than the SPMS group (95% CI 2.89 to 19.47, p=0.004), 13.04 years younger than the PPMS group (95% CI 4.75 to 21.34, p<0.001), and 9.59 years younger than the healthy controls (95% CI 1.30 to 17.88, p=0.017). No other differences between the groups reached p-values of <0.05.

Sex distribution

In terms of sex distribution, there were approximately twice as many women as men in the RRMS and PPMS groups, and in the SPMS and control groups approximately equal numbers of men and women were included (Table 10).

A chi-square test of independence was conducted between the four groups and gender distribution in each group. There was no significant association between group type and gender distribution ($\chi^2(3) = 1.88$, p=0.6).

Education

A one-way ANOVA indicated that the mean years of education were not significantly different between the groups (Table 10). In the RRMS group, mean education was 10.3±2.5 years, in the SPMS 10.1±2.7 years, in the PPMS group 11.2±1.9 years, and in the healthy control group 11.8±2.2 years.

EDSS scores at baseline

RRMS patients had lower EDSS scores than patients with progressive disease. In the RRMS group, 18 out of 22 patients (82%) had an EDSS of 3 or less. In the SPMS group, all patients had an EDSS of greater than 3, the majority of which (12 of 22, 54.5%) with an EDSS of ≥6.5. Disability in the PPMS group was intermediate, with the largest number of patients (11 of 22, 49.5%) having scores between 3 and 6.5 (Table 10).

Disease duration

Mean disease duration (time since MS diagnosis) was 8.2±6.2 years for the RRMS group, 6.1±4.5 years for the PPMS group and 14.6±8.1 years for the SPMS group. A one-way ANOVA indicated that the mean disease duration was significantly different between the study groups (p<0.001; Table 10). Games-Howell *post hoc* analysis revealed that the SPMS mean disease duration was 6.45 years longer than the RRMS group (95% CI 0.62 to 12.29, p=0.025) and 8.5 years longer than the SPMS group (95% CI 3.16 to 13.84, p=0.001).

Therapy

In this small patient group, fifteen separate prior or concomitant medications were reported. Therefore, for demographic purposes, we grouped patients according to type of therapies they were receiving at the start of the study. Patients may have had multiple therapies before study start; the assignment to therapy groups was based on the therapy the patients were receiving at the baseline visit.

The groups were as follows: 1) patients who had had no DMTs (treatment-naive); 2) patients being treated with first line therapies (interferons, glatiramer acetate, teriflunomide and dimethyl fumarate); 3) patients being treated with second-line therapies (fingolimod, siponimod and cladribine); 4) patients being treated with antibody therapies (ocrelizumab and natalizumab); 5) as some of our SPMS and PPMS patients took high-dose biotin, we included a fifth group for therapy with biotin (these patients were not taking other therapies).

In the RRMS group, 5 patients had no therapy, 7 were on first line therapy, and 5 on second line therapy. In the SPMS group, 9 patients had no therapy, 5 were on first line therapy, 3 on second line therapy, 2 on third line therapy and 3 took high-dose biotin. In the PPMS group, 12 patients had no therapy, 7 were on ocrelizumab, and 3 on high-dose biotin.

Disease activity

Between baseline and follow-up, 3 patients from the RRMS group and 2 patients from the SPMS group suffered a relapse and 1 patient from the SPMS group had 2 relapses. One patient in the RRMS group switched to a different DMT. Seven patients in SPMS group and 5 in the PPMS group were on a new therapy at the time of the follow-up visit. Only 2 patients—1 patient in the RRMS group and 1 in the SPMS group—showed new lesions on MRI at the follow-up visit.

3.3 Outcome measures

The data are presented as mean (standard deviation) in Table 11 for baseline and Table 12 for the follow-up after one year.

Table 11 Baseline cognitive tests results of MS patients and healthy controls, Ulm University Hospital (2017-2019)

Cognitive test results at baseline						
Variables Score (SD)	**RRMS**	**SPMS**	**PPMS**	**Healthy controls**	**p un-adjusted**	**p adjusted for age, education**
N	22	22	22	22		
Verbal episodic memory						
VLMT total correct	53.4 (9.5)	49.8 (12.5)	50.7 (9.9)	59.3 (8.4)	**0.011**	0.067
VLMT delayed recall	11.0 (2.8)	9.2 (3.6)	10.6 (3.3)	12.8 (1.9)	**0.002**	**0.014**
Visual episodic memory						
BVMT-R total correct	24.2(6.2)	20.1(8.2)	18.9(7.3)	26.4 (5.7)	**0.001**	**0.015**
BVMT-R delayed recall	9.3 (2.2)	7.5 (3)	8.1 (2.5)	10.5 (1.6)	**<0.001**	**0.004**
Verbal Attention-executive functions						
COWAT	30.9 (9.2)	26.9 (9.1)	28.2 (9.9)	39.5 (7.3)	**<0.001**	**< 0.001**
PASAT-3, total correct	46.2 (8.8)	40.3 (15.2)	37.3 (15.4)	47.9(6.3)	**0.014**	**0.043**
Visual Attention-executive functions						
SDMT, total correct	53.1 (9.9)	41.9 (15.1)	42.9 (13)	56.4 (8.2)	**<0.001**	**0.002**
BDT	50.2 (9.3)	40.6 (10.9)	38.5 (10.7)	52.0 (10.2	**<0.001**	**0.001**
Self-report questionnaires						
Fatigue scale cognition	27.1 (10.1)	34.4 (9.2)	29.2 (11.9)	19.2 (7.2)	**<0.001**	
Fatigue scale motoric	27.9 (9.8)	39.5 (5.4)	35.7(10.9)	18.5 (8.0)	**<0.001**	
Hamilton Scale						
Anxiety	5.8 (3.3)	6.7 (3.8)	6.6 (3.4)	4.7 (3.2)	0.212	
Depression	3.4 (2.5)	6.9 (4)	5.5 (3.1)	3.8 (3.2)	**0.002**	

SD-Standard Deviation, MS-Multiple Sclerosis,RRMS-Relapsing-Remitting Multiple Sclerosis. SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis, VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-3-Paced Auditory Serial Addition Test-3 seconds Version, BDT-Block Design Test

Table 12 Cognitive tests results after one year for MS patients and healthy controls, Ulm University Hospital (2017-2019)

Cognitive test results after 1 year						
Variables Score (SD)	**RRMS**	**SPMS**	**PPMS**	**Healthy controls**	**p unadjusted**	**p adjusted for age, education**
Verbal episodic memory						
VLMT total correct	58.7(6.2)	50.5(12.4)	53.8(10.3)	63.1(7.9)	**<0.001**	**0.003**
VLMT delayed recall	12.5(2)	9.8(3.6)	10.7(2.9)	13.5(1.8)	**<0.001**	**0.001**
Visual episodic memory						
BVMT-R total correct	24.3(4)	20.9(6.5)	20.5(4.7)	25.9(6.5)	**0.004**	**0.037**
BVMT-R delayed recall	9.1(1.4)	7.7(2.4)	7.9(1.9)	9.6(1.7)	**0.002**	**0.030**
Verbal Attention-executive functions						
COWAT	31.7 (9.5)	27.8 (8.5)	29.5(9.2)	40.5(7.2)	**<0.001**	**<0.001**
PASAT-3, total correct	48.5(8.4)	40.3(14.1)	41.4(12.5)	47.8(7.4)	**0.026**	0.137
Visual Attention-executive functions						
SDMT, total correct	56.8(10.7)	43.3(15.9)	43.8(10.7)	55.5(9.3)	**<0.001**	**0.004**
BDT	51.8(9.4)	41.6(11.5)	44(11.1)	52.4(9.4)	**0.001**	**0.035**
Self-report questionnaires						
Fatigue scale cognition	26.3(9.1)	33.6(10.6)	29(12.5)	19.6(7.2)	**<0.001**	
Fatigue scale motoric	27.7(9.2)	38.9(7.9)	35.9(9.7)	19.1(7.9)	**<0.001**	
Hamilton Scale						
Anxiety	5.9(3.9)	6.7(4.2)	5.9(4.2)	3.8(3.3)	0.090	
Depression	3.6(2.7)	8.1(3.8)	5.7(3.3)	3.1(2.4)	**<0.001**	

SD-Standard Deviation, MS-Multiple Sclerosis,RRMS-Relapsing-Remitting Multiple Sclerosis. SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis, VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-3-Paced Auditory Serial Addition Test-3 seconds Version, BDT-Block Design Test

1.1a) Do all MS types have more cerebral symptoms (cognitive impairment, fatigue, and psychopathology) compared with healthy controls?

After accounting for covariates, we found medium to large differences (0.50 to 1.75 SD, $p \leq 0.034$) in patients with all types of MS compared to healthy controls in overall cerebral symptoms, global cognition, executive function, episodic memory, verbal cognition, overall fatigue, cognitive and physical fatigue (see Table 13). Visual cognition was worse in both progressive types of MS, compared to healthy controls (≥ 0.92 SD, $p \leq 0.003$). Overall psychopathology and depression was worse in SPMS patients in contrast with the control group (≥ 0.70 SD, ps ≤ 0.014, see Table 13)

Results are described in more detail in the following. After adjustment for age and education, there was a significant difference between the four groups in terms of **cerebral symptoms** (see Table 13). In pairwise comparisons with healthy controls, all 3 MS groups had significantly more CNS pathology (SPMS group, mean difference 1.418, 95% CI 0.89 to 1.95, $p<0.001$; PPMS group mean difference 1.164, 95% CI 0.70 to 1.63, $p<0.001$; RRMS group mean difference 0.699, 95% CI 0.28 to 1.11, $p=0.001$).

After adjustment for age and education, there was a significant difference between the groups for the **global cognitive function score** (Table 13). In pairwise comparisons with healthy controls, all 3 MS groups had significantly lower global cognitive function (SPMS group, mean difference -1.072, 95% CI -1.69 to -0.45, $p=0.001$; PPMS group mean difference -1.097, 95% CI -1.54 to -0.66, $p<0.001$; RRMS group mean difference -0.553, 95% CI -0.98 to -0.12, $p=0.012$). In individual cognitive domains, the differences were also evident. After adjustment for age and education, the **executive function score** was significantly different between the groups (Table 13). In pairwise comparisons with healthy controls, all 3 MS groups had significantly worse executive function (SPMS group mean difference -1.101, 95% CI -1.69 to -0.52, $p<0.001$; PPMS group mean difference -1.216, 95% CI -1.69 to -0.74, $p<0.001$; RRMS group mean difference -0.505, 95% CI -0.97 to -0.04, $p=0.034$). Similarly, there was also a significant difference between the groups for the **episodic memory score** (Table 13). In pairwise comparisons with healthy controls, the differences were all 3 MS groups scored significantly worse (SPMS group mean difference -0.902, 95% CI -1.55 to -0.26, $p=0.007$; PPMS group mean difference -0.844, 95% CI -1.29 to -0.40, $p<0.001$; RRMS group mean difference -0.523, 95% CI -0.99 to -0.06, $p=0.027$). After

adjustment for age and education **verbal and visual cognitive scores** were significantly different between the four study groups. In pairwise comparisons of the **verbal cognitive score**, the SPMS and PPMS groups scored significantly worse than the healthy controls (SPMS mean difference -0.919, 95% CI -1.51 to -0.33, p=0.003; PPMS mean difference -1.010, 95% CI -1.47 to -0.55, p<0.001). In terms of the visual cognitive score, all 3 MS groups had significantly worse visual cognition than healthy controls (SPMS mean difference -1.067, 95% CI -1.70 to -0.43, p=0.001; PPMS mean difference -1.003, 95% CI -1.47 to -0.53, p<0.001; RRMS group mean difference -0.614, 95% CI -1.06 to -0.17, p=0.008).

After adjustment for age, there was also a significant difference between the groups in terms of **fatigue score, cognitive fatigue score,** and **physical fatigue score**. In pairwise comparisons with healthy controls, all 3 MS groups had a significantly higher **fatigue score** (SPMS group mean difference 1.555, 95% CI 0.19 to 1.92, p<0.001; PPMS group mean difference 1.131, 95% CI 0.65 to 1.62, p<0.001; RRMS group mean difference 0.871, 95% CI 0.43 to 1.31, p<0.001). The **cognitive fatigue scores** for all 3 MS groups were also higher than for the healthy control group in pairwise comparisons (SPMS group mean difference 1.359, 95% CI 0.91 to 1.80, p<0.001; PPMS group mean difference 0.862, 95% CI 0.32 to 1.40, p=0.002; RRMS group mean difference 0.814, 95% CI 0.34 to 1.29, p=0.001), as was the physical fatigue score (SPMS group mean difference 1.750, 95% CI 1.41 to 2.09, p<0.001; PPMS mean difference 1.400, 95% CI 0.92 to 1.88, p<0.001; RRMS mean difference 0.928, 95% CI 0.50 to 1.35, p<0.001).

Similarly, after adjustment for age, there was a significant difference between the groups for the **psychopathology score (Hamilton Anxiety and Depression scale)** (Table 13). In pairwise comparisons with healthy controls, the SPMS group had significantly more psychopathology (SPMS group mean difference 0.696, 95% CI 0.14 to 1.25, p=0.014). The **depression score** was also different between the four study groups. In pairwise comparisons, the SPMS group had significantly more depression than the healthy controls (mean difference 0.858, 95% CI 0.24 to 1.48, p=0.008). After age adjustment, the four study groups had significantly different **anxiety scores** (Table 13), but in pairwise comparisons the differences were not significant.

Table 13 Statistical assessment of MS groups vs. healthy group baseline scores

Parameter	RRMS	RRMS	SPMS	SPMS	PPMS	PPMS
Compared to healthy group	**Effect size**	**p-value**	**Effect size**	**p-value**	**Effect size**	**p-value**
Primary outcomes						
Cerebral symptoms	0.699	**0.001**	1.418	**<0.001**	1.164	**<0.001**
Global cognition score	-0.553	**0.012**	-1.072	**0.001**	-1.097	**<0.001**
Psychopathology score	0.235	0.279	0.696	**0.014**	0.467	0.065
Fatigue score	0.871	**<0.001**	1.555	**<0.001**	1.131	**<0.001**
Secondary outcomes						
Executive functions score	-0.505	**0.034**	-1.101	**<0.001**	-1.216	**<0.001**
Episodic memory score	-0.523	**0.027**	-0.902	**0.007**	-0.844	**<0.001**
Visual cognitive score	-0.409	0.072	-0.919	**0.003**	-1.010	**<0.001**
Verbal cognitive score	-0.614	**0.008**	-1.067	**0.001**	-1.003	**<0.001**
Depression	0.017	0.943	0.858	**0.008**	0.440	0.110
Anxiety	0.453	0.151	0.535	0.076	0.494	0.102
Fatigue cognitive score	0.814	**0.001**	1.359	**<0.001**	0.862	**0.002**
Fatigue physical score	0.928	**<0.001**	1.750	**<0.001**	1.400	**<0.001**

MS-Multiple Sclerosis, RRMS-Relapsing-Remitting Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis

1.1b) Do MS types differ in cerebral symptoms (cognitive impairment, fatigue and psychopathology)?

After accounting for covariates, we found medium to large differences (≥ 0.78 SD, $p_{\text{Holm adjusted}} \leq 0.023$) in SPMS patients, compared to patients with RRMS, in overall cerebral symptoms, overall fatigue, physical fatigue, and depression (see Table 14). After adjustment for multiple comparisons, we did not find any other significant differences between groups. However, SPMS compared with RRMS, showed at least medium-sized differences (> 0.5 SD) in global cognition, executive functions, visual cognition, cognitive fatigue and psychopathology that were at least marginally significant without adjusting for multiple comparisons ($p_{\text{unadjusted}} < 0.1$, see Table 14). Similarly, PPMS compared with RRMS showed trends of at least medium effect sizes (> 0.5 SD) for overall cerebral symptoms, global cognition, executive functions, visual cognition, and physical fatigue that were at least marginally significant without adjusting for multiple comparisons ($p_{\text{unadjusted}} < 0.1$, see Table 14). We did not found differences between both progressive types of MS. These differences were - apart from fatigue (0.41 SD, $p_{\text{unadjusted}} = 0.09$) - not even at trend level for all outcomes (ES: < 0.23 SD, $p_{\text{Holm adjusted}} > 0.99$, see Table 14).

Results are described in more detail in the following. After adjustment for age and education (see Table 14), the three MS groups were significantly different with respect to **cerebral symptoms**. The RRMS group had less CNS pathology than both the SPMS group (mean difference 0.783, 95% CI -1.35 to -0.22, p=0.008) and the PPMS group (mean difference 0.559, 95% CI -1.14 to 0.027 p=0.061). Although there was no overall difference between the three groups in terms of the adjusted **executive function score**, in pairwise comparisons, the RRMS group had a significantly higher score than the PPMS group (mean difference 0.740, 95% CI 0.11 to 1.37, p=0.021). After adjustment for age and education, there was no significant difference between the **visual cognitive score** of the three MS groups, but on pairwise comparisons the RRMS group performed significantly better than the PPMS group (mean difference 0.649 95% CI 0.04 to 1.26, p=0.038).

After adjustment for age, there was a significant difference between the 3 groups in terms of the **fatigue score** (see Table 14). The RRMS group had a significantly lower score than both the SPMS group (mean difference 0.785, 95% CI -1.34 to 0.23, p=0.007) and the PPMS group (mean difference 0.378, 95% CI -1.06 to 0.25, p=0.247). There was no

significant difference between the **fatigue cognitive score** of all 3 MS groups (Table 14), but in pairwise comparisons the SPMS group had significantly more cognitive fatigue than the RRMS group (mean difference 0.660, 95% CI 0.00 to 1.32, *p*=0.049). In terms of the **fatigue physical score**, both the SPMS group and the PPMS group had more physical fatigue than did the RRMS group (mean differences 0.909 95% CI 0.38 to 1.44, *p*=0.001 and 0.574, 95% CI 0.03 to 1.12, *p*=0.04, respectively).

After adjustment for age, there was a significant difference between the **depression scores** of the three MS groups (Table 14). The depression score was significantly higher for the SPMS group and PPMS groups in comparison with the RRMS group (mean differences 0.951, 95% CI 0.31 to 1.6, *p*=0.004 and 0.552, 95% CI -0.12 to 1.22, *p*=0.104, respectively).

Table 14 Statistical assessment MS group pairwise comparison at baseline

Group comparison	RRMS vs SPMS	RRMS vs SPMS		RRMS vs PPMS	RRMS vs. PPMS		SPMS vs. PPMS	SPMS vs. PPMS	
Parameter	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value
Primary outcomes									
Cerebral symptoms score	**-0.783**	**0.008**	**0.023**	**-0.559**	0.061	0.183	0.224	0.377	1.000
Global cognition score	**0.506**	0.099	0.296	**0.563**	0.076	0.229	0.057	0.833	1.000
Psychopathology score	**-0.541**	0.070	0.211	-0.325	0.292	0.875	0.216	0.408	1.000
Fatigue score	**-0.785**	**0.005**	**0.020**	-0.378	0.247	0.599	0.407	0.091	0.315
Secondary outcomes									
Executive function score	**0.591**	0.056	0.167	**0.740**	**0.021**	0.064	0.148	0.584	1.000
Episodic memory score	0.359	0.259	0.776	0.328	0.318	0.954	-0.031	0.912	1.000
Visual cognitive score	**0.523**	0.082	0.247	**0.649**	**0.038**	0.114	0.127	0.632	1.000
Verbal cognitive score	0.412	0.210	0.631	0.372	0.274	0.821	-0.040	0.890	1.000
Depression	**-0.951**	**0.004**	**0.013**	**-0.552**	0.104	0.312	0.399	0.164	0.491
Anxiety	-0.130	0.709	1.000	-0.098	0.788	1.000	0.032	0.916	1.000
Fatigue cognitive score	**-0.660**	**0.049**	0.146	-0.182	0.595	1.000	**0.477**	0.104	0.312
Fatigue physical score	**-0.909**	**0.001**	**0.003**	**-0.574**	**0.040**	0.121	0.336	0.154	0.461

MS-Multiple Sclerosis, RRMS-Relapsing-Remitting Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis,PPMS-Primary Progressive Multiple Sclerosis

1.1c) Are cerebral symptoms (cognitive impairment, fatigue and psychopathology) related to the existence of a relapse or progressive disease course?

After accounting for covariates, the presence of a progressive course in individual's history was adversely associated with all primary and secondary outcomes apart from anxiety (partial η^2: 0.061 to 0.261, *p*s ≤ 0.020, see Table 15). After accounting for covariates, individuals with the presence of a relapse in their history showed increased overall cerebral symptoms and fatigue, including cognitive and physical fatigue (partial η^2: 0.083 to 0.151, *p*s ≤ 0.008, see Table 15).

Table 15 Association of the presence of a relapse and a progressive course in an individual's history with outcomes at baseline

	Relapse		Progressive course	
Parameter	**partial η^2**	**p-value**	**partial η^2**	**p-value**
Primary outcomes				
Cerebral symptoms score	0.083	**0.008**	0.261	**<0.001**
Global cognition score	0.025	0.151	0.194	**<0.001**
Psychopathology score	0.015	0.274	0.064	**0.020**
Fatigue score	0.131	**0.001**	0.241	**<0.001**
Secondary outcomes				
Executive functions score	0.014	0.292	0.228	**<0.001**
Episodic memory score	0.027	0.135	0.110	**0.002**
Visual cognitive score	0.009	0.384	0.176	**<0.001**
Verbal cognitive score	0.035	0.089	0.143	**<0.001**
Depression	0.012	0.315	0.100	**0.003**
Anxiety	0.010	0.356	0.017	0.234
Fatigue cognitive score	0.096	**0.004**	0.122	**0.001**
Fatigue physical score	0.151	**<0.001**	0.349	**<0.001**

1.2a) Do MS types deteriorate more in cerebral symptoms (cognitive impairment, fatigue and psychopathology) compared with healthy controls?

In comparison with healthy controls, the RRMS and PPMS groups had a more favorable course in executive function over the course of one year (RRMS group mean difference 0.247 SD, 95% CI 0.02 to 0.48, *p*=0.013; PPMS group mean difference 0.260 SD, 95% CI 0.04 to 0.48, *p*=0.017, see Table 16).

In addition, the SPMS group showed a worsening of psychopathology, in contrast to the healthy control group (SPMS group mean difference 0.577, *p*=0.018). Other study outcomes did not show differences between the MS groups and the healthy control group in the changes over the course of one year (table 16).

Table 16 Statistical assessment of score differences between baseline and at one year MS groups vs. healthy group

Parameter	RRMS	RRMS	SPMS	SPMS	PPMS	PPMS
Compared to healthy group	**Effect size**	**p-value**	**Effect size**	**p-value**	**Effect size**	**p-value**
Primary outcomes						
Cerebral symptoms score	-0.091	0.585	0.129	0.422	0.125	0.427
Global cognition score	0.202	0.175	-0.101	0.480	-0.041	0.771
Psychopathology score	0.255	0.253	**0.577**	**0.018**	0.309	0.160
Fatigue score	-0.111	0.572	-0.068	0.721	0.012	0.949
Secondary outcomes						
Executive functions score	0.247	**0.013**	0.111	0.382	0.260	**0.017**
Episodic memory score	0.152	0.384	-0.269	0.134	-0.143	0.385
Visual cognitive score	0.187	0.259	0.009	0.955	0.070	0.659
Verbal cognitive score	0.177	0.248	-0.090	0.542	-0.041	0.777
Depression	0.081	0.765	0.439	0.095	0.281	0.277
Anxiety	0.236	0.330	0.318	0.175	0.136	0.554
Fatigue cognitive score	-0.146	0.493	-0.127	0.537	-0.066	0.747
Fatigue physical score	-0.142	0.465	-0.142	0.451	-0.021	0.908

MS-Multiple Sclerosis,RRMS-Relapsing-Remitting Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis

1.2b) Do MS types deteriorate differentially in cerebral symptoms (cognitive impairment, fatigue and psychopathology) over one year?

SPMS group showed deteriorated episodic memory performance over the course of one year, in contrast to the RRMS group (SPMS group: 0.589 SD, 95% CI 0.17 to 1.00, $p_{\text{Holm adjusted}}$ = 0.019). Without adjusting for multiple comparisons, also the PPMS group deteriorated in episodic memory in contrast to the RRMS group (0.471 SD, 95% CI 0.04 to 0.90, $p_{\text{unadjusted}}$ = 0.034) and the SPMS group deteriorated in global cognition in contrast to the RRMS group (see Table 17).

Other outcome measures did not show significant differences in the amount of change over 1 year for the different MS groups.

Table 17 Statistical assessment of score differences between baseline and at one year for the three MS groups

Group comparison	RRMS vs SPMS	RRMS vs SPMS		RRMS vs PPMS	RRMS vs. PPMS		SPMS vs. PPMS	SPMS vs. PPMS	
Parameter	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value
Primary outcomes									
Cerebral symptoms score	-0.237	0.205	0.616	-0.248	0.201	0.603	-0.011	0.949	1.000
Global cognition score	**0.375**	**0.034**	0.101	0.320	0.079	0.237	-0.056	0.719	1.000
Psychopathology score	-0.333	0.235	0.706	-0.067	0.817	1.000	0.266	0.286	0.858
Fatigue score	-0.073	0.745	1.000	-0.133	0.573	1.000	-0.059	0.767	1.000
Secondary outcomes									
Executive function score	0.103	0.433	1.000	-0.044	0.744	1.000	-0.147	0.210	0.629
Episodic memory score	**0.589**	**0.006**	**0.019**	**0.471**	**0.034**	0.101	-0.118	0.530	1.000
Visual cognitive score	0.258	0.163	0.488	0.191	0.311	0.933	-0.066	0.687	1.000
Verbal cognitive score	0.314	0.082	0.247	0.279	0.135	0.404	-0.035	0.825	1.000
Depression	-0.441	0.157	0.470	-0.211	0.514	1.000	0.230	0.405	1.000
Anxiety	-0.022	0.933	1.000	0.148	0.590	1.000	0.171	0.468	1.000
Fatigue cognitive score	-0.023	0.923	1.000	-0.070	0.778	1.000	-0.047	0.824	1.000
Fatigue physical score	-0.045	0.842	1.000	-0.139	0.553	1.000	-0.095	0.636	1.000

MS-Multiple Sclerosis, RRMS-Relapsing Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis

1.2c) Are relapse and progression of MS symptoms in the history associated with changes in cerebral symptoms (cognitive impairment, fatigue and psychopathology) over one year?

The presence of a progressive course in the history was associated with deterioration in episodic memory over the course of one year (partial η2 = 0.054, *p* = 0.034, see Table 18). In addition, participants with the presence of a progressive course showed a non-significant trend for increases in depression (partial η2 = 0.034, *p* = 0.097). The presence of a relapse in history did not predict changes in any outcomes over the course of 1 year after accounting for covariates.

Table 18 Statistical assessment of score differences between baseline and at one year for relapse and progression course in a subject's history

	Relapse		Progression	
Parameter	**partial η^2**	**p-value**	**partial η^2**	**p-value**
Primary outcomes				
Brain related pathology score	0.002	0.713	0.026	0.143
Global cognition score	0.006	0.499	0.032	0.102
Psychopathology score	0.019	0.218	0.033	0.102
Fatigue score	0.006	0.493	0.000	0.842
Secondary outcomes				
Episodic memory score	0.000	0.923	0.054	**0.034**
Executive functions score	0.004	0.552	0.007	0.458
Visual cognitive score	0.004	0.590	0.003	0.645
Verbal cognitive score	0.004	0.553	0.025	0.155
Depression	0.005	0.532	0.034	0.097
Anxiety	0.018	0.224	0.005	0.522
Fatigue cognitive score	0.006	0.492	0.000	0.877
Fatigue physical score	0.011	0.342	0.000	0.939

2a) Is MS disability measured with EDSS related to cerebral symptoms (cognitive impairment, fatigue, or psychopathology)?

A linear multiple regression established that MS disability was associated with all primary and secondary outcomes of cerebral symptoms with medium to large effect sizes (r = 0.316 to 0.603, ps ≤ 0.002), except of anxiety (see Table 19).

Table 19 Correlation EDSS to primary and secondary outcomes

Parameter	EDSS β	p-value
Primary outcomes		
Cerebral symptoms score	0.575	**<0.001**
Global cognition score	-0.477	**<0.001**
Psychopathology score	0.316	**0.002**
Fatigue score	0.603	**<0.001**
Secondary outcomes		
Executive function score	-0.539	**<0.001**
Episodic memory score	-0.357	**<0.001**
Visual memory score	-0.460	**<0.001**
Verbal memory score	-0.416	**<0.001**
Depression	0.383	**<0.001**
Anxiety	0.176	0.103
Fatigue cognitive score	0.512	**<0.001**
Fatigue physical score	0.645	**<0.001**

EDSS-Expanded Disability Status Scale, β-effect size

2b) Is MS disability measured with EDSS related to cognitive test results?

A linear multiple regression established that MS disability is related to performance in all tests. The link between COWAT and MS disability was the only with a large effect size (r = 0.543, see Table 20).

Table 20 Correlation EDSS and cognitive tests

Parameter	EDSS β	p-value
Verbal episodic memory		
VLMT total	-0.223	**0.031**
VLMT delayed	-0.275	**0.009**
Visual episodic memory		
BVMT-R total	-0.317	**0.001**
BVMT-R delayed	-0.413	**<0.001**
Verbal attention-executive functions		
COWAT	-0.543	**<0.001**
PASAT	-0.249	**0.026**
Visual attention-executive functions		
SDMT	-0.458	**<0.001**
BDT	-0.418	**<0.001**

EDSS-Expanded Disability Status Scale,VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-Paced Auditory Serial Addition Test, BDT-Block Design Test

3a) Which cognitive tests are most valid in detecting cognitive impairment related to relapse and progression?

The presence of a relapse in the past (RRMS and SPMS groups vs healthy and PPMS groups) was associated with worse performance in the COWAT and VLMT delayed recall (see Table 21).

The presence of progressive course in history was linked to worse performance on all tests (*p*s ≤ 0.048, partial η2 ≥ 0.047) with largest effect sizes in the BVMT-R delayed recall, BDT, COWAT and SDMT (partial η2 ≥ 0.09, see Table 21).

Table 21 Association of test performance at baseline with the presence of a relapse and a progressive course in a subject's history

	Relapse		Progression	
Parameter	**partial η^2**	**p-value**	**partial η^2**	**p-value**
Verbal episodic memory				
VLMT total score	0.014	0.276	0.047	**0.048**
VLMT delayed recall	0.057	**0.028**	0.061	**0.024**
Visual episodic memory				
BVMT-R total score	0.000	0.861	0.089	**0.006**
BVMT-R delayed recall	0.022	0.174	0.117	**0.001**
Verbal attention-executive functions				
COWAT	0.049	**0.043**	0.152	**<0.001**
PASAT	0.001	0.757	0.080	**0.010**
Visual attention-executive functions				
SDMT	0.015	0.270	0.143	**<0.001**
BDT	0.000	0.879	0.158	**<0.001**

VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-Paced Auditory Serial Addition Test, BDT-Block Design Test

3b) Which cognitive tests are most valid in detecting cognitive impairment in different MS types?

The COWAT and the VLMT delayed recall depict the only tests that were associated with the presence of both a relapse and a progressive course in the history. The differences between the groups for the **VLMT total z-score** were not significant ($F(3,82)=2.482$, $p=0.067$, $\eta^2=0.08$). The pairwise comparison analysis revealed significant differences between the healthy controls and the PPMS and SPMS groups. The mean score for the PPMS group was -0.671 lower than for healthy controls (95% CI -1.22 to -0.13, $p=0.017$) and the mean score for the SPMS group was -0.637 lower (95% CI -1.20 to -0.08, $p=0.026$). Between RRMS group and healthy control group there was no significant difference.

For the **VLMT delayed recall z-score**, the differences between the groups was significant $F(3,82)=3.734$, $p=0.014$, $\eta^2=0.12$. The pairwise comparison analysis indicated that the mean score for the SPMS group was -0.935 lower than for healthy controls (95% CI -1.50 to -0.37, $p=0.001$). The PPMS group had also a lower score than healthy controls groups by -0.573 95% CI -1.12 to -0.02, $p=0.041$. Between RRMS group and healthy control group, there was also a difference of 0.560 95% CI -1.14 to 0.02, but not significant $p=0.059$.

Age was unrelated to the VLMT delayed recall score ($F(1,82)=2.270$, $p=0.136$), but the education was significantly related ($F(1,82)=5.339$, $p=0.023$).

For the **BVMT-R total z-score**, the differences between the groups were significant ($F(3,82)=3.680$, $p=0.015$, $\eta^2=0.12$). Pairwise comparison analysis indicated that the score for the SPMS group was -0.591 lower than for healthy controls (95% CI -1.13 to -0.06, $p=0.064$), and that the score for the PPMS group was -0.844 lower than for the healthy control group (95% CI -1.37 to -0.32; $p=0.001$).
Both age and education were significantly related to performance ($F(1,82)=6.234$, $p=0.015$, $F(1,82)=10.803$, $p=0.001$).

BVMT-R delayed recall z-score differences between the groups was significant ($F(3,82)=4.703$, $p=0.004$,$\eta^2=0.15$). The pairwise comparison analysis indicated that the z-score for the SPMS group was -0.940 lower than for healthy controls (95% -1.53

to -0.36, p=0.002), and that the z-score for the PPMS group was -0.816 lower than for the healthy control group (95% CI -1.33 to -0.31; p=0.002).

The covariate age was not significantly related to the BVMT-R recall score (F(1,82)=4.703, p=0.159) but the covariate education was significantly related (F(1,82)=5.940, p=0.017).

The differences between the groups for the **COWAT z-score** was significant (F(3,82)=7.784, p<0.001, η^2=0.22). The pairwise comparison analysis revealed significant differences between the healthy controls and all 3 MS groups. The mean score for the RRMS group was 0.759 lower than for healthy controls (95% CI -1.33 to -0.18, p=0.010); the mean score for the SPMS group was -1.199 lower (95% CI -1.75 to -0.64, p<0.001); and the mean score for from PPMS group was -1.119 lower (95% CI -1.66 to -0.58, p<0.001). The covariates age and education were not related to the COWAT score (F(1,82)=0.259, p=0.612 and F(1.82)=0.565, p=0.455).

The differences between the groups for the **SDMT z-score** were significant (F(3,82)=5.535, p=0.002, η^2=0.17). Pairwise comparison analysis indicated that the SPMS group scored on average less than the healthy control group by -0.935 (95% CI -1.59 to -0.28, p=0.006) and the PPMS group scored less by -0.888 (95% CI -1.33 to -0.45, p<0.001).

Age was significantly related to the SDMT score (F(1,82)=7.798, p=0.007), but education was not related to the performance in the SDMT (F(1,82)=3.266, p=0.074).

For **PASAT z-score**, the differences between the groups was significant, F(3,81)=2.840, p=0.043, η^2=0.10). Pairwise comparison analysis revealed that only the difference between the PPMS group and the healthy control group was significant by -0.793 (95% CI -1.38 to -0.21, p=0.008).Covariates age and education were both not related to the performance in the PASAT test (F(1,81)=0.492, p=0.485, F(1,81)=1,001, p=0.320).

The differences between the groups for the **BDT z-score** were significant (F(3,82)=6.171, p=0.001, η^2=0.18).Pairwise comparison analysis indicated a significant lower z-score in the SPMS group in comparison with the healthy control group by -0.741 (95% CI -1.28 to -0.20, p=0.008), as well as a significantly lower z-score in the PPMS in comparison with the healthy control group by -0.976 (95% CI -1.49 to -0.46, p<0.001). Age and education were both significantly related to test performance (F(1,82)=13.742, p<0.001, F(1,82)=7.970, p=0.006) (see Table 22).

Table 22 Statistical assessment of MS groups vs. healthy group baseline scores

Parameter	RRMS	RRMS	SPMS	SPMS	PPMS	PPMS
Compared to healthy group	**Effect size**	**p-value**	**Effect size**	**p-value**	**Effect size**	**p-value**
Verbal episodic memory						
VLMT total score	-0.484	0.068	-0.637	0.062	**-0.671**	**0.010**
VLMT delayed recall	**-0.560**	**0.022**	**-0.935**	**0.004**	**-0.573**	**0.034**
Visual episodic memory						
BVMT-R total score	-0.323	0.190	**-0.591**	0.064	**-0.844**	**0.001**
BVMT-R delayed recall	-0.429	0.071	**-0.940**	**0.002**	**-0.816**	**0.002**
Verbal attention-executive functions						
COWAT	**-0.759**	**0.003**	**-1.199**	**<0.001**	**-1.119**	**<0.001**
PASAT	-0.141	0.532	**-0.516**	0.116	**-0.793**	**0.006**
Visual attention-executive functions						
SDMT	-0.385	0.143	**-0.935**	**0.006**	**-0.888**	**<0.001**
BDT	-0.290	0.208	**-0.741**	**0.008**	**-0.976**	**<0.001**

MS-Multiple Sclerosis,RRMS-Relapsing-Remitting Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis,VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-3-Paced Auditory Serial Addition Test-3 seconds Version, BDT-Block Design Test

3c) Which cognitive tests are most valid in detecting patients with MS versus healthy controls cognitive deficits?

In the pairwise comparison analysis, the RRMS group performed better than PPMS group in the BDT (RRMS vs. PPMS mean group difference 0.768 SD, $p_{\text{Holm adjusted}}$ =0.027, see Table 23). All other comparisons were not significant.

All tests used differentiated between MS patients and healthy controls. COWAT and SDMT revealed the most significant differences (MS groups vs. healthy controls in COWAT test -1.038 SD, p=0.001; MS groups vs. healthy controls in SDMT test-0,748 SD, p=0.001 see table 24).

Table 23 Cognitive tests baseline results for pairwise comparisons of MS groups

Group comparison	RRMS vs SPMS	RRMS vs SPMS		RRMS vs PPMS	RRMS vs. PPMS		SPMS vs. PPMS	SPMS vs. PPMS	
Parameter	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value	Effect size	P value	Adjusted p value
Verbal episodic memory									
VLMT total	0.122	0.708	1.000	0.178	0.598	1.000	0.056	0.848	1.000
VLMT delayed	0.304	0.370	1.000	-0.025	0.944	1.000	-0.329	0.276	0.829
Visual episodic memory									
BVMT-R total	0.265	0.405	1.000	0.540	0.104	0.311	0.275	0.332	0.996
BVMT-R delayed	0.542	0.111	0.332	0.433	0.216	0.647	-0.109	0.716	1.000
Verbal attention-executive functions									
COWAT	0.375	0.255	0.766	0.297	0.384	1.000	-0.079	0.787	1.000
PASAT	0.409	0.282	0.845	0.699	0.074	0.223	0.290	0.389	1.000
Visual attention-executive functions									
SDMT	0.543	0.099	0.297	0.525	0.123	0.368	-0.018	0.950	1.000
BDT	0.473	0.090	0.271	**0.768**	**0.009**	**0.027**	0.295	0.233	0.700

MS-Multiple Sclerosis, RRMS-Relapsing-Remitting Multiple Sclerosis, SPMS-Secondary Progressive Multiple Sclerosis, PPMS-Primary Progressive Multiple Sclerosis,VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-Paced Auditory Serial Addition Test, BDT-Block Design Test

Table 24 Cognitive test baseline results for comparison of MS groups and healthy controls

Parameter	Effect size	p-value
Episodic verbal memory		
VLMT total	-0.603	**0.009**
VLMT delayed	-0.682	**0.004**
Episodic visual memory		
BVMT-R total	-0.605	**0.007**
BVMT-R delayed	-0.736	**0.002**
Verbal attention-executive functions		
COWAT	**-1.034**	**<0.001**
PASAT	-0.505	**0.043**
Visual attention-executive functions		
SDMT	**-0.748**	**0.001**
BDT	-0.691	**0.001**

MS-Multiple Sclerosis,VLMT-Verbal Learning Memory Test, BVMT-R- Brief Visual Memory Test-Revised, COWAT-Controlled Oral Word Association Test, SDMT- Symbol Digit Modalities Test, PASAT-Paced Auditory Serial Addition Test, BDT-Block Design Test

4 Discussion

The study showed that patients with all types of MS, performed worse compared to healthy controls in overall cerebral symptoms, including: global cognition (executive function, episodic memory and verbal cognition) as well as fatigue (physical and cognitive fatigue). Furthermore, the presence of a progressive course in history was associated with worse outcomes in overall cerebral symptoms, global cognition (including executive function, episodic memory, visual and verbal cognition), psychopathology (including depression), and fatigue (including physical and cognitive fatigue), even after accounting for the existence of relapses in history. This association is also reflected in worse outcomes in patients with SPMS when compared to RRMS patients in overall cerebral symptoms, depression and fatigue-especially physical fatigue. We did not find any evidence to support a difference between SPMS and PPMS groups. MS disability – as measured with the EDSS - was associated directly proportionately with worse outcomes in terms of all cerebral symptoms (medium to large effect sizes).

Similarly, in the longitudinal analysis, we found an unfavorable change in episodic memory performance in participants with the presence of a progressive course in history. This association is reflected in the finding that SPMS showed a less favorable course in episodic memory compared to PPMS patients. Interestingly, PPMS and RRMS showed a more favorable change over 1 year in executive function, compared to the healthy control group. However, patients who had relapses in this time frame did not show this favorable change. Finally, we found a less favorable course of depressive symptoms over one year in patients with SPMS in contrast to RRMS. There was also a trend towards worse depression outcomes in patients with progressive disease.

With regards to the question of most valid neuropsychological tests, we found that both the COWAT and the VLMT delayed recall tests revealed differences between all types of MS and healthy controls. In addition, these two tests were the only ones to reflect both relapses and progressive disease. Furthermore, we showed that the COWAT was the only test that was related to MS disability with a large effect size ($r > 0.5$)

4.1 Baseline findings

Worse cerebral symptoms in all types of MS in contrast to controls

Our study's result is in accordance with the limited current data available in the literature. In a similar study carried out at the Vrije Universiteit Medical Center, on 234 patients divided in 4 different groups (RRMS, SPMS, PPMS and healthy controls), Huijbregts et al. also demonstrated that all MS groups had cognitive deficits in comparison with healthy controls. In addition, he demonstrated that RRMS patients performed better than PPMS patients-evidence supported by our findings as well. In contrast to our study's results, he has shown that PPMS patients performed better than SPMS patients.[36]

A further study showed that the patients with PPMS presented a wide range of cognitive deficits in executive functions, episodic memory, information processing speed and attention compared to their matched control group. For the RRMS patients, the cognitive impairment was limited to working memory and information processing speed [71].

Worse outcomes in individuals with a progressive course in history

To our knowledge, this is the first study that assessed the correlation between cerebral outcomes and a relapsing or a progressive MS course. Other studies assessed only the differences between the three MS subtypes. The progression-outcome link is in line with findings of a meta-analysis which concluded that SPMS and PPMS patients display more severe cognitive impairment than RRMS. They show that this link is due to more severe cortical gray matter atrophy and a neurodegenerative component [7, 68, 80]. Also, it has been reported that fatigue is more prevalent and severe amongst those with progressive MS. [69] These findings were supported by our data as well.

Our results showed that the RRMS group performed better than the PPMS group in terms of executive functions and visual cognition. It is known that patients with PPMS have greater cognitive deficits than RRMS patients [65, 71]. PPMS patients have pronounced deficits in verbal learning, processing speed, immediate and delayed verbal memory [38].

Similarly, some authors have previously reported that the two progressive forms of MS result in significantly greater deficits in verbal episodic memory than RRMS patients [26].

No difference between PPMS and SPMS

Our study did not indicate substantial cognitive differences between the PPMS and SPMS groups. In another study with 36 PPMS patients, 85 SPMS patients and 40 healthy controls, there were no significant differences between PPMS and SPMS patients overall, although PPMS patients had a generally poorer performance in verbal learning and in verbal fluency [81]. Our results support previous literature findings.

4.2 Longitudinal findings

Deterioration of episodic memory over the course of one year in individuals with a progressive course

To our knowledge, this is the first study investigating the course of cerebral symptoms in different types of MS. Our results provide evidence that a progressive MS course correlates to deterioration in episodic memory, even after adjusting for the presence a relapse.

Improvement of executive function in both relapsing types in contrast to healthy controls

Twelve months follow-up showed an improvement in the executive functions score in the RRMS and PPMS groups compared to healthy subjects. We were unable to determine a direct cause of this finding. In our opinion, this improvement could potentially be explained by either better testing performance by the subject or subclinical disease activity at baseline.

In previous literature, PASAT and SDMT have been used to detect cognitive deterioration in MS [50]. It has been reported that the PASAT is cognitively more demanding and more sensitive to the progression of disease over a 5-year follow-up period [13]. In contrast to this finding, another study found a deterioration in PASAT over a 5 year period. However, this study did not assess a control group or

different MS types. Therefore, age-related and MS-related deterioration cannot be separated.

Llufriu et al showed that PASAT performance depends on the integrity of a larger number of brain connections than the SDMT and is therefore able to identify cognitive deficits in slightly disabled patients [49]. Improvement of executive function could reflect a neuroplasticity-based recovery between the two assessments of previous relapses/temporary inflammatory process. However, even if patients with relapses in the year before the first assessment were excluded, we found this association. That means that silent inflammatory process could have lead to decrements that recovered within this year.

Worsening in psychopathology in SPMS

SPMS group showed a worsening in psychopathology in comparison with the control group. To our knowledge, this is the first study that assessed psychopathology in MS longitudinally. Results currently available in the literature suggest that this finding is not unexpected. In contrast Wood et. al [83], found no variation in prevalence of depression according to disease duration at study entry using the same Hamilton Anxiety and Depression scale used in our study. Nevertheless, they reported a marked increase in depression in association with both higher (at cohort entry) and increasing (over cohort observation) EDSS score. In a large cohort study with 739 MS patients, the patients with advanced MS experienced more clinically significant depressive symptoms than subjects with minimal disease. [17]

Link of MS disability with all cerebral symptoms

To our knowledge there are no previous research studies published in the literature that report correlation between MS disability and cerebral symptoms score as used in our study.

Link of MS disability with performed tests

A high correlation between cognitive deficits and higher EDSS have been previously reported [54, 70]. Some publications have shown a consistent correlation between SDMT and EDSS [14, 73]. As per previous research publications, reported correlation coefficients were large between the EDSS and SDMT (r=0.55), and EDSS and BVMT-R (r=0,54) and moderate between EDSS and CVLT (r = 0.40) [14]. Our results suggest that the COWAT could be used as a valid test to detect MS-related cognitive deficits. Due to its short administration time (3 minutes), the COWAT could be added to the SDMT as the current gold standard for screening and monitoring of MS-related cognitive changes [11, 75].

COWAT could demonstrate validity in all parameters

Various battery tests such as MACFIMS[10], BRB-N[66, 72] and BICAMS are used to measure one or more cognitive domains in patients with MS.

The international standard to screen for cognitive impairment in MS patients is BICAMS (SDMT, BVMT-R and VLMT). [21] However in time-restricted clinical settings, it has been suggested that the combination of SDMT and BVMT-R is an acceptable alternative. These two tests showed the strongest agreement with the total battery and require only 10 minutes to administer [8]. In line with this finding, in our study, the SPMS and PPMS groups had lower scores than the healthy group in the BVMT-R delayed recall and SDMT. However, we also saw similar results on the Design block test, which to our knowledge has not been used before in MS populations.

It is well known that the SDMT has proved to be a valuable screening tool for cognitive impairment [42, 60]. In addition, our study's findings suggest that the COWAT test is also able to differentiate between MS patient groups and healthy controls. Even more so, for patients with lower COWAT scores, the correlation with the EDSS was as high as the one between the EDSS and SDMT.

Strengths, limitations and future research:

The strengths of our study are firstly due to the thorough assessment of a diverse set of CNS-related symptoms (cognitive, psychological, fatigue-related) and MS disability. Secondly, the inclusion of a healthy control group, has allowed the investigation of the effect of a relapse and a progressive disease course on cognitive outcomes.

Moreover, the longitudinal design of this study has provided statistically significant evidence in terms of detailed evaluation of all types of MS and correlation with 12 months' outcomes. In addition, the calculated power of a total sample size of 88 subjects is required for the detection of a group difference. Our calculations assumed an error probability of $\alpha=0.05$ and a test power of $1-\beta=0.95$.

Our study also had several limitations. Age and education differed in the groups at baseline. Therefore, we accounted for these covariates statistically. However, in our analysis, these variables did not predict longitudinal change, thereby indicating that they were not important covariates. The follow-up period of one year was relatively short. As the EDSS remained stable over the 12 months of the study, disease activity was apparently low in the study patients as a whole and this might have limited our ability to detect MS-related changes between the MS groups and healthy controls.

Follow-ups over 5 to 10 years could bring more insight in the development of cerebral symptoms. Furthermore, only 5 relapses were reported over the time frame of the study, limiting our statistical power to demonstrate any correlation between relapses and cognitive outcomes. Due to the limited time frame for recruiting and the size of the available patient pool, we did not include any patients with a clinical isolated syndrome or early MS, and we are therefore not able to provide any data on how these conditions affect cognition.

4.3 Conclusions

This study aimed 1) to clarify the cerebral symptoms of different MS types and their course over a period of one year, 2) to investigate the association of a wide range of cerebral symptoms (cognitive impairment, fatigue and psychopathology) with MS-related disability, and 3) to assess the validity of time-efficient cognitive tests that are not part of the current gold standard (BICAMS).

Cerebral symptoms, including cognition impairment, fatigue, depression and anxiety occur frequently as a first symptom or in the course of the MS disease. In our study we found that all our MS patients have these symptoms and these results are consistent with previous findings. We have also observed a higher prevalence of cerebral symptoms in patients with a progressive course in the disease history and that they appear to show a cognitive decline even within the period of one year. In comparison, the patients with a relapsing-remitting MS appear to exhibit less substantial cerebral symptoms and may even display signs of remission in some cognitive impairment, but in contrast they have more pronounced fatigue. In our study, MS-related disability, as measured with EDSS, was not only associated with cognitive impairment but also with the level of fatigue and psychopathology (including depression and anxiety). These results differ from previous works, which demonstrated no significant association between severity of fatigue and EDSS score in patients with MS. [9, 25, 44] However, the association between the degree of disability, measured with EDSS, and fatigue is controversial. The different results are most likely due to different study design and size, as well as different statistical analyses.

Lastly, including all cognitive tests administered in the study, the COWAT appears to be a valid and reliable method in detecting cognitive impairment in MS. Since COWAT takes only 5 minutes to administer, it could be suitable in time-restricted settings in clinical practice and research.

5 Abstract

Background: Cerebral symptoms (cognitive impairment, fatigue, and psychopathology) are commonly observed in multiple sclerosis (MS). However, little is known about the course of cerebral symptoms in MS types (relapse-remitting MS [RRMS], primary progressive MS [PPMS], secondary progressive MS [SPMS]). Our study characterized cerebral symptoms over 1 year for each MS type, which were compared with each other and with healthy controls (HC). The effect of relapses and a progressive course was also evaluated, as was the relationship between MS related disability, cognitive impairment, psychopathology and fatigue. Recent research indicates that a short cognitive test battery (BICAMS) can detect cognitive impairment in MS. However, other cognitive tests may be even more efficient. Here, we provide evidence for the use of less time-consuming tests.

Methods: The study included 88 participants (22 HC, and 22 patients each with RRMS, PPMS, and SPMS). Therefore, 44 individuals with a history of relapses (RRMS, SPMS) and 44 without relapses (HC, PPMS), as well 44 with a progressive course (PPMS, SPMS) and 44 with no progressive course (HC, RRMS) were assessed. Cerebral symptoms were evaluated at baseline and at a 1-year follow-up visit. Overall cognition, episodic memory, executive function, visual cognition, and verbal cognition were measured with a comprehensive test battery (BICAMS, Paced Auditory Serial Addition Test, Block Design Test, Controlled Oral Word Association Test [COWAT]). Psychopathology was measured with the Hospital Anxiety and Depression Scale. Fatigue was assessed with the Fatigue Scale for Motor and Cognitive Functions. A composite score was constructed by averaging z-standardized scores of cognitive impairment, psychopathology, and fatigue. Cerebral symptoms and subcategories were defined as primary outcomes. All other subscores were secondary outcomes. MS-related disability was assessed with the Expanded Disability Status Scale. Covariates were age and education for cognitive outcomes and overall cerebral symptoms, and age for psychopathology and fatigue. ANCOVAs (factors: MS groups [HC, RRMS, PPMS, SPMS], history of a progressive course/relapses) and multiple regressions were used for statistical analyses.

Results: Statistically significant effects ($p<0.05$) were as follows. At baseline, all MS types had more cerebral symptoms than HC (effect size [ES]≥0.70 SD), including

cognitive impairment (ES≥0.55 SD) and fatigue (ES≥0.87 SD). In SPMS patients compared with HC, psychopathology was worse at baseline (ES≥0.70 SD) and increased at 1 year (ES=0.58 SD). Surprisingly, executive function improved over the course of 1 year in RRMS and PPMS compared with HC (ES≥ 0.25 SD). Cerebral symptoms were related to a relapsing course (partial η^2=0.08) and to a progressive course (partial η^2=0.26). A progressive course was linked to all primary and secondary outcomes at baseline, other than anxiety (partial η^2:0.06 – 0.35) and to a decline in episodic memory over 1 year (partial η^2:0.05). History of relapses was associated with motor and cognitive fatigue at baseline (partial η^2:0.10 – 0.15) but not with changes over 1 year. SPMS had more overall cerebral symptoms, depression, and fatigue (including physical fatigue) in comparison with RRMS (ES≥0.78 SD). MS-related disability was associated with overall cerebral symptoms (β=0.58) and all other primary and secondary outcomes (β≥0.32), apart from anxiety. In all cognitive tests, MS patients had worse performance than HC, but only the COWAT showed a large effect size (ES=-1.03 SD). In addition, only the COWAT was associated with MS-related disability with a large effect size (*r*=0.54). In comparison with HC, all MS types had worse performance in the delayed Verbal Learning Memory Test (VLMT) (ES≤-0.56 SD) and COWAT (ES≤-0.76 SD). History of both relapses and a progressive course was linked to worse performance in the delayed VLMT (partial η^2:0.06) and COWAT (partial η^2:0.05 – 0.15). All other comparisons were not statistically significant.

Conclusion: Our study confirms the presence of cerebral symptoms - including cognitive impairment and fatigue - in all MS types. Individuals with a progressive disease course had more substantial cerebral symptoms and showed cognitive decline over the one year study period. For SPMS, psychopathology also worsened within the one year period. Surprisingly, patients with a history of relapses had less substantial cerebral symptoms that were primarily driven by fatigue. For RRMS, results suggested improvement in some areas of cognitive impairment over the course of the study. As expected, MS-related disability was not only associated with cognition but also with fatigue and psychopathology. Finally, the COWAT - which takes 5 minutes to administer - showed the largest effect size in detecting MS-related cognitive impairment, and could easily be included in clinical practice and research.

6 References

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8 Curriculum vitae

Aus Datenschutzgründen entfernt