Cognitive impairment in multiple sclerosis

Zohari, Meytar

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Meytar Zohari

COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

Graduate thesis

Zagreb, 2021

According to the graduation requirements, the following thesis was completed at the University Hospital Center Zagreb, Department of Neurology, under the mentorship of Tereza Gabelić, MD PhD, and was submitted for evaluation in the academic year 2020/21.

Abbreviations

AChEI – Acetylcholinesterase Inhibitors

AD – Alzheimer's Disease

AAN - American Academy of Neurology

APT – Attention Process Training

BENEFIT – Betaseron/Betaferonin in newly Emerging Multiple Sclerosis for Initial Treatment

BICAMS – Brief International Cognitive Assessment for Multiple Sclerosis

BRB-N – Brief Repeatable Battery of Neuropsychological Tests

BVMT-R – Brief Visuospatial Memory Test Revised

CBT – Cognitive Behavioral Therapy

CHILP – Chitinase-Like Proteins

CHI3L1 – Chitinase-3-Like 1 Protein

CHI3L2 – Chitinase-3-Like 2 Protein

CI – Cognitive Impairment

CIS – Clinically Isolated Syndrome

CL – Cortical lesions

CNS – Central Nervous System

COGIMUS – Cognitive Impairment in Multiple Sclerosis

CPS – Cognitive Processing Speed

CSF – Cerebrospinal Fluid

CVLT-II – California Verbal Learning Test-Second Edition

DD – Differential Diagnosis

DMDs – Disease Modifying Drugs

DMT – Disease-Modifying Therapy

DKEFS – Delis-Kaplan Executive Function System

EDSS - Expanded Disability Status Scale

fMRI – functional Magnetic Resonance Imaging

GM – Grey Matter

IFNb – Interferon Beta

IFG - Inferior Frontal Gyrus

IPS – Information Processing Speed

IQ – Intelligence quotient

MACFIMS – Minimal Assessment of Cognitive Functioning in Multiple Sclerosis

MASC – Movie Assessment Social Cognition

MBI – Mindfulness-Based Intervention

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

NfH – Neurofilament Heavy chains

NfL – Neurofilament Light chains

NSBMS – Neuropsychological Screening Battery for MS

OCT – Optical Coherence Tomography

PASAT – Paced Auditory Serial Addition Test

PPMS – Primary Progressive Multiple Sclerosis

PwMS – Patient with Multiple Sclerosis

QoL – Quality of Life

RNFL – Retinal Nerve Fiber Layer

RRMS – Relapsing Remitting Multiple Sclerosis

SD – Standard Deviation

SDMT – Symbol Digit Modalities Test

SPART – Spatial Recall Test

SPMS – Secondary Progressive Multiple Sclerosis

SRT – Selective Reminding Test

SVD – Small Vessel Disease

TNF – Tumor Necrosis Factor

WHO – World Health Organization

WLGT - Word List Generation Test

WM – White Matter

.

Table of contents

Abstract

Title: Cognitive impairment in multiple sclerosis

Author: Meytar Zohari

Multiple sclerosis (MS) is a neuroinflammatory, potentially disabling demyelinating disease of the central nervous system (CNS), with neurodegeneration being the most prominent in progressive phenotypes. The disease results in motor, sensory and cognitive symptoms, all of which can occur independently of one another.

Patients with multiple neurological signs or CNS lesions that are separated in time are diagnosed with relapsing-remitting (RR) or primary progressive multiple sclerosis (PPMS). A progressive course refers to worsening of the neurological disability, independent of relapses.

Cognitive impairment (CI) is a common but still challenging expression of MS and a frequent cause of socioeconomic decline and disability for MS patients. There is still no data regarding the direct relationship between cognitive impairment and the clinical course of the disease. Thus, cognitive deficits which occur during the early stages of the disease are the ones that need to be specially identified and addressed, to prevent worsening of CI, implicating a poor prognosis in MS.

The Symbol Digit Modalities Test (SDMT) test is a valuable screening tool for CI and can be the starting point when assessing CI in MS patients when other comprehensive screening tools are not available. The neuropsychological assessment should also discriminate between CI and other causes of perceived deficits, including quality of life (QoL), depression, and anxiety.

A healthy diet, no addiction lifestyle, regular physical exercise and the proper control of co-morbidities can positively affect cognition in patients with MS. Recent data also indicate that proper disease-modifying therapy (DMT) implemented early in the course of RRMS can stabilize or even improve cognition.

Since there is no standardized protocol for identification and assessment of CI, further studies are needed in order to elaborate a "golden standard" for screening and diagnosing of cognitive deficits in MS, and for the development of evidence-based effective preventive methods and treatment approaches.

Keywords: multiple sclerosis; cognitive impairment; SDMT; neuropsychological assessment; treatment of cognitive impairment

Sažetak

Naslov rada: Kognitivno oštećenje u multiploj sklerozi

Autor: Meytar Zohari

Multipla skleroza (MS) je upalna, potencijalno onesposobljavajuća demijelinizirajuća bolest središnjeg živčanog sustava (CNS), a neurodegeneracija je najistaknutija u progresivnim fenotipovima bolesti. Bolest rezultira motoričkim i kognitivnim simptomima, koji se svi mogu pojaviti neovisno jedni o drugima. Bolesnicima s višestrukim neurološkim znakovima ili lezijama CNS-a koje su vremenski odvojene dijagnosticira se relapsno-remitirajuća (RR) ili primarno progresivna multipla skleroza (PPMS). Progresivni tijek bolesti odnosi se na pogoršanje neuroloških simptoma i onesposobljenosti, neovisno o relapsima.

Kognitivno oštećenje (KO) čest je, ali i dalje izazovan simptom MS-a i čest uzrok lošijeg socioekonomskog statusa i invaliditeta MS bolesnika. Još uvijek nema podataka o izravnoj vezi između kognitivnih oštećenja i kliničkog tijeka bolesti. Kognitivni deficit, pogotovo u ranoj fazi bolesti, je onaj koji treba identificirati i liječiti kako bi se spriječilo pogoršanje KO-a, koje implicira lošiju prognozu u MS-u.

SDMT test je dragocjen alat za provjeru KO-a i može biti početna točka za procjenu KO-a u bolesnika s MS-om kada drugi sveobuhvatni alati nisu dostupni. Neuropsihološka procjena također bi trebala razlikovati kognitivna oštećenja i druge moguće uzroke uključujući kvalitetu života, depresiju i anksioznost.

Zdrava prehrana, životni stil bez ovisnosti, redovita tjelovježba te pravilna kontrola komorbiditeta mogu pozitivno utjecati na kogniciju u bolesnika s MS-om. Nedavni podaci također ukazuju da pravovremena terapija za modificiranje tijeka bolesti koja se uvodi rano tijekom RRMS-a može stabilizirati ili čak poboljšati kogniciju.

Budući da ne postoji standardizirani protokol za identifikaciju i procjenu KO, potrebna su daljnja istraživanja kako bi se razvio "zlatni standard" za probir i dijagnosticiranje kognitivnog deficita u MS-u te razvile učinkovite preventivne metode i pristupi liječenju utemeljenom na dokazima.

Ključne riječi: multipla skleroza; kognitivno oštećenje; SDMT; neuropsihološka procjena, terapija kognitivnog oštećenja.

Introduction

Multiple Sclerosis (MS) is a chronic, neurodegenerative and neuroinflammatory disease of the Central Nervous System (CNS), involving both cortical and subcortical grey matter (GM) and white matter (WM). The neurodegenerative part of the disease is playing a key role in contributing to cognitive and physical disability which negatively affects multiple aspects of the patient's QoL and daily living activities[1].

Usually, the disease affects the brain, optic nerves and spinal cord, with an acute inflammation seen during early phases and relapses, and with different degrees of neurodegenerative processes and chronic inflammation related to disability progression in later stages of the disease[2]. In about 85% of the patients, MS begins as a relapsing-remitting (RR) course and later evolves to a progressive stage (secondary-progressive ((SP)) MS) in roughly 50-60% of untreated patients after 15-20 years[3,4].

The diagnosis of MS is established according to McDonald 2017 criteria[5]. Recently published data show that by applying these criteria, MS can be diagnosed more frequently at the time of first clinical event as compared to the 2010 McDonald criteria. However, to avoid misdiagnoses, careful differential diagnosis (DD) is essential in patients with atypical clinical manifestations[6].

Around 15% of the MS patients will develop a primary progressive (PP) course after the onset of the disease[7]. Most MS patients experience their first symptoms between the ages of 20 and 40. The clinical heterogeneity of the disease, as well as having different pathological patterns, suggests that MS may be a spectrum of diseases representing different processes, rather than a single disease[8]. It can be clinically categorized into different phenotypes, including RRMS, PPMS and SPMS, and the first presenting symptom without fulfilment of complete criteria is called clinically isolated syndrome (CIS)[9]. The different phenotypes are related to potentially different disease mechanisms, including axonal/neuronal loss and gliosis, acute/chronic inflammation, and variable degrees of tissue repair, as well as plasticity and clinical recovery, mainly related to each individual[10].

The most common symptoms and affected neuroanatomical system in MS are urinary/bowel hesitancy, incontinence, or retention; tremor, dysmetria, or ataxia (cerebellar); numbness (sensory); motor dysfunction (pyramidal); diplopia or nystagmus (brainstem); disturbances in vision and cognitive impairment (CI). The affection of functional systems and severity of MS can

be measured with the Expanded Disability Status Scale (EDSS), which ranges from 0 – normal neurological examination, to 10 – which refers to death due to MS[11].

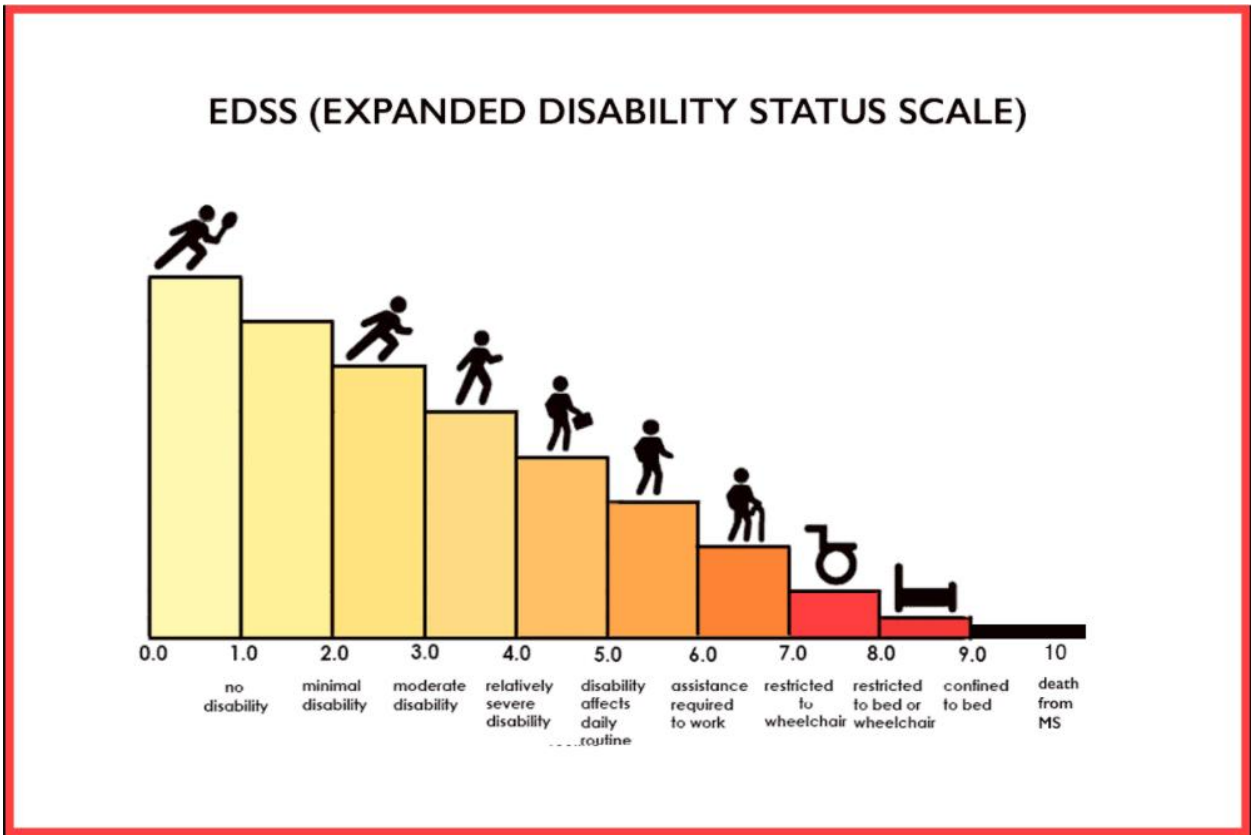

Fig. 1 | **Expanded disability status scale**[12]. The neurologist John Kurtzke came up with the scale in 1983 as an advance from his previous 10 step Disability Status Scale (DSS). The EDSS scale focuses mainly on the ability to walk. It is a basic measure of other types of multiple sclerosis disability.

Although EDSS scale is the most widely used disability score around the world, CI related to the disease is under-represented, even when neuropsychiatric and cognitive symptoms are a major cause of loss of employment, disability, and overall poor QoL of the patients and their families[13].

About 40-70% of adults with MS[14] and around 30% of pediatric patients[15] are handling CI symptoms. It can be detected in all disease subtypes, in all stages of the disease and even in subjects with low physical disability, as measured on the EDSS[11].

The following graduate thesis aims to raise awareness on the CI in MS patients. It will discuss about importance of cognitive dysfunction in affected patients with MS, what is known regarding the underlying pathology based on neuroimaging studies and neural

correlates, including the most affected cognitive domains and related neuropsychological batteries for their assessment. Moreover, it will focus on the known and hypothesized risk factors and protective factors for CI, discussing the latest research findings in the field. Finally, this thesis is going to address prevention strategies for CI, patient counselling, clinical management, and available treatment strategies.

Literature review

1. Cognitive functions in MS - Background

Until the last 30 years, CI in MS was considered as occurring almost exclusively in the late stages of the disease and in patients with high degrees of physical disability. Nowadays, it is recognized that CI can arise in all phases of the disease[16] although it is most often influenced by patient's increasing age and physical disability[17]. There is a different prevalence of CI between studies, with estimation usually ranging from 40 to 70% of the adult patients[14] and of about 30% of the pediatric patients[15].

Cognitive functioning can be affected during clinical relapses of the disease and a decreasing cognitive performance can represent the only clinical expression of a relapse, so-called "isolated cognitive relapse"[18]. In this way, MS disease activity can be redefined by neuropsychology tools. Present in the early stages of the disease CI seems to be associated with a worse prognosis, and CIS[19] patients with CI are at higher risk to develop clinically defined MS.

Overall, monitoring of cognition and systematic evaluation in clinical practice are highly recommended, to better understand the disease activity and severity, and provide patient counselling and management strategies. It is important to note, that different definitions of CI have been used over time in the literature[20]. Usually, a patient is defined as cognitive impaired if he/she fails in two or more cognitive tests. Failure in a test is defined as a score below 1.5 standard deviations (SD)[21] or below the 5th percentile in comparison with normative values[22].

1.1. Neuropsychological pattern

MS disease course variably affects cognitive functions, most often compromising working and episodic memory (33-65%), information processing speed ((IPS), 20-50% of patients)), visuo-spatial abilities (up to 25%), attention (12-25%) and executive functions (17-19%), whereas language deficits are rarely involved[23,24]. Recently, researchers that were using an extensive battery of neuropsychological tests, proposed a classification of CI into four cognitive phenotypes: a) not impaired; b) IPS-impaired; c) memory impaired; d) IPS+memory impaired. In the study's population of those researchers, CI prevalence was 43.7%, while memory impairment was the

predominant pattern (18.8%), followed by IPS+memory impairment (17.2%) and lastly, IPS impairment only (7,8%)[25].

2. Prevalence, cognitive profile, and phenotypes

Cognitive deficits can occur in very early stages of MS, even in the absence of other neurological deficits[26]. After accounting for demographic criteria such as age and education, the convention in neuropsychology is to ascribe CI to a score where performance falls less than 1.5 SD below normative expectation. In diagnosing CI, clinicians should account for psychiatric comorbidities, medication side effects, and MS symptoms that might affect cognitive performance as well[27].

The severity of CI differs among clinical courses of MS. It is assumed that cognitive dysfunction is present in the early stage of the disease, even in patients with CIS, and progresses in parallel to accumulating disability[17(ruano)]. Data indicates that cognitive decline is more prominent in progressive forms of the disease[28]. In one of the studies, an isolated decrease in phonemic fluency was observed in RRMS patients with a disease duration of less than three years. In the group of patients with a disease duration above 10 years, the digit span test and SDMT results indicated the patients were impaired, whereas patients with a progressive disease scored below normal in all neuropsychological tests except for the inhibition task. Interestingly, there was no significant differences between the SPMS and PPMS forms[29].

In two large studies, patients were categorized as having CI if their performance was impaired on two of 11 tests[30] or four of 31 tests[31] in a multidomain neuropsychological test battery. According to these standards for designating impairment, the prevalence of CI in adults with MS ranges from 34% to 65%, varying by disease course and research setting[17(ruano),32]. Like all symptoms of MS, CI is characterized by high variability between the patients. When results were taken together for a group of people with MS – cognitive processing speed (CPS), learning and memory were most frequently involved. Deficits in executive function and visuospatial processing are also reported, but less frequently[30,31]. In particular, in a representative sample of 291 adult patients with different types of MS, the frequencies of CI (varying by test) were as follows: 27–51% in CPS, 54–56% in visual memory, 29–34% in verbal memory, 15–28% in executive function, and 22% in visuospatial processing. Attention span, basic language and semantic memory are rarely impaired – only in about 10% of patients with MS[30].

CI occurs in all MS phenotypes[28,32] and estimates are that 20–25% of the CIS patients, 30–45% of RRMS patients and 50–75% of SPMS patients are suffering from CI[27]. The prevalence in PPMS varies greatly, as this phenotype comprises less than 15% of the overall disease population and study samples are very small. In patients with radiologically isolated syndrome, in which MRI findings suggestive of MS are incidentally found in an asymptomatic individual, cognitive defects can appear prior to the onset of other signs and symptoms and are associated with CNS lesions seen on MRI[33].

3. Pathophysiology of cognitive impairment

Quantitative MRI techniques are used to estimate different aspects of MS pathology, while different MRI metrics have been related to CI. Both regional and global damage of WM and GM in terms of focal lesions and diffuse microstructural damage[34,35] have been showed to be significantly related to the presence and severity of CI. WM lesions (T1 hypointense and T2 hyperintense lesions) volume, distribution and load have been associated with cognitive dysfunction in patients with MS and different disease courses[36].

In the earliest phases of the disease, cognitive dysfunctions might be clinically silent, a finding that could be explained by the compensatory activations of other cerebral areas not involved directly in the specific task, and then become evident over time. Accordingly, fMRI studies have shown an altered activation pattern during cognitive tasks in CIS[37] and RRMS patients[38]. Changes in the activation pattern can result from diffuse WM and GM damage and may also represent a poor adaptation response to severe tissue injury, especially in the advanced stages of the disease[39].

4. Cognitive dysfunction in MS - most affected cognitive domains

The cognitive impairment pattern in MS has been defined as "fronto-subcortical syndrome" or "disconnection syndrome"[40]. The most affected cognitive domains in patients with MS are reviewed in following sections.

4.1. Information Processing

In 40–70% of the patients with MS, the information processing speed can be affected. The efficiency in information processing in MS refers both to working memory — to manipulate and maintain information for a short period, and to the processing speed — the speed at which a certain series of cognitive operations can be performed. Both are affected in MS and interact with each other, although some researchers believe that it is more common to find the processing speed affected, especially in patients with a SPMS[41].

The slowing in information processing seems to be the most frequent cognitive change in MS and one of the first cognitive symptoms that can be detected[41,42]. This can also affect the ability to follow a certain conversation.

Among the tests used to evaluate processing speed are SDMT - evaluates visual processing speed, and PASAT (Paced Auditory Serial Addition Test) - evaluates auditory processing speed. When comparing the performance between patients with MS and healthy controls, greater effect sizes were evidenced with the SDMT[43]. That is why, the SDMT is the measure of choice for MS trials in assessing cognitive processing speed[44].

4.2. Memory

Memory difficulties have been found in 40–65% of MS patients, with 30% of patients having severe memory problems[45]. In those patients, the alterations occur mainly at the explicit memory (declarative), having to do with deliberate recall and the recovery about the knowledge of the world and personal experiences. Generally, there is preservation of implicit memory (non-declarative), in which previous experiences facilitate the execution of a task, with conscious perception of it[46].

Tests that evaluate this domain include both auditory-verbal such as the Selective Reminding Test (SRT) and California Verbal Learning Test while for visuospatial information the Spatial Recall Test (SPART) is used[47].

4.3. Attention

Between 20-50% of MS patients have specific attentional difficulties[45]. The most affected components of attention in MS are selective, sustained, alternating and divided attention. On the other hand, focused attention and alert level are components not so frequently impaired. People

with MS most frequently refer to have difficulties with following a television program or a conversation, keep doing a task at work, maintaining focus on a particular stimulus when other competing stimuli exist, or resuming a certain activity after an interruption[48].

Alterations at the attention level have been related to difficulties both in processing speed and working memory. Thus, most of the tests that evaluate attention components also take into consideration working memory and processing speed[49].

4.4. Executive Functions

Executive functions are the skills needed to carry out effective, creative, and socially accepted behavior, and include a set of processes which are anticipation, planning, goal-setting, and self-regulation. Between 15 to 25% of MS patients struggle with executive difficulties[45], and between 20 and 25% have difficulties in verbal fluency tasks[50], making executive alterations less frequent.

4.5. Language and Intelligence

Most studies showed that both intelligence and language skills are generally preserved in patients with MS. However, some authors have shown a slight decline in the intelligence quotient (IQ) – specifically in the manipulative IQ, vs. the preservation of verbal IQ. When the disease begins early in the life, a greater alteration in language and IQ is manifested [51].

Basic verbal skills, such as expression and understanding, are often preserved, except for occasional difficulties in naming. If there are problems in verbal comprehension, these seem to be related more to difficulties with working memory or in information processing. The most prevalent verbal difficulty is the low performance in verbal fluency tasks – especially phonemic fluency over semantic, which are more often related to executive functioning[45].

4.6. Visuoperceptive Functions

The main alterations are observed with angle matching and facial recognition[45]. Although visual disturbances such as optic neuritis may exert a negative influence on perceptual processing, in up to 25% of patients, perceptual deficits have been observed regardless of the existence of primary visual impairment[52].

4.7. Social Cognition

Social cognition is the individual's ability to understand his own and others' minds and feelings to give adequate answers in the person's social environment[53]. Also, it can be defined as the way we perceive the social world around us. MS has been associated with social cognition impairment, which might have a drastic impact on the QoL and social relationships[54].

Social cognition can be evaluated using few different tests: Faces Test, Reading the Mind in the Eyes Test, Faux-Pas Test, and the MASC - Movie Assessment Social Cognition examination. It seems that fatigue, an invisible symptom of MS, might correlate with social cognition performance, which could be due to common underlying neuronal networks[55]. Mindfulness-based intervention (MBI), could be useful to improve social cognition[56].

5. Assessment of cognitive impairment in MS

There are many tools available to assess cognitive impairment that have been validated during more than 40 years of research. These tools range from quick screening instruments to full neuropsychological assessment batteries[57,58]. This assessment is crucial given that patient self-reporting of CI does not correlate well with objectively measured impairment[59], and there is a possibility that neurological assessment as ascertained by objective neuropsychological testing can underestimate actual cognitive impairment[60].

Due to that, specific recommendations and guidelines are published, establishing the need for regular objective assessment of cognition in patients with MS. For example, in the USA, the National MS Society has published guidelines for cognitive assessment in both pediatric and adult patients, recommending screenings at least annually, or more frequently if needed[61]. Regular assessments have been recommended also by the American Academy of Neurology (AAN), the National Institute for Health and Care Excellence in the UK[62], and a consensus group in Italy[63].

It is important to note, that tests such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), which mostly assess cortical function, are commonly used to screen cognitive deficits in dementias, but are not sensitive or specific enough to test cognition in MS patients because other domains are typically affected in this condition[64].

5.1. Neuropsychological Assessment

One of the first batteries of neuropsychological assessment presented to evaluate MS-related deficits was the Neuropsychological Screening Battery for MS (NSBMS), developed by neuroscientists from the USA's Cognitive Function Study Group. This battery includes the 7/24 Spatial Recall Test (SPART), the Selective Reminding Test (SRT), PASAT, and the Word List Generation Test (WLGT). Later, the same group proposed the applicability of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), supplemented with the SDMT using the 10/36 SPART instead of the 7/24 version[65].

Later on, due to the increased need for improved diagnostic accurateness, a new reliable test battery named the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS) emerged. In this assessment, the SRT was replaced with the California Verbal Learning Test-Second Edition (CVLT-II) and the 10/36 SPART was replaced with the Brief Visuospatial Memory Test Revised (BVMT-R). Moreover, two newly developed tests were added: the Judgment of Line Orientation and the Delis-Kaplan Executive Function System, which tests executive and visuospatial functions[65].

The BRB-N and MACFIMS performed similarly and suitably in the identification of cognitive decline in MS[67]. Even though these batteries have high sensitivity, their implementation in clinical practice requires time and money, since these are long tests and a trained neuropsychologist is needed to administer them. Thus, a more cost-effective way to assess cognition in MS is still necessary[66].

Currently, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is becoming more and more popular, especially because it can be easily performed by clinicians and takes 15 min to complete. The BICAMS includes the SDMT, CVLT-II, and BVMT-R and is currently regarded as a recommended and widely validated screening tool for CI in patients with MS[67]. A diagnosis of CI is established when a patient is performing at least two tests from a battery below the normal range, of either 2 SD[68] or 1.5 SD below the control group[69].

According to observations suggesting that information processing speed and attention may be impaired in the early stages of MS, the SDMT seems to be the best single tool and the most effective to assess cognition even in the initial stages of the disease[70]. Due to this fact, clinical neuropsychologists have abandoned lengthy, comprehensive test batteries for patients with MS, in

favor of more targeted, sensitive tests that evaluate affected domains such as the SDMT or PASAT[71]. Cognitive domains measured by tests included in neuropsychological batteries used in MS are summarized in Table 1[72].

Table 1 | **Common neuropsychological tests applied in MS research**

Battery	Purpose	Time	Individual tests included	Targeted cognitive domain
Brief Repeatable Battery of Neuropsychological tests (BRB-N)[211]	Neuropsychological test battery for MS	25–30 min	Selective Reminding Test	Verbal learning and memory
			10/36 Spatial Recall Test or 7/24 Spatial Recall Test	Visuospatial learning and memory
			Symbol Digit Modalities Test	Processing speed
			Paced Auditory Serial Addition Test	Working memory and/or processing speed
			Word list generation test or Controlled Oral Word Association Test	Verbal fluency and/or word retrieval
Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)[212]	Neuropsychological test battery for MS	90 min	Paced Auditory Serial Addition Test	Working memory and/or processing speed
			Symbol Digit Modalities Test	Processing speed
			California Verbal Learning Test-II	Verbal learning and memory
			Brief Visuospatial Memory Test — Revised	Visuospatial learning and memory
			Delis–Kaplan Executive Function System Sorting Subtest	Executive functioning and problem solving
			Judgement of Line Orientation	Visuospatial processing
			Controlled Oral Word Association Test	Verbal fluency or word retrieval
Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)[213]	Cognitive screening battery for MS	15 min	Symbol Digit Modalities Test	Processing speed
			California Verbal Learning Test-II	Verbal learning and memory
			Brief Visuospatial Memory Test — Revised	Visuospatial learning and memory

MS, multiple sclerosis.

5.2. Brain imaging assessment

The relationship between CI and neuroimaging parameters in patients with MS is highly complex. CI is associated with various structural imaging metrics in patients with MS, including cortical and subcortical atrophy, lesion burden, and structural connectivity[35]. Early studies reported that greater impairments in processing speed, memory, learning and executive function were associated with increased lesion burden and brain atrophy in affected patients[73]. More recent longitudinal studies indicated that reduced cortical thickness, GM atrophy and increased total lesion burden predict cognitive decline in people with MS[74].

Evidence shows that specific brain regions atrophy, particularly the thalamus and hippocampus[75,76], is associated with specific cognitive dysfunctions in MS patients, like processing speed, learning and memory[77]. In addition to focal lesions and brain atrophy, it is evidently clear that MS-related CI is a product of synaptic dysfunction across several neuronal networks[78,79].

5.2.1. MRI

CI can result from damage of various structures and connections in the CNS; for that reason, many different techniques have been employed to seek appropriate imaging correlations. Magnetic resonance imaging (MRI) allows the detection of Gd-enhancing lesions, T1 lesions (so-called "black holes"), T2 lesions, and brain atrophy[35].

In several studies focusing on the deep GM, mesial temporal cortex and neocortex, GM volume correlated with cognitive performance. The clinical significance of damage to deep GM structures was further established by studying atrophy and diffusivity changes of the thalamus, which were both independently correlated with CI. Besides the thalamus and the cortical GM, hippocampal volume and function are changed in patients with MS, and the hippocampus is one of the predilection sites for occurrence of demyelinated lesions[27].

Several studies evaluated associations between the T1 and T2 lesion load and cognitive deficits. In a study of 62 patients with CIS, the researchers demonstrated that deterioration in the overall cognitive score and executive function over seven years of observation could be correlated with the number of T1 lesions in the first year following diagnosis of CIS. Moreover, an increased number of T2 lesions in the first three months after CIS can predict the patient's future executive function performance[80]. Also, it was shown that a higher T2 lesion load obtained in a short period following CIS was correlated with cognitive decline after five years[16]. Another important factor was early inflammatory activity, counted as the number of Gd enhancing lesions. According to the literature, this parameter may predict memory, executive, and overall scores on neuropsychological tests after seven years of follow-up[80].

On the other hand, few authors described a correlation between CI and the number of cortical lesions. In one of the studies, GM pathology was associated with poorer cognitive outcomes in MS, and the number of cortical lesions (CL) correlated positively with the level of decline in the working memory (PASAT) and semantic word fluency (Regensburger Word Fluency Test)[81].

Cortical thickness represents another imaging and anatomical parameter of potential value in the context of assessing cognitive function. It is highly heritable, very stable, and is not affected by pseudoatrophy but rather by neurodegenerative processes such as demyelination and axonal, neuronal, and synaptic loss. Nevertheless, the association of cortical thickness with cognitive performance has some controversy. It was demonstrated that cortical thickness was related to clinical symptoms of MS, such as depression, cognitive deficits, physical disability and fatigue[82,83].

Other MRI parameters and techniques have also been implicated as correlates of cognitive function in MS, including diffuse axonal loss in normal appearing white matter [80,84]. Recently, retinal thickness measured by OCT method was found to be potentially useful in clinical detection and monitoring of axonal loss in MS, as a noninvasive and less expensive technique. In particular, one parameter, the peripapillary retinal nerve fiber layer (RNFL), was associated with brain atrophy[85]. The RNFL was shown to correlate positively with the result of the SDMT in the early stages of MS[86].

5.2.2. - fMRI

In addition to the described structural damage, studies in the last years have increasingly focused on the functional connectivity of GM structures, such as the hippocampus, thalamus, and cerebral cortex, by use of resting state functional MRI. According to these studies, there is an altered connectivity patterns in patients with MS who have CI[87,88].

In early stages of the disease, increased connectivity can signify that neuronal resources are compensating for demyelination and neuronal loss. In later stages, once these reserve resources are exhausted, connectivity diminishes, and CI is more apparent. Overall, these network fMRI studies indicate that cognitive decline could be explained by an accruing destabilization of the brain network physiology[27].

Different functional neuroimaging approaches involving task-related paradigms, like fMRI, have been applied to examine other possible neural correlates of MS-related CI. Studies have reported that people with MS who are in the early stages of the disease course demonstrate increased prefrontal cortical activation during region specific tasks compared with healthy individuals[89,90]. This finding suggests the existence of an adaptive compensatory mechanisms (neuroplasticity) in people with MS.

fMRI paradigms can be applied when there is a need to measure functional connectivity and effective connectivity of different regions in neural networks, that might be relevant and important in understanding MS-related CI. Of note, effective connectivity, but not functional connectivity, can demonstrate directionality and causality in brain connections. Some fMRI research suggests that functional connectivity is reduced in people with MS versus healthy individuals, and is also reduced in cognitively impaired compared with cognitively preserved MS patients[91,92].

5.3. Multiple Sclerosis Biomarkers Related to Cognitive Dysfunction

There are several biomarkers measured in serum or in cerebrospinal fluid (CSF) that have been implicated as potentially effective in monitoring the MS course from the earliest stages of the disease[93].

Neurofilaments have recently become biomarkers of the highest interest in this area. These are axonal cytoskeletal proteins composed of three chains: light, medium, and heavy. They are released into body fluids when axonal damage occurs; thus, in all stages of MS, increased levels of neurofilaments have been observed in the CSF and blood serum. To date, most neurofilament light and heavy chains (NfL and NfH, respectively) have been investigated in MS[94]. Higher levels of NfL were found in CIS patients[95] and NfH levels in CSF have been correlated with the brain volume reductions and progressive disability over time[96].

In a preliminary study of fMRI assessing 21 untreated, cognitively intact patients with CIS, higher CSF NfL levels were associated with lower activity in the putamen, while performing a task that required increasing levels of attentional control processing. This result may suggest that NfL can be used as a marker of abnormal cognitive pathway recruitment even preceding the first clinical signs of CI in patients in the earliest stages of MS[97].

The other widely investigated biomarkers are chitinase-like proteins (CHILPs). The biological role of these proteins is still unknown, but it is believed that they are involved in cell survival and tissue remodeling inflammation. Moreover, higher levels of CHILP in CSF may reflect a high degree of axonal damage[98]. Chitinase 3-like 1 protein (CHI3L1) on the other hand, is a molecule suggested to play a role in inflammation and the way tissue responds to the injury[99]. It was found that its

level in CSF may predict progression in early MS, illustrating neuronal damage from the beginning of the disease[98]. Another member of this protein family, chitinase-3-like 2 protein (CHI3L2), the closest homolog of CHI3L1, was suggested as a biomarker of the transition from isolated optic neuritis to MS. Moreover, after a 14-year follow-up period, the increased level of CHI3L2 in patients diagnosed with optic neuritis as a first demyelinating episode was associated with poorer performance in PASAT[99].

6. Risk factors and protective factors for cognitive impairment

Several factors are known to influence the level of CI. In the following chapter, the main documented or hypothesized risk factors and protective factors for CI are going to be presented. Some of these are disease-related and others may be involved in cognitive dysfunction independently from MS. Factors pertaining to demographic, psychological and clinical, disease-related variables; then environment and lifestyle-related factors, comorbidities, and genetic factors, will be covered first[36].

6.1. Demographical and clinical

6.1.1. Age and age at onset of the disease

Aging in the general population is a known risk factor for CI. In adult-onset MS, most of the published longitudinal and cross-sectional studies have associated aging with increasing frequency and degrees of CI[100]. On the other hand, younger age of MS onset was suggested to be a risk factor for CI and reduced IQ in a cohort study of pediatric MS patients that were followed up for five years[101,102]. Moreover, comparing adult-onset and pediatric-onset patients, a pediatric onset of MS was found to be associated with an increased risk of CI in adulthood[103]. It has been suggested that the development of the disease in early age may interfere with myelinization and ongoing brain maturation, causing damage to the GM and WM networks and disrupts neuroplasticity, thus reducing the brain reserv[15].

6.1.2. Sex and sex hormones

MS affects mainly females but has a more aggressive disease course in males. However, in animal models, testosterone seemed to have a protective role on neurodegeneration and inflammation. A study showed that male patients with low testosterone levels may have a more severe course of disease[104].

6.1.3. Disease course

It appears that CI is present in all disease subtypes; however, it tends to be prominent and more severe in PPMS and SPMS patients due to the cortical involvement and extensive neurodegenerative brain process[17,28,105]. Overall, the evidence shows that SPMS and especially PPMS patients are at higher risk for CI[36].

In comparison of PPMS and RRMS patients, different disease duration may represent a confounding factor. A retrospective population-based study, showed that even after 10 years of disease duration, PPMS and SPMS patients were more severely and frequently impaired than RRMS patients[106]. A recent meta-analysis of published studies demonstrated that PPMS patients exhibited prominent CI, highlighting that these patients may need a more specialized disease management, not only for the accumulation of physical disability, but also for the greater degree of cognitive dysfunction[105].

6.1.4. Disease duration

The relationship between duration of the disease, clinical disability and CI depends on few factors, including also the age of the disease onset. For instance, in the pediatric patients also a short disease duration could have a greater impact than in older MS patients. A study with a long follow-up has reported that a disease duration of 10 years or more was significantly associated with CI[107]. Others studies, on the contrary, have failed to identify any significant association[108]. In a large cross-sectional study of 1040 patients representing different subtypes of the disease, CI was mainly driven by increasing age and physical disability, but not by disease duration: this might be because of the effect of ageing on cognition and due to the reduction of cognitive reserve (CR) in older population[17].

6.2. Comorbidities and other disease-related factors

Comorbidities represent an area of high interest in MS research[109]. Physical (i.e., hypertension, diabetes, thyroid dysfunction) and psychiatric comorbidities (i.e., anxiety, depression, bipolar) might be associated with an increased prevalence of cognitive deficits in patients with mild cognitive impairment (MCI) or other neurodegenerative diseases[110]. Patients with MS may have an increased risk of anxiety and depression and more frequent consuming of antidepressant and anxiolytic drugs compared to the general population[111].

As for physical comorbidities and MS, there is some evidence that more than three comorbidities as well as self-reported CI are associated with low QoL and increased health service usage. Moreover, comorbidities in MS have been associated with a worse disease outcome[109]. Specifically, cardiovascular risk factors have been associated with brain lesion burden and brain atrophy[112]. In a study that was conducted recently, small vessel disease (SVD) was identified as a potential contributor to neurodegeneration and possibly to CI[113].

6.2.1. Depression

People with MS in general have a greater prevalence of psychiatric comorbidities compared with the general population, most commonly depression. The prevalence of depression in MS patients ranges from 20 to 40% [114]. It is not clear, however, whether in MS depression is simply reactive to the chronic disease condition, due to the organic damage in relevant brain regions or it is due to the dysimmune, inflammatory status. Most probably, etiology of depression has a diverse, multifactorial origin in different subjects[115,116]. Depression and anxiety are associated with poorer QoL[114] and low work performance (absenteeism and presenteeism) in MS patients[115].

Moreover, depressive symptoms are independently associated with increased physical disability and more aggressive disease course[117]. Depression has both direct and indirect effects on cognitive functioning by slowing processing speed and reducing the subject dedication to leisure activities, a determinant of CR. Furthermore, depression contributes to attention deficits, partly explaining the lower working performances of this group of patients[118]. Lastly, depression has been associated with higher frequency of self-reported cognitive deficits[119]. Given its prevalence and influence on various disease outcomes, including cognitive performance, depression represents an important therapeutic target to improve cognition in MS patients[120].

6.2.2. Anxiety

Anxiety is reported to affect 23-41% of the MS patients[121] and higher anxiety levels have been associated with MS physical severity and greater incidence of self-reported cognitive deficits[124]. Anxiety is more prominent in the initial phases of the disease, more in female patients than in male and often associated with depression and fatigue, a relationship that is difficult to untangle when trying to assess the impact of the single variables on CI[122]. In a study of 140 patients with MS, anxiety was demonstrated to be the major influencing factor of poor performances in tests assessing complex attention and IPS[123].

6.2.3. Fatigue

Mills and Young had defined fatigue in MS as a "reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion"[123]. Fatigue can present itself as 'physical/general/peripheral' or 'cognitive/mental/central'. The first presentation is more related to the disability level while the latter becomes evident when performing cognitive tasks and is more related to CI[124]. Fatigue is reported by around 80% of adult MS patients and is evaluated subjectively by two-thirds of them as one of the most disabling MS symptoms[125,126]. Central fatigue is a characteristic of hypothalamic, pituitary, and diencephalic syndromes. In hypothalamic-pituitary diseases, it is associated with endocrine disturbances and changes in sleep pattern and bodyweight. Fatigue, anorexia, and sleepiness are the most frequent symptoms of neurological disorders, which are attributable to reduced concentrations of substance P, cytokines, prostaglandins, and leptins[124,125].

6.2.5. Pain

According to a review of 17 studies, the prevalence of pain in MS patients was 62.8%[127]. Pain can be classified as chronic or acute and further into generalized, localized and neuropathic. The most common form of pain in MS is neuropathic pain, classified in Lhermitte's sign, trigeminal neuralgia and neuropathic pain within the extremities. Chronic pain may cause cognitive deficits via indirect mechanisms, such as worsening QoL, reducing leisure and physical activities, increasing intake of painkillers, and via direct mechanisms such as functional exertion of cognitive areas used for pain processing, lowering of attention and IPS[128].

Even if there is some evidence of a role of pain as a risk factor for CI in MS, due to its link to inflammation and its disrupting role on attention, decision making and memory[129], there are no studies directly assessing this relationship in MS patients. Other studies, however, have presented pain and cognitive dysfunction as part of a cluster of symptoms next to depression and fatigue, and suggested a common etiology[130].

6.3. Environmental and Lifestyle factors

6.3.1. Smoking

Smoking is a risk factor for Alzheimer's disease and is related to preclinical changes in the brain, higher risk of cognitive decline and increased risk of dementia[131]. It seems that smoking in MS has a role as risk factor for the development of the disease as well as a prognostic role, negatively influencing the disease course[132] and cognitive functions[133] of the patients through its effects on nicotinic acetylcholine receptors. MS patients who were heavy smokers compared to non-smokers showed poorer performance on the SDMT and PASAT[134] and this could be due to the pro-inflammatory substances inside cigarettes.

Moreover, Zivadinov et al. proved the association of smoking with an increased blood-brain barrier disruption, higher brain lesion volumes, and more recognizable brain atrophy, all factors that may contribute to the loss of brain tissue and brain reserve, thus accelerating the development of cognitive deficits in MS patients[135].

6.3.2. Cannabis

Cannabis, ingested or inhaled, is used in up to 20% of MS patients to treat a different symptoms, especially pain and spasticity. Many trials have investigated the effects of cannabis in MS, some of them also considered the cognitive effects of this therapy, reporting no association between usage of cannabis and reduced cognitive functions[136]. On the other hand, in the general population effect of cannabis usage is associated with important implications on various neurobehavioral processes, including anxiety and mood regulation, learning, motivation, reward processing, motor control, memory and executive functions.

Furthermore, Sagar et al. reported that cannabis use is associated with negative health outcomes, poor psychosocial and CI as well as other different neurobehavioral consequences[137]. Besides this trial results, in MS patients, inhaled or ingested cannabis has been associated with a doubled probability to develop CI in cannabis users in comparison with non-users[138].

6.3.3. Alcohol

Alcohol is an important risk factor in various diseases such as cancer, infectious diseases, neuropsychiatric diseases, diabetes, liver and pancreas disease, cardiovascular disease, and unintentional and intentional injury[139]. Moreover, chronic heavy intake of alcohol is a cause

of dementia and brain atrophy later in life[140]. Anxiety and depression have been associated with increased alcohol consumption among MS patients, making their disease course more complicated[115]. In MS patients, the relation between alcohol consumption and CI has been poorly explored and results appear to be controversial. In a study that was conducted within MS subjects, heavy alcohol usage was present in 14% of participants and was associated with mild cognitive deficits in these patients[141].

6.3.4. Sleep

Sleep disturbances in MS are very common. In a recent study, 19-67% of patients with reported fatigue and sleepiness were found to have various cognitive difficulties[142].

The association between sleep disturbances and CI in patients with MS has been hardly explored. In a recent study, sleep difficulties were associated with more self-perceived cognitive dysfunction, partially mediated by increased fatigue which was evident in organization, planning, and prospective memory[143]. Another study showed that excessive daytime sleepiness was linked with a poorer performance in a computerized version of the SDMT with distracters, pointing out the role of sleep in attention[144]. As sleep represents a potential modifiable risk factor for CI, more research in the field is needed.

6.3.5. Other factors: sodium, caffeine intake, vitamin D

CI and diet in MS may be connected through the gut microbiota. High-fat consumption and sodium intake have been connected in some studies to an increased frequency of CI compared to the general population[145] and to the dysbiosis implying the dysfunction of gut-brain-axis[146]. Other studies on MS patients have reported no association between high salt intake in the diet and CI[147].

As for caffeine intake, in healthy adults it has been reported that after low to moderate caffeine doses, vigilance, alertness, reaction time and attention can improve, while less effects are observed on memory and higher-order executive functions[148]. Current data shows that a higher mean number of coffees per day are related with preserved cognitive functions[132]. A preliminary report suggested that caffeine intake may reduce MS-related disability and fatigue[149].

Vitamin D deficiency is being investigated as a risk factor for the development of MS and a prognostic factor related to a worse disease course[131]. In the BENEFIT trial in CIS

patients, smoking, as well as lower levels of vitamin D at baseline, were associated with poorer PASAT performance during the follow-up period[150].

6.4. Cognitive reserve

CR has gained attention also in the field of MS over the past decade, in order to account for the differences between the clinical manifestations of the disease and the degree of brain damage measured by MRI[151], while trying to translate the results obtained in AD research to MS[152]. Educational level is one of the most relevant correlates of CR. In the general population low levels of education have been connected with higher risk for dementia[153], although socioeconomic status - commonly considered associated with education, has not been surely associated with a higher risk of dementia[154].

As per today, only a few longitudinal studies have been conducted on this subject. A longitudinal study of a 1.6 year follow-up showed that high CR index and cortical volumes were related with better performances in neuropsychological tests at baseline but no longer at follow-up, due to increasing degrees of cortical atrophy, stressing the importance of early interventions[155]. Furthermore, in a sample of 40 patients, a longitudinal study conducted over 4.5 years has shown a significant association of high intellectual enrichment and large Maximal Lifetime Brain Growth with lower rates of CI[156].

6.5. Physical exercise

Physical exercise is linked to an increased hippocampal volume, as reported by a study on physical exercise and mild CI in women aged 70-80 years[157]. A recent systematic review about physical exercise in MS patients concluded that there was an overall positive effect of physical activity and physical fitness on cognition among MS patients[158].

6.6. Genetics

APOE - Apolipoprotein E, one of the most studied genes related to cognitive functioning, is the main known genetic risk factor for sporadic and late-onset familial Alzheimer's disease. In MS, several studies investigated APOE ε4 allele status related to disease severity, providing mainly inconsistent or negative results. An MRI study found a relation between higher levels of brain atrophy in MS patients carrying the APOE ε4allele, however, in this study cognitive assessment was not provided[159].

Nevertheless, considering recent data looking into detrimental effect of APOE ε4 on late-life cognition, independent of AD pathology[160], it remains possible that genetic variations in APOE exert significant effects on the trajectories of CI in late stages of MS.

Due to studies that found no cognitive differences between HLA-DR15– and HLA-DR15+ patients, HLA-DR15, even though is a main risk factor for MS, has been excluded as risk factor for CI[161].

Lastly, brain reserve is a hereditary factor that can influence also CR. Brain reserve is expressed as maximal lifetime brain accepted manuscript growth and can play an important role as a protective factor against CI, together with CR[159,162].

7. Treatment of Cognitive Impairment in MS

Interventions for treating CI can be classified as pharmacological and nonpharmacological. Even though the disease modifying drugs (DMDs) can have a positive impact on the subject's cognitive outcome, by decreasing the progressive atrophy and lesion burden in the brain, or via potential direct neuroprotective effects, the evidence existing from clinical trials is limited, while published observational studies have some important methodological limitations[163,164].

7.1. Pharmacological Interventions

DMTs might improve cognition in patients with MS as these agents are primarily designed to prevent relapses and arrest the disease, but if they directly improve cognition remains unclear. Evidence does exist of positive effects of DMTs on correlates of cognition — for example, reduced progression of brain atrophy and decreased inflammatory activity in MS patients, reductions in T2 and T1 brain lesion load[165]. Nevertheless, evidence supporting the efficacy of DMTs for MS-related CI treatment is limited, and there is no approved therapy yet for this purpose[166].

RCTs investigating symptomatic pharmacological treatment including drugs such as donepezil, modafinil, memantine and l-amphetamine sulfate, have shown conflicting effects on MS-related CI[165]. Dalfampridine has been identified as a possible pharmacological treatment for CI related to MS, given its effects on ambulation[167]. The data regarding the effects of this drug on cognition are mixed, with one RCT reporting no effect on processing speed[168] and a second RCT

reporting transient improvements in processing speed[169]. A well conducted RCTs with cognition as the primary outcome will be required in the future in order for any pharmacotherapy to be approved for CI related to MS[72].

7.1.1. MS Disease Modifying Therapies

MS specific DMTs the injectables glatiramer acetate and interferon beta; oral agents such as teriflunomide, fingolimod, and dimethyl fumarate; monoclonal antibodies such as ocrelizumab, alemtuzumab and natalizumab, have shown significant benefits in reduction of the annualized relapse rate, with lower efficacy on the brain atrophy rate or reduction in disability progression[4].

Nevertheless, their impact on CI specifically remains unclear, since most phase III clinical trials did not established CI as a primary outcome measure. Due to the different neuropsychological batteries used, the differences between populations included in the trials and the different methods for evaluation and outcome analysis, comparative efficacy on cognitive outcomes across trials is more difficult[2].

Pivotal glatiramer acetate and interferons clinical trials did not include cognitive evaluation as primary outcomes. Intramuscular interferon beta 1a versus placebo included neuropsychological evaluation as a secondary outcome measure and showed 52.7% improvement in comparison with 29% in the placebo group[170], including episodic memory outcomes and processing speed. In the COGIMUS (Cognitive Impairment in Multiple Sclerosis) study, subcutaneous interferon 1a had a protective effect on RRMS patients on general cognitive decline when reevaluated at 3[171] and 5 years[172] after the beginning of therapy. As for interferon beta 1b, Pishkin reported only improvement of delayed visual reproduction performance[173], and the Betaseron/Betaferonin in newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial revealed that in patients with CIS, interferon beta 1b had beneficial effects on working memory, and the effects lasted over 8 years[174]. Glatiramer acetate trials included BRB-N evaluation but did not show significant differences versus placebo[175].

The GOLDEN Study using oral fingolimod once daily, was compared with interferon beta 1b using a trial design that included CI as the primary outcome. This study showed improvement in cognitive function (DKEFS and BRB-N) in both treatment arms, with fingolimod being favored on MRI parameters[176].

Natalizumab studies showed that compared with placebo, this treatment can reduce the risk of progressive working memory impairment by 43%[177]. In a long-term observational study conducted by Jacques et al. using a computed test and the SDMT, natalizumab was reported to preserve cognition over 7 years of continuous therapy. Over a 24-month period, no patient showed evidence of prolonged cognitive deterioration[178]. In a study that was conducted during a 15-month follow-up period, including 21 patients, alemtuzumab showed a stable cognitive function using an extensive neuropsychological battery[179]. Compared with interferon beta 1a, ocrelizumab has shown improvement in MS Functional Composite Score (a composite measure of upper-limb movements, walking speed and cognition assessed by PASAT)[180].

7.1.2. Cognitive Impairment-Specific Treatment

Use of acetylcholinesterase inhibitors (AChEI) in MS patients is debatable. While Krupp in 2004 in a cohort of 69 patients reported the positive impact of donepezil on memory and verbal learning, he also reported no significant effect in a 2011 conducted study that included 120 MS patients[181]. Regarding memantine, similar findings were reported in a small number of studies showing negative outcomes for this drug[182]. Amphetamines significantly improved verbal memory and visuospatial memory[183], fampridine has shown to be able to improve alertness, cognitive fatigue, verbal fluency and psychomotor speed[184], while using modafinil resulted in no additional benefit on learning[185].

7.2. Non-Pharmacological Interventions

7.2.1. Cognitive rehabilitation

Only recently, the field of cognitive rehabilitation has been established as a beneficial therapeutic tool. Cognitive and behavioral rehabilitation strategies are designed to enhance an individual's capacity to interpret and process information in order to function in all aspects of community and family life[72]. Computer-assisted training, cognitive-behavioral interventions, and combinations of the two, have been showing consistently better results[186,187], especially when adjusted to individual needs. In a recent meta-analysis and review article including data from 2007 to 2016 only one intervention received support for a practice standard in memory and verbal learning (modified Story Memory Technique—mSMT[188]), two computer programs received support as a practice guideline for multi-cognitive domains and attention (RehaCom[189] and Attention Process

Training—APT[190]), and several studies provided support for the practice option in learning, memory and attention[191].

Studies suggest that cognitive rehabilitation has a long-term impact beyond the treatment period and might enhance cognition in the face of future brain changes[192]. These effects have been documented in the literature on ageing, where it was stated that cognitive rehabilitation not only improved everyday life activities (reducing the incidence of driving accidents for example)[193], but also resulted in a reduction of 29% in dementia risk 10 years after treatment[192]. Such information will be crucial to legitimate the use of cognitive rehabilitation in MS patients in order to protect against cognitive decline in the future as the disease progresses (Fig. 1)[72].

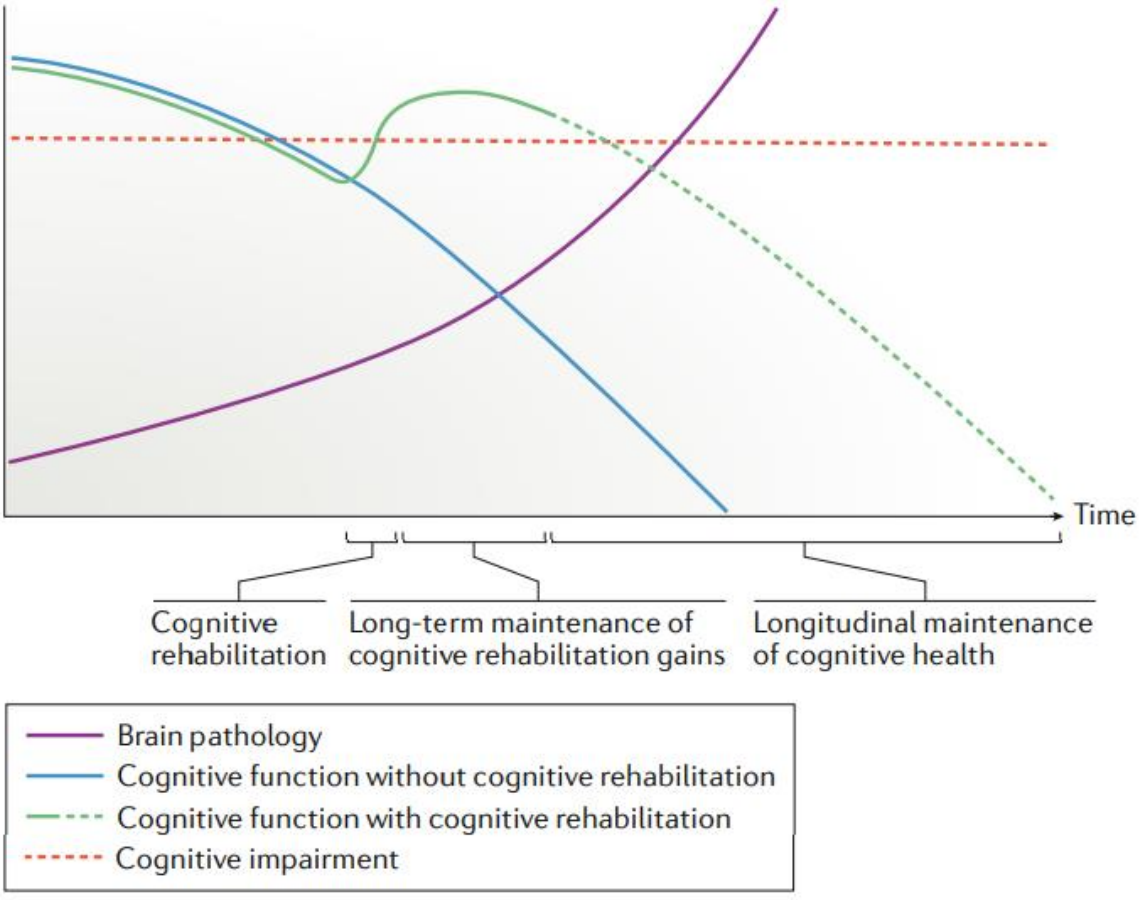

Fig. 2 | **Cognitive rehabilitation in multiple sclerosis.** Theoretical model of the potential impact of cognitive rehabilitation benefits in the progression of cognitive impairment over time in MS. The figure is not based on data but could potentially be used to guide future research since it depicts theoretical trajectories that research can test empirically in the future.

7.2.2. Exercise training and cognition in MS

A lot of publications have shown a positive impact of physical exercise on different clinical parameters, but evidence still needs to be demonstrated, as clinical trials have shown ambiguous results[194,195]. A systematic review by Sandroff et al. showed that a few comparable studies did not yield a significant positive impact of physical exercise on CI outcomes[196]. A different systematic review of the impact of yoga also failed to show any effect of this discipline on CI[197]. This can be the result of insufficient well–designed research, and also the fact that cognitive impairment is maintained as a secondary outcome. The cognitive effects of physical exercise in MS still needs to be researched, as one relevant intervention both in improving and preventing poor cognitive outcomes[186].

Conclusions

In the past 30 years, increasing knowledge in the field of MS-related CI has arisen. Improvements in all areas have been make from defining the most sensitive neuropsychological tests and compound batteries for research and clinical practice to better understanding the neural correlates in specific populations. There is a valuable assistance from non-conventional/functional and conventional-structural neuroimaging with better and more effective treatment, rehabilitation, and prevention strategies.

More than 50% of MS patients have some cognitive deficits, which are among the most disabling symptoms of the disease. Cognitive performance is a potential predictive marker of progression of MS and serves also as a potential predictor for patient's future employment status and QoL. Identifying CI at the earliest stages should be a crucial part of the assessment of the patient's clinical status. Thereafter, when diagnosed at an early stage, cognitive dysfunction may suggest implementing highly effective DMTs in addition to promoting a healthy lifestyle, focusing on cognitive rehabilitation.

Currently, there is no absolute definition of the early stage of MS as well as specific criteria for the diagnosis of CI. Therefore, further investigation and extensively characterization of cognition in MS should be made. In parallel, novel effective methods for cognition assessment in MS patients should be continuously developed to become an inseparable part of the extensive examination of patients with a diagnosis of CIS, in early and further stages of the disease.

Assessment of cognitive function should be included in the standard clinical evaluation of MS patients and should be a part of clinical trials involving these patients. Furthermore, treatment strategies should be implemented as supported by current evidence. Limitations are still present, especially due to the standardization and validation of both therapeutic and diagnostic tools. Due to the devastating impact over the self-care, social interaction and working status of MS patients, improvement in all the aforementioned areas, as well as education to the general community, patients and their families, should be stated as a priority.

Knowledge regarding protective and risk factors is of critical importance to implement prevention strategies, identify patients with higher risk for developing cognitive dysfunction, and improve patient's medical counselling and clinical management.

Research should strive to understand the mechanisms of action of the protective and risk factors for MS-related CI that are documented in the literature. Studies typically examine few protective factors or risk factors at a time, but there is a need for larger studies of numerous factors in the same large cohort to understand whether and to what extent each protective or risk factor contribute to the patient's cognitive outcome and to assess possible interactions between different environmental and genetic factors.

Furthermore, patient modifiable lifestyle factors to build or maintain cognitive and brain reserve include mentally active lifestyles, management of psychiatric disorders, management of cardiovascular risk factors and other comorbidities, physical exercise, smoking cessation and treatment of pain and sleep abnormalities.

There is a need to improve the level of evidence that links cognition to these lifestyle factors and explore better a few variables that were only preliminarily evaluated in research or were not mentioned (e.g., stress, vitamin D, diet). The evidence for exercise, although promising, remains preliminary and more work is to be done in order to establish a clear role in clinical practice.

Moreover, insufficient data is currently available to support pharmacological approaches for treating CI. Therefore, there is a need for well designed, long-term studies to assess the effects of currently available DMDs administered early in the disease course to delay or prevent cognitive dysfunction in MS patients.

By contrast, although there is insufficient evidence, cognitive rehabilitation has shown consistent beneficial effects in MS patients and currently counts as the best approach for treating MS-related CI. Nonetheless, there are still some challenges regarding treatment approaches, including delineation of the setting, dosing, timing, and specificity of treatment, as well as the shortage of trained professionals to provide these services. The complex interaction between depression, fatigue and cognition must also be taken into account in future studies.

Relatedly, an important focus of future research should be on the degree of specificity of treatment — meaning, generalized cognition treatment versus targeting specific cognitive domains. Given

the evidence supporting exercise training approaches and cognitive rehabilitation for improving multiple cognitive domains, it is not clear yet whether holistic or targeted training approaches might be better for treating MS-related CI.

For conclusion, CI is a devastating and relatively common manifestation of MS, and the application of successful treatment approaches is essential. Although some relevant data have been published in this area, much work is still needed, as MS-related CI is still poorly managed. Patients with CI and MS deserve effective treatment, and it is important to provide the most recently available treatment options in clinical practice and to continually evaluate and develop optimized pharmacological, exercise training therapies and cognitive rehabilitation for future consideration.

Acknowledgments

First, I would like to thank my mentor – assistant prof. Dr. Tereza Gabelić for professional guidance, pleasant cooperation, support and help in preparing the thesis.

I would like to thank the University of Zagreb for giving me the opportunity to accomplish my dream of becoming a medical doctor.

Special thanks to my good friend Mrs. Abby Richter and her husband – Mr. Yochai Richter, who supported me throughout this journey, believed in me and helped me to pursue my dream.

Many thanks to my relatives and all my friends for their understanding, patience, and endless support during the entire medical degree.

I would like to thank my wife for making me a better person, being a great support system during difficult times, and sharing this journey with me.

Last but not least, I would like to thank my dear son, who enlightened the way for me and became a huge part of my life during this special journey.

References

[1] Filippi M, Bar- A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple Sclerosis. Nat Rev Dis Prim. 2018;4: 1–27

[2] Macías Islas MÁ, Ciampi E. Assessment and impact of cognitive impairment in multiple sclerosis: an overview. Biomedicines. 2019 Mar;7(1):22.

[3] Cree, B.A.; Gourraud, P.A.; Oksenberg, J.R.; Bevan, C.; Crabtree-Hartman, E.; Gelfand, J.M.; Goodin, D.S.; Graves, J.; Green, A.J.; Mowry, E.; et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann. Neurol. 2016, 80, 499–510.

[4] Thompson, A.J.; Baranzini, S.E.; Geurts, J.; Hemmer, B.; Ciccarelli, O. Multiple sclerosis. Lancet 2018, 391, 1622–1636.

[5] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018 Feb 1;17(2):162-73.

[6] Schwenkenbecher P, Wurster U, Konen FF, Gingele S, Sühs KW, Wattjes MP, Stangel M, Skripuletz T. Impact of the McDonald criteria 2017 on early diagnosis of relapsing-remitting multiple sclerosis. Frontiers in neurology. 2019 Mar 15;10:188.

[7] Miller, D.H.; Leary, S.M. Primary-progressive multiple sclerosis. Lancet Neurol. 2007, 6, 903–912.

[8] Kakalacheva, K.; L€unemann, J.D. Enviromental triggers of multiple sclerosis. FEBS Lett. 2011, 585, 3724–3729.

[9] Lublin, F.D.; Reingold, S.C.; Cohen, J.A.; Cutter, G.R.; Sørensen, P.S.; Thompson, A.J.; Wolinsky, J.S.; Balcer, L.J.; Banwell, B.; Barkhof, F.; et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014, 83, 278–286.

[10] Fletcher, J.M.; Lalor, S.J.; Sweeney, C.M.; Tubridy, N.; Mills, K.H.G.; Lalor, S. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin. Exp. Immunol. 2010, 162, 1–11.

[11] Kurtzke, J.F. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology. 1983;

[12] https://www.hsctstopsms.com/hsct-for-ms/edss-scale/. Retrieved June 13th, 2021.

[13] Clemens, L.; Langdon, D. How does cognition relate to employment in multiple sclerosis? A systematic review. Mult. Scler. Relat. Disord. 2018, 26, 183–191.

[14] Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology. 2018;90: 278–288.

[15] Amato MP, Krupp LB, Charvet LE, Penner I, Till C. Pediatric multiple sclerosis: Cognition and mood. Neurology. 2016; doi:10.1212/WNL.0000000000002883

[16] Reuter F, Zaaraoui W, Crespy L, Faivre A, Rico A, Malikova I, et al. Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011; doi:10.1136/jnnp.2010.213744

[17] Ruano L, Portaccio E, Goretti B, Niccolai C, Severo M, Patti F, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler. 2017;23: 1258–1267.

[18] Pardini M, Uccelli A, Grafman J, Yaldizli Ö, Mancardi G, Roccatagliata L. Isolated cognitive relapses in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2014;85: 1035–1037.

[19] Zipoli V, Goretti B, Hakiki B, Siracusa G, Sorbi S, Portaccio E, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. Mult Scler. 2010; doi:10.1177/1352458509350311

[20] Fischer M, Kunkel A, Bublak P, Faiss JH, Hoffmann F, Sailer M, et al. How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? J Neurol Sci. 2014;

[21] Kalb R, Beier M, Benedict RHB, Charvet L, Costello K, Feinstein A, et al. Recommendations for cognitive screening and management in multiple sclerosis care. Mult Scler J. 2018; doi:10.1177/1352458518803785.

[22] Amato MP, Portaccio E, Goretti B, Zipoli V, Ricchiuti L, De Caro MF, et al. The Rao's Brief Repeatable Battery and Stroop test: normative values with age, education and gender corrections in an Italian population. Mult Scler J. 2006;12: 787–793. doi:10.1177/1352458506070933

[23] Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol. 2008;7: 1139–1151. doi:10.1016/S1474-4422(08)70259-X

[24] Grzegorski T, Losy J. Cognitive impairment in multiple sclerosis - A review of current knowledge and recent research. Reviews in the Neurosciences. 2017. doi:10.1515/revneuro-2017-0011

[25] Leavitt VM, Tosto G, Riley CS. Cognitive phenotypes in multiple sclerosis. J Neurol. 2018;265: 562–566.

[26] Leavitt VM, Tosto G, Riley CS. Cognitive phenotypes in multiple sclerosis. J Neurol. 2018;265: 562–566.

[27] Benedict RH, Amato MP, DeLuca J, Geurts JJ. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. The Lancet Neurology. 2020 Oct 1;19(10):860-71.

[28] Johnen A, Landmeyer NC, Burkner PC, Wiendl H, Meuth SG, Holling H. Distinct cognitive impairments in different disease courses of multiple sclerosis—a systematic review and meta-analysis. Neurosci Biobehav Rev. 2017;83:568–578. https://doi.org/101016/j.neubiorev.2017.09.005.

[29] Brissart H, Morele E, Baumann C, Perf ML, Leininger M, Taillemite L, et al. Cognitive impairment among different clinical courses of multiple sclerosis. Neurol Res. 2013;35(8):867–72. https://doi.org/10.1179/1743132813Y.0000000232.

[30] Benedict RHB, Cookfair D, Gavett R, et al. Validity of the Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006; 12: 549–58.

[31] Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41: 685–91.

[32] McKay KA, Manouchehrinia A, Berrigan L, Fisk JD, Olsson T, Hillert J. Long-term cognitive outcomes in patients with pediatric-onset vs adult-onset multiple sclerosis. *JAMA Neurol* 2019; 76: 1028–34.

[33] Amato MP, Hakiki B, Goretti B, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. *Neurology* 2012; 78: 309–14.

[34] Filippi M, Rocca MA, Barkhof F, Brück W, Chen JT, Comi G, et al. Association between pathological and MRI findings in multiple sclerosis. The Lancet Neurology. 2012. doi:10.1016/S1474-4422(12)70003-0

[35] Rocca MA, Amato MP, De Stefano N, Enzinger C, Geurts JJ, Penner I-K, et al. Clinical and imaging assessment of cognitive dysfunction in Accepted Manuscript multiple sclerosis. Lancet Neurol. 2015;14(3): 302–17.

[36] Amato MP, Prestipino E, Bellinvia A. Identifying risk factors for cognitive issues in multiple sclerosis. Expert review of neurotherapeutics. 2019 Apr 3;19(4):333-47.

[37] Mainero C, Caramia F, Pozzilli C, Pisani A, Pestalozza I, Borriello G, et al. fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. Neuroimage. 2004; doi:10.1016/j.neuroimage.2003.10.004

[38] Rocca MA, Valsasina P, Ceccarelli A, Absinta M, Ghezzi A, Riccitelli G, et al. Structural and functional MRI correlates of stroop control in benign MS. Hum Brain Mapp. 2009; doi:10.1002/hbm.20504

[39] Rao SM and the CFSG of the NMSS. A manual for brief repeatable battery of the neuropsychological tests in multiple sclerosis. Medical College of Wisconsin, Milwaukee, WI.; 1990.

[40] GrzegorskiT, Losy J. Cognitive impairment in multiple sclerosis - a review of current knowledge and recent research. Rev Neurosci. (2017) 28:845– 60. doi: 10.1515/revneuro-2017-0011

[41] Migliore S, Curcio G, Couyoumdjian A, Ghazaryan A, Landi D, Moffa F et al. Executive functioning in relapsing-remitting multiple sclerosis patients without cognitive impairment: a task-switching protocol. Mult Scler. (2017) 24:1328–36. doi: 10.1177/1352458517719149

[42] Van Schependom J, D'hooghe MB, Cleynhens K, D'hooge M, Haelewyck MC, De Keyser J et al. Reduced information processing speed as primum movens for cognitive decline in MS. Mult Scler. (2015) 21:83– 91. doi: 10.1177/1352458514537012

[43] López-Góngora M, Querol L, Escartín A. A one-year follow-up study of the symbol digit modalities test (SDMT) and the paced auditory serial addition test (PASAT) in relapsing-remitting

multiple sclerosis: an appraisal of comparative longitudinal sensitivity. BMC Neurol. (2015) 22:15:40. doi: 10.1186/s12883-015-0296-2

[44]Strober L, DeLuca J, Benedict RH, Jacobs A, Cohen JA, Chiaravalloti N et al. Multiple Sclerosis Outcome Assessments Consortium (MSOAC). Symbol digit modalities test: a valid clinical trial endpoint for measuring cognition in multiple sclerosis. Mult Scler. (2018) 18:1352458518808204. doi: 10.1177/1352458518808204

[45] Arnett PA, Strober LB. Cognitive and neurobehavioral features in multiple sclerosis. Expert Rev Neurother. (2011) 11:411–24. doi: 10.1586/ern.11.12

[46] González Torre JA, Cruz-Gómez ÁJ, Belenguer A, Sanchis-Segura C, Ávila C, Forn C. Hippocampal dysfunction is associated with memory impairment in multiple sclerosis: A volumetric and functional connectivity study. Mult Scler. (2017) 23:1854-63. doi: 10.1177/1352458516688349

[47] Oreja-Guevara C, Ayuso Blanco T, Brieva Ruiz L, Hernández Pérez MÁ, Meca-Lallana V, Ramió-Torrentà L. Cognitive dysfunctions and assessments in multiple sclerosis. Frontiers in neurology. 2019 Jun 4;10:581.

[48] Tóth E, Faragó P, Király A, Szabó N, Veréb D, Kocsis K et al. The contribution of various MRI parameters to clinical and cognitive disability in multiple sclerosis. Front Neurol. (2019) 9:1172. doi: 10.3389/fneur.2018.01172

[49] Tóth E, Faragó P, Király A, Szabó N, Veréb D, Kocsis K, et al. The contribution of various MRI parameters to clinical and cognitive disability in multiple sclerosis. *Front Neurol.* (2019) 9:1172.

[50] Rao S, Cognitive Function Study Group, National Multiple. A Manual for the Brief Repeatable Battery of Neuropsychological Test in multiple sclerosis. New York, NY: National Multiple (1990).

[51] Amato M, Portaccio E, Goretti B, Zipoli V, Iudice A, Della Pina D et al. Relevance of cognitive deterioration in early relapsing remitting MS: a 3-year follow-up study. Mult Scler. (2010) 16:1474–82. doi: 10.1177/1352458510380089

[52] Poole JL, Nakamoto T, McNulty T, Montoya JR, Weill D, Dieruf K et al. Dexterity, visual perception, and activities of daily living in persons with multiple sclerosis. Occup Ther Health Care. (2010) 24:159– 70. doi: 10.3109/07380571003681202

[53] Pöttgen J, Lau S, Penner I, Heesen C, Moritz S. Managing neuropsychological impairment in multiple sclerosis: pilot study on a standardized metacognitive intervention. Int JMS Care. (2015) 17:130–7. doi: 10.7224/1537-2073.2014-015

[54] Dulau C, Deloire M, Diaz H, Saubusse A, Charre-Morin J, Prouteau A et al. Social cognition according to cognitive impairment in different clinical phenotypes of multiple sclerosis. J Neurol. (2017) 264:740– 48. doi: 10.1007/s00415-017-8417-z

[55] Neuhaus M, Bagutti S, Yaldizli Ö, Zwahlen D, Schaub S, Frey B et al. Characterization of social cognition impairment in multiple sclerosis. Eur J Neurol. (2018) 25:90–96. doi: 10.1111/ene.13457

[56] Oreja-Guevara C, Soto T, Irimia A, San Jose AM, Lorenzo SC, Bayon C et al. Could mindfulness-based intervention (MBI) improve social cognition in multiple sclerosis? Eur J Neurol. (2017) 24 (Suppl. 1):578

[57] Benedict, R. H. et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol. 12, 55 (2012).

[58] Gromisch, E. S. et al. Assessing the criterion validity of four highly abbreviated measures from the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *Clin. Neuropsychol.* 30, 1032–1049 (2016).

[59] O'Brien, A. et al. Relationship of the multiple sclerosis neuropsychological questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch. Clin. Neuropsychol.* 22, 933–948 (2007).

[60] Romero, K., Shammi, P. & Feinstein, A. Neurologists' accuracy in predicting cognitive impairment in multiple sclerosis. *Mult. Scler. Relat. Disord.* 4, 291–295 (2015).

[61] Kalb, R. et al. Recommendations for cognitive screening and management in multiple sclerosis care. *Mult. Scler.* 24, 1665–1680 (2018).

[62] National Institute for Health and Care Excellence. Multiple sclerosis in adults: management (NICE, 2019).

[63] Amato, M. P. et al. Cognitive assessment in multiple sclerosis — an Italian consensus. *Neurol. Sci.* 39, 1317–1324 (2018)

[64] McNicholas N, O'Connell K, Yap SM, Killeen RP, Hutchinson M, McGuigan C. Cognitive dysfunction in early multiple sclerosis: a review. QJM. 2018;111(6):359–64. https://doi.org/10.1093/qjmed/hcx070.

[65] Strober L, Englert J, Munschauer F, Weinstock-Guttman B, Rao S, Benedict RH. Sensitivity of conventional memory tests in multiple sclerosis: comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. Mult Scler. 2009;15(9):1077–84.

[66] Oset M, Stasiolek M, Matysiak M. Cognitive Dysfunction in the Early Stages of Multiple Sclerosis—How Much and How Important?. Current Neurology and Neuroscience Reports. 2020 Jul;20:1-9.

[67] Corfield F, Langdon D. A systematic review and meta-analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS). Neurol Ther. 2018;7(2):287–306.

[68] Feuillet L, Reuter F, Audoin B, Malikova I, Barrau K, Cherif AA, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler. 2007;13(1): 124–7.

[69]Migliore S, Ghazaryan A, Simonelli I, Pasqualetti P, Squitieri F, Curcio G, et al. Cognitive impairment in relapsing-remitting multi ple sclerosis patients with very mild clinical disability. Behav Neurol. 2017;2017:7404289–10. https://doi.org/10.1155/2017/ 7404289.

[70] Korakas N, Tsolaki M. Cognitive impairment in multiple sclerosis: a review of neuropsychological assessments. Cogn Behav Neurol. 2016;29(2):55 – 67. https://doi.org/10.1097/WNN. 0000000000000097.

[71] Smith A. Symbol Digit Modalities Test: manual. Los Angeles, CA: Western Psychological Services, 1982.

[72] DeLuca J, Chiaravalloti ND, Sandroff BM. Treatment and management of cognitive dysfunction in patients with multiple sclerosis. Nature Reviews Neurology. 2020 Jun; 16(6): 319-32.

[73] Rao, S. M., Leo, G. J., Haughton, V. M., St Aubin-Faubert, P. & Bernardin, L. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology* 39, 161–166 (1989).

[74] Calabrese, M., Favaretto, A., Martini, V. & Gallo, P. Grey matter lesions in MS: from histology to clinical implications. *Prion* 7, 20–27 (2013).

[75] Rocca, M. A. et al. The hippocampus in multiple sclerosis. *Lancet Neurol.* 17, 918–926 (2018).

[76] Bergsland, N., Zivadinov, R., Dwyer, M. G., Weinstock-Guttman, B. & Benedict, R. H. B. Localized atrophy of the thalamus and slowed cognitive processing speed in MS patients. *Mult. Scler.* 22, 1327–1336 (2016).

[77] Benedict, R. H. B., Ramasamy, D., Munschauer, F., Weinstock-Guttman, B. & Zivadinov, R. Memory impairment in multiple sclerosis: correlation with deep grey matter and mesial temporal atrophy. *J. Neurol. Neurosurg. Psychiat.* 80, 201–206 (2009).

[78] Di Filippo, M., Portaccio, E., Mancini, A. & Calabresi, P. Multiple sclerosis and cognition: synaptic failure and network dysfunction. *Nat. Rev. Neurosci.* 19, 599–609 (2018).

[79] Mandolesi, G. et al. Synaptopathy connects inflammation and neurodegeneration in multiple sclerosis. *Nat. Rev. Neurol.* 11, 711–724 (2015).

[80] Summers M, Swanton J, Fernando K, Dalton C, Miller DH, Cipolotti L, et al. Cognitive impairment in multiple sclerosis can be predicted by imaging early in the disease. J Neurol Neurosurg Psychiatry. 2008;79(8):955–8. https://doi.org/10.1136/jnnp.2007. 138685.

[81] Kolber P, Montag S, Fleischer V, Luessi F, Wilting J, Gawehn J, et al. Identification of cortical lesions using DIR and FLAIR in early stages of multiple sclerosis. J Neurol. 2015;262(6):1473–82. https:// doi.org/10.1007/s00415-015-7724-5.

[82] Hanken K, Eling P, Klein J, Klaene E, Hildebrandt H. Different cortical underpinnings for fatigue and depression in MS? Mult Scler Relat Disord. 2016;6:81–6. https://doi.org/10.1016/j.msard. 2016.02.005.

[83] Steenwijk MD, Geurts JJ, Daams M, Tijms BM, Wink AM, Balk LJ, et al. Cortical atrophy patterns in multiple sclerosis are non random and clinically relevant. Brain. 2016;139(Pt 1):115–26. https://doi.org/10.1093/brain/awv337.

[84] Deloire MS, Salort E, Bonnet M, Arimone Y, Boudineau M, Amieva H, et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2005;76(4):519–26. https://doi.org/ 10.1136/jnnp.2004.045872.

[85] Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, Garcia-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnor malities in predicting disease activity in MS. Neurology. 2007;68(18):1488–94. https://doi.org/10.1212/01.wnl. 0000260612.51849.ed.

[86] El Ayoubi NK, Ghassan S, Said M, Allam J, Darwish H, Khoury SJ. Retinal measures correlate with cognitive and physical disability in early multiple sclerosis. J Neurol. 2016;263(11):2287–95. https:// doi.org/10.1007/s00415-016-8271-4.

[87] Meijer KA, Eijlers AJC, Douw L, et al. Increased connectivity of hub networks and cognitive impairment in multiple sclerosis. *Neurology* 2017; 88: 2107–14.

[88] d'Ambrosio A, Valsasina P, Gallo A, et al. Reduced dynamics of functional connectivity and cognitive impairment in multiple sclerosis. *Mult Scler* 2020; 26: 476–88.

[89] Audoin, B. et al. Magnetic resonance study of the influence of tissue damage and cortical reorganization on PASAT performance at the earliest stage of multiple sclerosis. *Hum. Brain Mapp.* 24, 216–228 (2005).

[90] Loitfelder, M. et al. Brain activity changes in cognitive networks in relapsing-remitting multiple sclerosis — insights from a longitudinal fMRI study. *PLoS One* 9, e93715 (2014).

[91] Bonavita, S. et al. Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Mult. Scler.* 17, 411–422 (2011).

[92] . Louapre, C. et al. Brain networks disconnection in early multiple sclerosis cognitive deficits: an anatomofunctional study. *Hum. Brain Mapp.* 35, 4706–4717 (2014).

[93] Harris VK, Sadiq SA. Disease biomarkers in multiple sclerosis: potential for use in therapeutic decision making. Mol Diagn Ther. 2009;13(4):225–44. https://doi.org/10.2165/11313470-000000000-00000 10.1007/bf03256329.

[94] Cai L, Huang J. Neurofilament light chain as a biological marker for multiple sclerosis: a meta-analysis study. Neuropsychiatr Dis Treat. 2018;14:2241–54. https://doi.org/10.2147/NDT.S173280.

[95] Teunissen CE, Khalil M. Neurofilaments as biomarkers in multiple sclerosis. Mult Scler. 2012;18(5):552–6. https://doi.org/10.1177/ 1352458512443092.

[96] Kuhle J, Leppert D, Petzold A, Regeniter A, Schindler C, Mehling M, et al. Neurofilament heavy chain in CSF correlates with relapses and disability in multiple sclerosis. Neurology. 2011;76(14):1206– 13. https://doi.org/10.1212/WNL.0b013e31821432ff.

[97] . Tortorella C, Direnzo V, Taurisano P, Romano R, Ruggieri M, Zoccolella S, et al. Cerebrospinal fluid neurofilament tracks fMRI correlates of attention at the first attack of multiple sclerosis. Mult Scler. 2015;21(4):396–401. https://doi.org/10.1177/ 1352458514546789.

[98] Modvig S, Degn M, Roed H, Sorensen TL, Larsson HB, Langkilde AR, et al. Cerebrospinal fluid levels of chitinase 3-like 1 and neu rofilament light chain predict multiple sclerosis development and disability after optic neuritis. Mult Scler. 2015;21(14):1761–70. https://doi.org/10.1177/1352458515574148.

[99] Mollgaard M, Degn M, Sellebjerg F, Frederiksen JL, Modvig S. Cerebrospinal fluid chitinase-3-like 2 and chitotriosidase are poten tial prognostic biomarkers in early multiple sclerosis. Eur J Neurol. 2016;23(5):898–905. https://doi.org/10.1111/ene.12960

[100] Amato MP, Goretti B, Ghezzi A, Hakiki B, Niccolai C, Lori S, et al. Neuropsychological features in childhood and juvenile multiple sclerosis: Five-year follow-up. Neurology. 2014 doi:10.1212/WNL.0000000000000885

[101] Hosseini B, Flora DB, Banwell BL, Till C. Age of onset as a moderator of cognitive decline in pediatric-onset multiple sclerosis. J Int Neuropsychol Soc. 2014; doi:10.1017/S1355617714000642

[102] Ruano L, Branco M, Portaccio E, Goretti B, Niccolai C, Patti F, et al. Patients with paediatric-onset multiple sclerosis are at higher risk of cognitive impairment in adulthood: An Italian collaborative study. Mult Scler J. 2018; doi:10.1177/1352458517717341

[103] Golden LC, Voskuhl R. The importance of studying sex differences in disease: The example of multiple sclerosis. Journal of Neuroscience Research. 2017. doi:10.1002/jnr.23955

[104] Beatty WW, Aupperle RL. Sex Differences in Cognitive Impairment in Multiple Sclerosis. Clin Neuropsychol (Neuropsychology, Dev Cogn Sect D). 2002; doi:10.1076/clin.16.4.472.13904

[105] Ruet A, Deloire M, Charré-Morin J, Hamel D, Brochet B. Cognitive impairment differs between primary progressive and relapsing-remitting {MS}. Neurology. 2013;80: 1501–1508.

[106] Lynch SG, Parmenter BA, Denney DR. The association between cognitive impairment and physical disability in multiple sclerosis. Mult Scler. 2005; doi:10.1191/1352458505ms1182oa

[107] Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: A reappraisal after 10 years. Arch Neurol. 2001; doi:10.1001/archneur.58.10.1602

[108] Hojjat SP, Cantrell CG, Carroll TJ, Vitorino R, Feinstein A, Zhang L, et al. Perfusion reduction in the absence of structural differences in cognitively impaired versus unimpaired RRMS patients. Mult Scler. 2016; doi:10.1177/1352458516628656

[109] Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged

people: a longitudinal, population-based study. Lancet Neurol. 2006; doi:10.1016/S1474-4422(06)70537-3

[110] Hoang H, Laursen B, Stenager EN, Stenager E. Psychiatric co-morbidity in multiple sclerosis: The risk of depression and anxiety before and after MS diagnosis. Mult Scler J. 2016; doi:10.1177/1352458515588973

[111] Kappus N, Weinstock-Guttman B, Hagemeier J, Kennedy C, Melia R, Carl E, et al. Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2016; doi:10.1136/jnnp-2014-310051

[112] Geraldes R, Esiri MM, DeLuca GC, Palace J. Age-related small vessel disease: a potential contributor to neurodegeneration in multiple sclerosis. Brain Pathology. 2017. doi:10.1111/bpa.12460

[113] Patten SB, Marrie RA, Carta MG. Depression in multiple sclerosis. International Review of Psychiatry. 2017. doi:10.1080/09540261.2017.1322555

[114] Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nature Reviews Neurology. 2014. doi:10.1038/nrneurol.2014.139

[115] Rossi S, Studer V, Motta C, Polidoro S, Perugini J, Macchiarulo G, et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. Neurology. 2017; doi:10.1212/WNL.0000000000004411

[116] Bsteh G, Ehling R, Lutterotti A, Hegen H, Pauli F Di, Auer M, et al. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis: Insights from a 10-Year observational study. PLoS One. 2016; doi:10.1371/journal.pone.0158978

[117] Patel VP, Walker LAS, Feinstein A. Revisiting cognitive reserve and cognition in multiple sclerosis: A closer look at depression. Mult Scler. 2018; doi:10.1177/1352458517692887

[118] Lester K, Stepleman L, Hughes M. The association of illness severity, self reported cognitive impairment, and perceived illness management with depression and anxiety in a multiple sclerosis clinic population. J Behav Med. 2007; doi:10.1007/s10865-007-9095-6

[119] CARONE DA, BENEDICT RHB, III FEM, FISHMAN I, WEINSTOCK GUTTMAN B. Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. J Int Neuropsychol Soc. 2005;11: 574–83. doi:10.1017/S135561770505068X

[120] Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler. 2007; doi:10.1177/1352458506071161

[121] Marrie RA, Walld R, Bolton JM, Sareen J, Walker JR, Patten SB, et al. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. J Psychosom Res. 2017; doi:10.1016/j.jpsychores.2017.07.015

[122] Goretti B, Viterbo RG, Portaccio E, Niccolai C, Hakiki B, Piscolla E, et al. Anxiety state affects information processing speed in patients with multiple sclerosis. Neurol Sci. 2014;35. doi:10.1007/s10072-013-1544-0

[123] Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. QJM. 2008; doi:10.1093/qjmed/hcm122

[124] Feinstein A. Is there a cognitive signature for multiple sclerosis-related fatigue? Multiple Sclerosis. 2015. doi:10.1177/1352458514563099

[125] Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler. 2006;12: 367–368. doi:10.1191/135248506ms1373ed

[126] Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage. 2007; doi:10.1016/j.neuroimage.2007.02.033

[127] Benson C, Kerr BJ. Pain and Cognition in Multiple Sclerosis. Current topics in behavioral neurosciences. 2014. pp. 201–215. doi:10.1007/7854_2014_309

[128] Landrø NI, Fors EA, Våpenstad LL, Holthe Ø, Stiles TC, Borchgrevink PC. The extent of neurocognitive dysfunction in a multidisciplinary pain center population. Is there a relation between reported and tested neuropsychological functioning? Pain. 2013; doi:10.1016/j.pain.2013.01.013

[129] Moriarty O, Finn DP. Cognition and pain. Current Opinion in Supportive and Palliative Care. 2014. doi:10.1097/SPC.0000000000000054

[130] Shahrbanian S, Duquette P, Kuspinar A, Mayo NE. Contribution of symptom clusters to multiple sclerosis consequences. Qual Life Res. 2015; doi:10.1007/s11136-014-0804-7

[131] Amato MP, Derfuss T, Hemmer B, Liblau R, Montalban X, Soelberg Sørensen P, et al. Environmental modifiable risk factors for multiple sclerosis: Report from the 2016 ECTRIMS focused workshop. Multiple Sclerosis Journal. 2018. doi:10.1177/1352458516686847

[132] Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nature Reviews Neurology. 2016. doi:10.1038/nrneurol.2016.187

[133] Ozcan ME, Asil T, Ince B, Bingol A, Erturk S, Altinoz MA, et al. Association between smoking and cognitive impairment in multiple sclerosis. Neuropsychiatr Dis Treat. 2014;10: 1715. doi:10.2147/NDT.S68389

[134] Zivadinov R, Weinstock-Guttman B, Hashmi K, Abdelrahman N, Stosic M, Dwyer M, et al. Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis. Neurology. 2009; doi:10.1212/WNL.0b013e3181b2a706

[135] Fernández O. Advances in the management of multiple sclerosis spasticity: Recent clinical trials. Eur Neurol. 2014; doi:10.1159/000367616

[136] Honarmand K, Tierney MC, O'Connor P, Feinstein A. Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology. 2011; doi:10.1212/WNL.0b013e318212ab0c

[137] Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. Neuropsychology Review. 2000. doi:10.1023/A:1009020914358

[138] Patel VP, Feinstein A. Cannabis and cognitive functioning in multiple sclerosis: The role of gender. Mult Scler J – Exp Transl Clin. 2017; doi:10.1177/2055217317713027

[139] Topiwala A, Ebmeier KP. Effects of drinking on late-life brain and cognition. Evid Based Ment Heal. 2018;21: 12–15. doi:10.1136/eb-2017-102820

[140] Bombardier CH, Blake KD, Ehde DM, Gibbons LE, Moore D, Kraft GH. Alcohol and drug abuse among persons with multiple sclerosis. Mult Scler. 2004; doi:10.1191/1352458504ms989oa

[141] Ahuja S, Chen RK, Kam K, Pettibone WD, Osorio RS, Varga AW. Role of normal sleep and sleep apnea in human memory processing. Nat Sci Sleep. Dove Press; 2018;10: 255–269. doi:10.2147/NSS.S125299

[142] Hughes AJ, Parmenter BA, Haselkorn JK, Lovera JF, Bourdette D, Boudreau E, et al. Sleep and its associations with perceived and objective cognitive impairment in individuals with multiple sclerosis. J Sleep Res. 2017;26: 428– 435. doi:10.1111/jsr.12490.

[143] Patel VP, Walker LAS, Feinstein A. Processing speed and distractibility in multiple sclerosis: the role of sleep. Mult Scler Relat Disord. 2017; doi:10.1016/j.msard.2016.11.012

[144] Matveeva O, Bogie JFJ, Hendriks JJA, Linker RA, Haghikia A, Kleinewietfeld M. Western lifestyle and immunopathology of multiple sclerosis. Annals of the New York Academy of Sciences. 2018. doi:10.1111/nyas.13583

[145] Cortese M, Yuan C, Chitnis T, Ascherio A, Munger KL. No association between dietary sodium intake and the risk of multiple sclerosis. Neurology. 2017; doi:10.1212/WNL.0000000000004417

[146] Haase S, Haghikia A, Gold R, Linker RA. Dietary fatty acids and susceptibility to multiple sclerosis. Mult Scler. 2018; doi:10.1177/1352458517737372

[147] McLellan TM, Caldwell JA, Lieberman HR. A review of caffeine's effects on cognitive, physical and occupational performance. Neuroscience and Biobehavioral Reviews. 2016. doi:10.1016/j.neubiorev.2016.09.001

[148] Maljaie MB, Shaygannejad V, Moosavian SP et al. Relationship between caffeine intake, EDSS and fatigue scale in patients with multiple sclerosis. J Neurol Neurorehabilitation Res. 2017;2.

[149] Fredholm BB. Adenosine, Adenosine Receptors and the Actions of Caffeine. Pharmacol Toxicol. 1995; doi:10.1111/j.1600-0773.1995.tb00111.x

[150] Sumowski JF. Cognitive reserve as a useful concept for early intervention research in multiple sclerosis. Front Neurol. 2015; doi:10.3389/fneur.2015.00176

[151] Stern Y. Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology. 2012. doi:10.1016/S1474-4422(12)70191-6

[152] Sharp ES, Gatz M. Relationship between education and dementia: An updated systematic review. Alzheimer Disease and Associated Disorders. 2011. doi:10.1097/WAD.0b013e318211c83c

[153] Goldbourt U, Schnaider-Beeri M, Davidson M. Socioeconomic status in relationship to death of vascular disease and late-life dementia. J Neurol Sci. 2007; doi:10.1016/j.jns.2007.01.021

[154] Sattler C, Toro P, Schönknecht P, Schröder J. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Res. 2012; doi:10.1016/j.psychres.2011.11.012

[155] Sumowski JF, Rocca MA, Leavitt VM, Dackovic J, Mesaros S, Drulovic J, et al. Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. Neurology. 2014; doi:10.1212/WNL.0000000000000433

[156] Biedermann S V., Fuss J, Steinle J, Auer MK, Dormann C, Falfán-Melgoza C, et al. The hippocampus and exercise: histological correlates of MR-detected volume changes. Brain Struct Funct. 2016; doi:10.1007/s00429-014-0976-5

[157] Kjølhede T, Siemonsen S, Wenzel D, Stellmann JP, Ringgaard S, Pedersen BG, et al. Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis? Mult Scler J. 2018; doi:10.1177/1352458517722645

[158] Langeskov-Christensen M, Eskildsen S, Stenager E, Boye Jensen H, Hvilsted Nielsen H, Petersen T, et al. Aerobic Capacity Is Not Associated with Most Cognitive Domains in Patients with Multiple Sclerosis—A Cross-Sectional Investigation. J Clin Med. 2018;7: 272. doi:10.3390/jcm7090272

[159] Yang HS, Yu L, White CC, Chibnik LB, Chhatwal JP, Sperling RA, et al. Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to APOE ε4 haplotype status: a community-based cohort study. Lancet Neurol. 2018; doi:10.1016/S1474-4422(18)30251-5

[160] Jensen CJ, Stankovich J, Van der Walt A, Bahlo M, Taylor B V., van der Mei IAF, et al. Multiple sclerosis susceptibility-associated SNPs do not influence disease severity measures in a cohort of Australian MS patients. PLoS One. 2010; doi:10.1371/journal.pone.0010003

[161] Cerasa A, Tongiorgi E, Fera F, Gioia MC, Valentino P, Liguori M, et al. The effects of BDNF Val66Met polymorphism on brain function in controls and patients with multiple sclerosis: An imaging genetic study. Behav Brain Res. 2010; doi:10.1016/j.bbr.2009.10.022

[162] Sumowski JF, Rocca MA, Leavitt VM, Riccitelli G, Comi G, Deluca J, et al. Brain reserve and cognitive reserve in multiple sclerosis: What you've got and how you use it. Neurology. 2013; doi:10.1212/WNL.0b013e318296e98b

[163] Pitteri M, Magliozzi R, Bajrami A, Camera V, Calabrese M. Potential neuroprotective effect of Fingolimod in multiple sclerosis and its association with clinical variables. Expert Opin Pharmacother. 2018;19: 387–395.

[164] Roy S, Benedict RHB, Drake AS, Weinstock-Guttman B. Impact of Pharmacotherapy on Cognitive Dysfunction in Patients with Multiple Sclerosis. CNS Drugs. 2016;30: 209–225.

[165] Amato, M. P. et al. Treatment of cognitive impairment in multiple sclerosis: position paper. *J. Neurol.* 260, 1452–1468 (2013).

[166] Miller, E., Morel, A., Redlicka, J., Miller, I. & Saluk, J. Pharmacological and non-pharmacological therapies of cognitive impairment in multiple sclerosis. *Curr. Neuropharmacol.* 16, 475–483 (2018).

[167] Goodman, A. D. et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann. Neurol.* 68, 494–502 (2010).

[168] Satchidanand, N. et al. Dalfampridine benefits ambulation but not cognition in multiple sclerosis. *Mult. Scler.* 26, 91–98 (2020).

[169] De Giglio, L. et al. Effect of dalfampridine on information processing speed impairment in multiple sclerosis. *Neurology* 93, e733–e746 (2019).

[170] Fisher, R.L.; Priore, R.L.; Jacobs, L.D.; Cookfair, D.L.; Rudick, R.A.; Herndon, R.M.; Richert, J.R.; Salazar, A.M. Neuropsychological effects of interferón beta 1 a in relapsing multiple sclerosis. Ann. Neurol. 2000, 48, 885–892.

[171] Patti, F.; Amato, M.P.; Bastianello, S.; Caniatti, L.; Di Monte, E.; Ferrazza, P.; Goretti, B.; Gallo, P.; Brescia Morra, V.; Lo Fermo, S.; et al. Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis. Mult. Scler. 2010, 16, 68–77.

[172] Patti, F.; Morra, V.B.; Amato, M.P.; Trojano, M.; Bastianello, S.; Tola, M.R.; Cottone, S.; Plant, A.; Picconi, O. Subcutaneous interferon β-1a may protect against cognitive impairment in patients with relapsing-remitting multiple sclerosis: 5-year follow-up of the COGIMUS study. PLoS ONE 2013, 8, e74111.

[173] Pliskin, N.H.; Hamer, D.P.; Goldstein, D.S.; Towle, V.L.; Reder, A.T.; Noronha, A.; Arnason, B.G. Improved delayed visual reproduction test performance in multiple sclerosis patients receiving interferon beta-1b. Neurology 1996, 47, 1463–1468.

[174] Edan, G.; Kappos, L.; Montalbán, X.; Polman, C.H.; Freedman, M.S.; Hartung, H.-P.; Miller, D.; Barkhof, F.; Herrmann, J.; Lanius, V.; et al. Longterm impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. J. Neurol. Neurosurg. Psychiatry 2014, 85, 1183–1189.

[175] Cutter, G.R.; Baier, M.S.; Rudick, R.A.; Cookfair, D.L.; Fischer, J.S.; Petkau, J.; Syndulko, K.; Weinshenker, B.G.; Antel, J.P.; Confavreux, C.; et al. Development of a Multiple Sclerosis Functional Composite as a clinical trial outcome measure. Brain 1999, 122, 101–112.

[176] Smith, S.M.; Zhang, Y.; Jenkinson, M.; Chen, J.; Matthews, P.M.; Federico, A.; de Stefano, N. Accurate, robust and automated longitudinal and cross-sectional brain change analysis. NeuroImage 2002, 17, 479–489.

[177] Weinstock-Guttman, B.; Galetta, S.L.; Giovannoni, G.; Havrdova, E.; Hutchinson, M.; Kappos, L.; O'Connor, P.W.; Phillips, J.T.; Polman, C.; Stuart, W.H.; et al. Additional efficacy

endpoints from pivotal natalizumab trials in relapsing-remitting MS. *J. Neurol.* **2012**, *259*, 898–905.

[178] Jacques, F.H.; Harel, B.T.; Schembri, A.J.; Paquette, C.; Bilodeau, B.; Kalinowski, P.; Roy, R. Cognitive evolution in natalizumab-treated multiple sclerosis patients. MSJ 2016, 2.

[179] Riepl, E.; Pfeuffer, S.; Ruck, T.; Lohmannt, H.; Wiendl, H.; Meuth, S.G.; Johnen, A. Alemtuzumab improves cognitive proccesing speed in active multiple sclerosis—A longitudinal observational study. Front. Neurol. 2018, 8, 730.

[180] Hauser, S.L.; Bar-Or, A.; Comi, G.; Giovannoni, G.; Hartung, H.-P.; Hemmer, B.; Lublin, F.; Montalban, X.; Rammohan, K.W.; Selmaj, K.; et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N. Engl. J. Med. 2017, 376, 221–234.

[181] Krupp, L.B.; Christodoulou, C.; Melville, P.; Scherl, W.F.; Pai, L.Y.; Muenz, L.R.; He, D.; Benedict, R.H.; Goodman, A.; Rizvi, S.; et al. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. Neurology 2011, 76, 1500–1507.

[182] Lovera, J.F.; Frohman, E.; Brown, T.; Bandari, D.; Nguyen, L.; Yadav, V.; Stuve, O.; Karman, J.; Bogardus, K.; Heimburger, G.; et al. Memantine for cognitive impairment in multiple sclerosis: A randomized placebo-controlled trial. Mult. Scler. 2010, 16, 715–723.

[183] Sumowski, J.F.; Chiaravalloti, N.; Erlanger, D.; Kaushik, T.; Benedict, R.H.B.; DeLuca, J. L-amphetamine improves memory in MS patients with objective memory impairment. Mult. Scler. 2011, 17, 1141–1145.

[184] Broicher, S.D.; Filli, L.; Geisseler, O.; Germann, N.; Zörner, B.; Brugger, P.; Linnebank, M. Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years. J. Neurol. 2018, 265, 1016–1025.

[185] Ford-Johnson, L.; DeLuca, J.; Zhang, J.; Elovic, E.; Lengenfelder, J.; Chiaravalloti, N.D. Cognitive effects of modafinil in patients with multiple sclerosis: A clinical trial. Rehabil. Psychol. 2016, 61, 82–91.

[186] Sokolov, A.A.; Grivaz, P.; Bove, R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. Curr. Treat. Options Neurol. 2018, 20, 53.

[187] Millera, E.; Morelc, A.; Redlickaa, J.; Millera, I.; Salukc, J. Pharmacological and Non-pharmacological Therapies of Cognitive Impairment in Multiple Sclerosis. Curr. Neuropharmacol. 2018, 16, 475–483.

[188] Chiaravalloti, N.D.; Moore, N.B.; Nikelshpur, O.M.; DeLuca, J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. Neurology 2013, 81, 2066–2072.

[189] De Giglio, L.; De Luca, F.; Prosperini, L.; Borriello, G.; Bianchi, V.; Pantano, P.; Pozzilli, C. A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: A pilot study. Neurorehabil. Neural Repair. 2015, 29, 453–461.

[190] Amato, M.P.; Goretti, B.; Viterbo, R.G.; Portaccio, E.; Niccolai, C.; Hakiki, B.; Iaffaldano, P.; Trojano, M. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: Results of a randomized, double-blind trial. Mult. Scler. J. 2014, 20, 91–98.

[191] Goverover, Y.; Chiaravalloti, N.D.; O'Brien, A.R.; DeLuca, J. Evidenced-Based Cognitive Rehabilitation for Persons with Multiple Sclerosis: An Updated Review of the Literature From 2007 to 2016. Arch. Phys. Med. Rehabil. 2018, 99, 390–407.

[192] Rebok, G. W. et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *J. Am. Geriatr. Soc.* 62, 16–24 (2014)

[193] Ball, K., Edwards, J. D., Ross, L. A. & McGwin, G. Cognitive training decreases motor vehicle collision involvement of older drivers. *J. Am. Geriatr. Soc.* 58, 2107–2113 (2010).

[194] Carter, A.; Daley, A.; Humphreys, L.; Snowdon, N.; Woodroofe, N.; Petty, J.; Roalfet, Al.; Tosh, J.; Sharrack, B.; Saxton, J. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: A randomised controlled trial. Mult. Scler. 2014, 20, 1112–1122.

[195] Briken, S.; Gold, S.M.; Patra, S.; Vettorazzi, E.; Harbs, D.; Tallner, A.; Ketels, G.; Schulz, K.H.; Heesen, C. Effects of exercise on fitness and cognition in progressive MS: A randomized, controlled pilot trial. Mult. Scler. 2014, 20, 382–390.

[196] Sandroff, B.M.; Motl, R.W.; Scudder, M.R.; DeLuca, J. Systematic, Evidence-Based Review of Exercise, Physical Activity, and Physical Fitness Effects on Cognition in Persons with Multiple Sclerosis. Neuropsychol. Rev. 2016, 26, 271–294.

[197] Cramer, H.; Lauche, R.; Azizi, H.; Dobos, G.; Langhorst J Yoga for Multiple Sclerosis: A Systematic Review and Meta-Analysis. PLoS ONE 2014, 9, e112414.

Biography

Meytar Zohari was born on the 17th of August 1988, in Rehovot, Israel.

During the years 2000-2006 Meytar studied in Midrashiat Amalia high school and took biology and psychology majors.

Between the years 2006-2011 she served in the IDF as an EMT-Paramedic and as an instructor for the medical corps.

Meytar started her medical school in 2015 in the international medical program in the faculty of medicine, University of Zagreb, Croatia. During six years in Croatia she passed all her exams in excellence, and is ready to begin a new chapter in her medical future.