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Cognitive Deterioration in Otherwise Clinically Stable Patients with Multiple Sclerosis

Progrese kognitivního deficitu u jinak klinicky stabilních pacientů s roztroušenou sklerózou

DISSERTATION THESIS

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Declaration

I hereby declare that I have worked on this dissertation thesis independently, using only the primary and secondary sources listed in the bibliography. I declare that this work was not submitted in support of any other candidature for academic degrees, neither other nor the same.

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This thesis was written on the eve of the Vladimir Putin's war on Ukraine. The depressing war which is so close but still so far away from the circumstances under which this thesis was written. My thoughts go to all the victims of the war, those who were killed, wounded, or displaced, those who lost their homes, loved ones, or ideals and hopes for a better future. My thoughts also go to those who took the courage to stand for their destiny, to protect their beliefs, home, and country, or to those who chose to help in this crisis even though they did not have to or were far away.

'Precisely at the same hour in which Mehring and Langner were being done to death, the overwhelming plurality of human beings, two miles away on the Polish farms, five thousand miles away in New York, were sleeping or eating or going to a film or making love or worrying about the dentist. This is where my imagination balks. The two orders of simultaneous experience are so different, so irreconcilable to any common norm of human values, their coexistence is so hideous a paradox – (…) – that I puzzle over time. Are there, as science fiction and Gnostic speculation imply, different species of time in the same world, 'good time' and enveloping fold of inhuman time, in which men fall into the hands of the living damnation?'

Willian Styron, Sophie's Choice, quote on George Steinar

Abstract

Neuropsychological assessment of cognitive functions in multiple sclerosis (MS) is increasingly considered as an important paraclinical marker of disease stability or progression in MS. Recent recommendations proposed an annual screening of cognitive functions in all MS patients as a standard of neuropsychological monitoring in MS. There is a clear trend to diagnose possible disease progression as early as possible, to be able to respond quickly.

The theoretical part of this thesis presents the current state of knowledge on cognitive impairment in MS, its correlates, predictors, and treatment possibilities. In addition, a comprehensive overview of the neuropsychological assessment and the diagnosis of cognitive deterioration in MS is presented. The highly relevant topics such as cutoff criteria of a meaningful change on individual neuropsychological examination, possibilities of treatment of cognitive deterioration, or the so-called isolated cognitive relapses, are discussed in a particular detail.

The empirical part extends current knowledge in the field of MS. I present and discuss six original publications that follow these four main objectives: first, to describe the prevalence of isolated cognitive decline in MS and to put isolated cognitive decline in context with current knowledge on MS disease progression. Second, to identify methods that can improve the quality of the diagnostic process of cognitive deterioration in MS, third, to explore the concept of subjective cognitive decline, the workability of MS patients, and volumetric MRI markers that can predict future cognitive deterioration. And the last objective plans to evaluate compensatory and rehabilitation strategies used to cope with cognitive deterioration in MS.

Keywords: Isolated Cognitive Decline, Neuropsychological Assessment, Multiple Sclerosis, Cognitive Deterioration, Cognitive Impairment

Abstrakt

Neuropsychologické vyšetření kognitivních funkcí při roztroušené skleróze (RS) je stále častěji považováno za důležitý marker progrese onemocnění. V nedávné době publikované odborné stanovisko doporučuje každoroční screeningové vyšetření kognitivních funkcí všech pacientů s RS jako součást běžné monitorace onemocnění RS. To je součástí trendu včasné diagnostiky progrese onemocnění, zajišťující co nejdřívější reakci na případnou progresi RS.

Teoretická část této práce se věnuje současnému stavu poznání v oblasti kognitivních potíží při RS, popisuje jejich koreláty a prediktory, představuje možnosti v léčbě. Práce také komplexně představuje současnou podobu vyšetření kognitivních funkcí u pacientů s RS a dále také proces diagnostiky kognitivní deteriorace. V tomto ohledu jsou rozebírána především témata klinicky významné změny výsledku v individuálním neuropsychologickém vyšetření, možnosti léčby kognitivního poklesu, nebo téma takzvaných izolovaných kognitivních relapsů.

Empirická část práce dále prohlubuje poznání v této oblasti. V této části prezentuji a diskutuji šest původních vědeckých publikací, které sledují čtyři hlavní cíle práce. Zaprvé: popsat prevalenci izolovaného kognitivního poklesu při RS a propojit tyto poznatky se současným poznáním o progresi onemocnění RS. Zadruhé, identifikovat metody, které mohou napomoci zlepšení kvality diagnostiky kognitivní deteriorace při RS. Zatřetí: prozkoumat koncept subjektivního kognitivního zhoršení, práceschopnost lidí s RS, a identifikovat volumetrické MRI prediktory kognitivního zhoršení. Posledním cílem je zhodnocení kompenzačních a rehabilitačních strategií užívaných při zvládání kognitivního zhoršení u lidí s RS.

Klíčová slova: izolovaný kognitivní pokles, neuropsychologické vyšetření, roztroušená skleróza, kognitivní deteriorace, kognitivní porucha

Abbreviations and Definitions

9-HPT – 9-Hole Peg Test

25-FWT – 25-Foot Walk Test

APT-III – Attention Process Training III

AUC – Area under ROC Curve

BDI-II – Beck Depression Inventory, 2nd Edition

BICAMS - Brief International Cognitive Assessment for MS

BPF – Brain Parenchymal Fraction

BRB-N - the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis

BVMT-R – Brief Visuospatial Memory Test, Revised

CC – Corpus Callosum

CIS – Clinically Isolated Syndrome

CNS – Central Nervous System

COWAT – Controlled Oral Word Association Test (interchangeable term with WLG)

CRT – Czech Reading Test

CSCT – Computerised Speed Cognitive Test

CSF – Cerebrospinal Fluid

CTT – Classical Test Theory

CVLT / CVLT-II / CVLT-3 – California Verbal Learning Test or Similar Methods

DMD – Disease Modifying Drugs

DRS-2 – Mattis Dementia Rating Scale, 2nd Edition

DSS – Disability Status Scale

EBV – Epstein-Barr Virus

EDSS – Expanded Disability Status Scale

fMRI – Functional Magnetic Resonance Imaging

FSS – Fatigue Severity Scale

Gd+ – Gadolinium Enhancing (Lesion)

GM – Grey Matter

HADS – Hospital Anxiety and Depression Scale

IQ – intelligence quotient is a total score derived from a set of standardized tests or subtests designed to assess human intelligence. In modern IQ tests, the raw score is transformed to a normal distribution with mean 100 and standard deviation ±15.

IRT – Item Response Theory

JLO – Benton Judgment of Line Orientation Test

MACFIMS - Minimal Assessment of Cognitive Function in MS

MATRICS – Measurement and Treatment Research to Improve Cognition in Schizophrenia

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

MSFC – Multiple Sclerosis Functional Composite

MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire

MSPT – Multiple Sclerosis Performance Test

NART – National Adult Reading Test

NEDA – No Evidence of Disease Activity

NfL – Neurofilament Light Chain (sNfL: blood-based serum neurofilament light chain; CSF-NfL: Cerebrospinal Fluid-based neurofilament light chain

NMR – Nuclear Magnetic Resonance

NSB – Neuropsychological Screening Battery

OCT – Optical Coherence Tomography

PASAT – Paced Auditory serial Addition Test

PP-MS – Primary Progressive Multiple Sclerosis

PR-MS – Progressive Relapsing Multiple Sclerosis

PROs – Patient Reported Outcomes

PST – Processing Speed Test

RAVLT – Ray Auditory Verbal Learning Test

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

RCI – Reliable Change Index

RIS – Radiologically Isolated Syndrome

ROC – Receiver Operating Characteristics

RR-MS – Relapsing Remitting Multiple Sclerosis

SCWT – Stroop Color and Word Test

SDMT – Symbol Digit Modalities Test

SEM – Standard Error of Measurement

SP-MS – Secondary Progressive Multiple Sclerosis

SPART – 10/36 Spatial Recall Test

SRB – Standardized Regression-Based Change

SRT – Selective Reminding Test

T1/T2-LL – T1 or T2 Lesion Load

TMT – Trail Making Test

UDS – Uniform Data Set

UVB – Ultraviolet B Light

VEP – Visual Evoked Potentials

VR – Virtual Reality

WAIS-III / WAIS-IV – Wechsler Adult Intelligence Scale

WCST – Wisconsin Card Sorting Test

WLG – Word List Generation (interchangeable term with COWAT)

WM – White Matter

Z-Score – The raw score is transformed to a standardized score with mean 0 and standard deviation ±1.

Content

1. INTRODUCTION

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic autoimmune neurodegenerative disease of the central nervous system (CNS). It is the most widespread non-traumatic cause of physical disability in the young adult population and the most widespread neurological condition in this population around the world, with a prevalence ranging from 16/100 000 to 253/100 000 (Kingwell et al., 2013).

The underlying cause of MS remains uncertain. The research suggested many genes that modestly increase disease susceptibility in addition to several environmental factors, in particular exposure to vitamin D or ultraviolet B-light (UVB), Epstein-Barr virus (EBV) infection, obesity and smoking (Ascherio, 2013; Bjornevik et al., 2022; Dobson & Giovannoni, 2019). It is the most frequent representative of the group of demyelinating diseases. The first symptoms of MS appear mostly between the 20th and 40th decade of life, but cases in children or older populations are also well documented. It affects women more frequently, with a female-male incidence ratio of approximately 3: 1 (Dobson & Giovannoni, 2019; Trojano et al., 2012). As the disease is associated with progressive physical disability and as it affects young people of productive age, MS is associated with a large socioeconomic burden (Blahova Dusankova, Kalincik, Dolezal, Kobelt, & Havrdova, 2012; Havrdova et al., 2017) and a sociopsychological burden (P. A. Arnett, Barwick, & Beeney, 2008; Hilt Pfleger, Meulengracht Flachs, & Koch-Henriksen, 2010a, 2010b). The main characteristic pathological process behind MS are brain and spinal cord focal and diffuse inflammation formatting demyelinating plaques and diffuse CNS tissue abnormalities. The inflammatory lesions contain T-lymphocytes; B-cells and plasma cells are also present, although in much lower numbers. As a result of inflammatory processes, damage to oligodendrocytes and demyelination occurs. In the early stages, axons are relatively preserved, but as the disease develops, irreversible axonal damage occurs (Dobson & Giovannoni, 2019; Trapp et al., 1998).

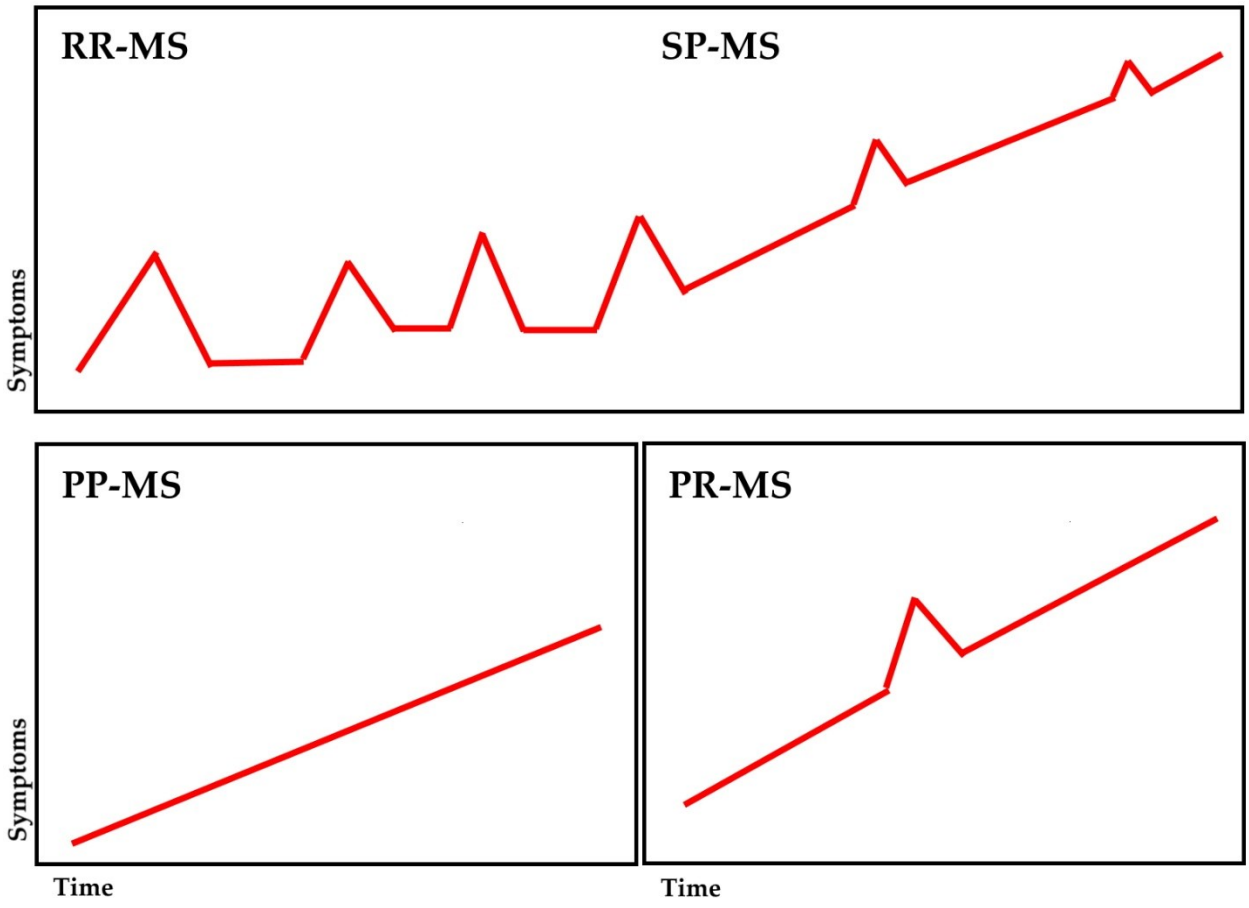
Our understanding of the pathological processes behind MS, the possibilities of disease monitoring and immunomodulatory treatment of MS has advanced rapidly during the last two decades (Dobson & Giovannoni, 2019; Hauser & Cree, 2020; Trapp et al., 1998). Many individual and populational risk factors for the development of MS were identified (Bjornevik et al., 2022; Dobson & Giovannoni, 2019); however, our understanding of why a person develops MS is still limited. Not only do we not exactly know why one person develops symptoms characterized by MS and the other not, we still lack enough capabilities to make successful predictions of the disease course and the response to treatment at the individual level. One of the issues is the so-called clinico-radiological paradox in MS (Barkhof, 2002) or cognitive-radiological paradox (T. Uher et al., 2018); characterized as a discrepancy between clinical or cognitive manifestations of the disease and its radiological correlates as seen on MRI.

1.1.1 Disease Course & MS Subtypes

The most common clinical manifestations of MS are usually associated with progressive physical disability and various sets of symptoms such as paresthesia, hypoesthesia, and other motor symptoms (Dobson & Giovannoni, 2019). However, the symptoms of MS are very heterogeneous, including also optic neuritis, bladder dysfunction, sexual dysfunction, mood disorders, behavioral changes, fatigue, or various cognitive changes (P. A. Arnett et al., 2008; Ralph H. B. Benedict, Amato, DeLuca, & Geurts, 2020; Hauser & Cree, 2020; Krupp, Serafin, & Christodoulou, 2010).

FIGURE 1.1: MS SUBTYPES, AS CLASSIFIED BY LUBLIN & REINGOLD (1996)

Figure adapted from the originals published by Lublin & Reingold (1996). The x-axis represents time, and the y-axis represents the severity of MS symptoms. The red line shows the generalized course of the disease for the subtypes of RR-MS, SP-MS, PP-MS and PR-MS disease.

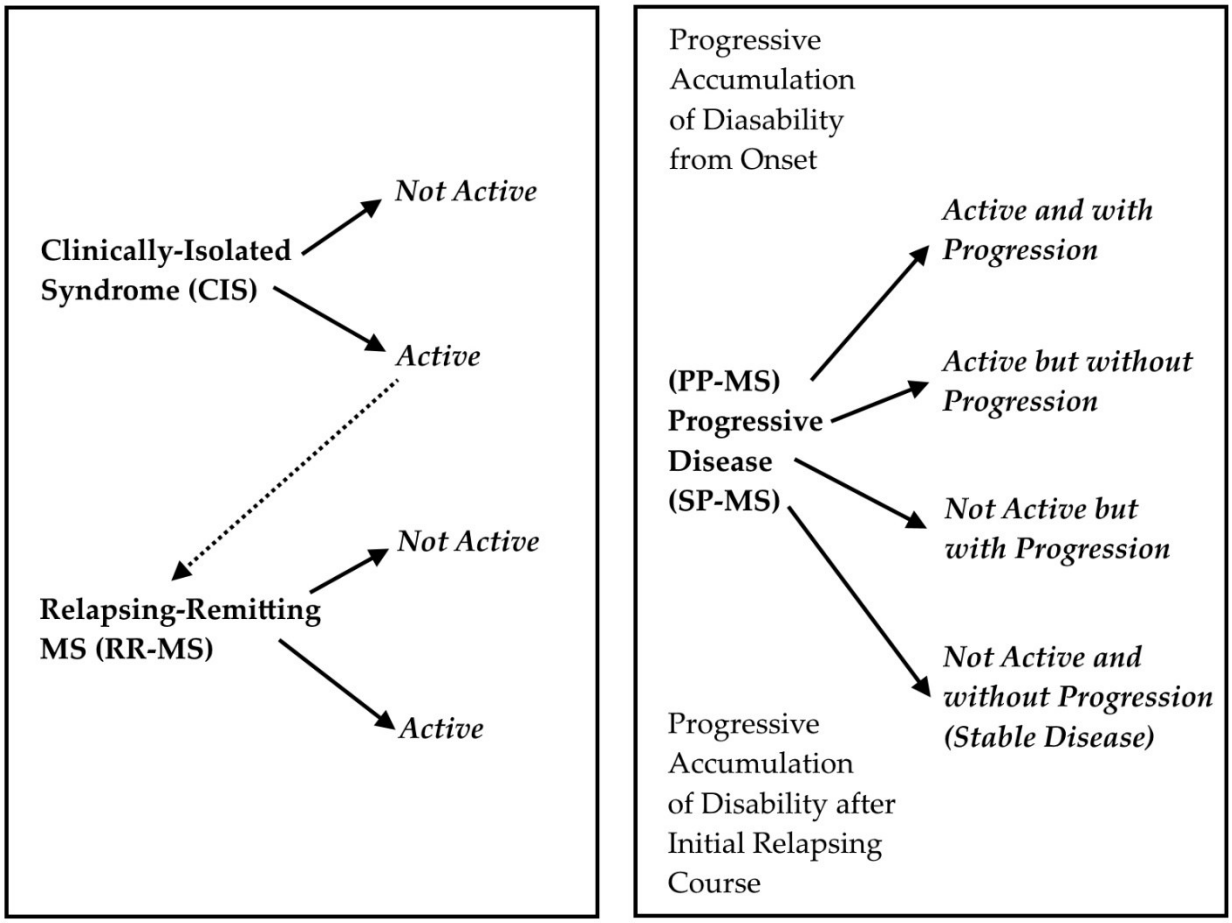


From a clinical perspective, MS can follow two basic paths: relapsing or progressive (Hauser & Cree, 2020). Classically, the following subtypes of the disease were recognized: Relapsing-Remitting MS (RR-MS), Secondary-Progressive MS, Primary-Progressive MS (PP-MS), and Progressive-Relapsing MS (PR-MS) (Lublin

& Reingold, 1996). The disease course of the classical MS subtypes is presented in Figure 1.1. There are two stages of symptoms suggestive of MS but not meeting the criteria (Thompson et al., 2018) of definitive MS: radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS) (Granberg, Martola, Kristoffersen-Wiberg, Aspelin, & Fredrikson, 2013; Miller, Chard, & Ciccarelli, 2012). Typically, the onset of the disease is represented by the RR-MS phase, manifested as acute episodes of neurological dysfunction (relapses), followed by complete or partial remission. Later, as the disease progresses, patients switch to the SP-MS phase, where the phases of relapses and remissions disappear and the disease continues to progress. A small portion of patients can experience progressive form of the disease since onset, i.e., PP-MS or PR-MS subtypes (Hauser & Cree, 2020; Lublin & Reingold, 1996).

FIGURE 1.2: REVISED MS SUBTYPES, AS CLASSIFIED BY LUBLIN ET AL. (2014)

Revised MS subtypes (Lublin et al., 2014), based on the original subtypes published by Lublin & Reingold (1996).



Because the classical MS subtypes published in 1996 were based on a survey of international MS experts at the time, without comprehensive imaging and biological correlates, a revision of the subtypes was published in 2013 after more than a decade of ongoing research in the field of MS (Lublin et al., 2014). Although imaging and biological correlates were still not at such a level to make a final decision on the MS classification, the 17 years of research since 1996 allowed the following progress to be made (Lublin et al., 2014): 1) CIS was

included in the spectrum of MS phenotypes; 2) An important modifier of these core phenotypes is the evaluation of disease activity, as defined by the clinical evaluation of relapse occurrence or lesion activity detected by CNS imaging; 3) A determination of whether progression of disability has occurred over a given time period was included; 4) The core distinction of relapsing and progressive disease was retained; 5) PR-MS form was eliminated, newly classified as active PP-MS form with relapsing disease activity; 6) Differences between PP-MS and SP-MS are not considered as large as before; these two subtypes can be considered generally as progressive MS; 7) RIS keeps its place outside of MS classification, with a prospective follow-ups being recommended (Lublin et al., 2014). The revised classification is presented in Figure 1.2.

1.1.2 Diagnostic Criteria

Although the first descriptions of MS symptoms date back to the 14th century, it was Jean Martin Charcot (1825-1893) who delivered a series of lectures in which he established MS as a novel disease of the nervous system (Lublin, 2005; Zalc, 2018). He named the disease *Sclérose en plaques*, together with Alfred Vulpian described the typical lesions, and gave a detailed description of the clinical signs of MS in its wide heterogeneity: amblyopia, diplopia, the classic triad of nystagmus, dysarthria, ataxia, but also the presence of cognitive manifestations, and more characteristics of spinal forms: weakness, spasticity, ankle clonus (Zalc, 2018).

The lectures by Charcot were a great step forward in establishing MS as a single nosological unit. The diagnostic criteria of MS have developed significantly since then. Let's focus on the last sixty years, when Schumacher et al. postulated probably the first modern diagnostic criteria in 1965 to standardize research and clinical trials in MS (Schumacher et al., 1965). Many things have changed since these first diagnostic criteria, but two core criteria remain the same: the signs of CNS lesions disseminated in time and space. Schumacher et al. (1965) postulated that MS is a neurological disease of the CNS of a younger population, with the age of the patient at the onset of the disease falling within the range of 10 to 50 years, inclusive. They also stated that there must be evidence of involvement of two or more separate parts of CNS (i.e., dissemination in space) and that the involvement must happen: 1) in two or more episodes of worsening separated by a period of one month or more, each episode lasting at least 24 hours; or 2) slow or stepwise progression of signs and symptoms, over a period of at least six months (i.e., dissemination in time) (Schumacher et al., 1965).

Another step toward an earlier and more precise diagnosis was the diagnostic criteria postulated by Poser et al. (1983). They introduced four diagnostic units: 1) Clinically Definite MS, 2) Laboratory-Supported Definite MS, 3) Clinically Probable MS, 4) Laboratory-Supported Probable MS; and for the first time also included the possibility of paraclinical evidence of a CNS lesion which could serve as a sign of dissemination in space: *‚Paraclinical evidence of CNS lesions may be elicited by a variety of means, including induced hyperthermia, evoked potential studies, CT and NMR scans, or special urological studies.'* From the perspective of this thesis, it is worth mentioning that neuropsychological assessment was considered as an auxiliary paraclinical assessment of CNS lesions: *'Neuropsychological evaluation by an expert examiner that indicates definite cognitive impairment in a patient under the age of 50 may be suggestive and helpful but not yet specific enough to be fully diagnostic'* (Poser et al., 1983).

The introduction of MRI on a regular basis throughout the 1980s meant a huge improvement for the diagnostic process of MS, and it soon required suggestions of new accurate criteria interpreting MRI findings suggestive of MS (Barkhof et al., 1997; Fazekas et al., 1988; Paty et al., 1988). This work was finalized by the International Panel on MS Diagnosis, which presented in 2001 the first version of the McDonald criteria (McDonald et al., 2001). McDonald et al. (2001) used radiological and laboratory investigations, including magnetic resonance imaging, cerebrospinal fluid (CSF) analysis, and visual evoked potentials (VEP), as additions to a clinical diagnosis that could serve as proofs of dissemination in time and space and thus allowed an earlier diagnosis of clinically definite MS. McDonald criteria underwent several revisions, with the 2017 last revision of the criteria (Thompson et al., 2018), presented in Table 1.1.

TABLE 1.1: THE 2017 MCDONALD CRITERIA FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS IN PATIENTS WITH AN ATTACK AT ONSET, SIMPLIFIED (THOMPSON ET AL., 2018)

	Number of lesions with objective clinical evidence	Additional data needed for the diagnosis of multiple sclerosis
≥ 2 Clinical Attacks	≥ 2	None
≥ 2 Clinical Attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥ 2 Clinical Attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 Clinical Attack	≥ 2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands
1 Clinical Attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands

1.1.3 Disease Activity Monitoring

As MS is a very heterogeneous disease with an unknown underlying cause (Dobson & Giovannoni, 2019), we cannot provide a causal treatment aimed at the cause of the disease. The best current practice is to reach a state in which the patient may still need treatment but has no signs of an active disease. This state is called NEDA-3 (No Evidence of Disease Activity-3) (Giovannoni, Tomic, Bright, & Havrdová, 2017). Theoretically, if a patient reaches, and lasts in, a NEDA state, he or she should not experience clinical (disability progression or relapsing activity) or radiological (occurrence of active CNS lesions) disease activity anymore, and in a

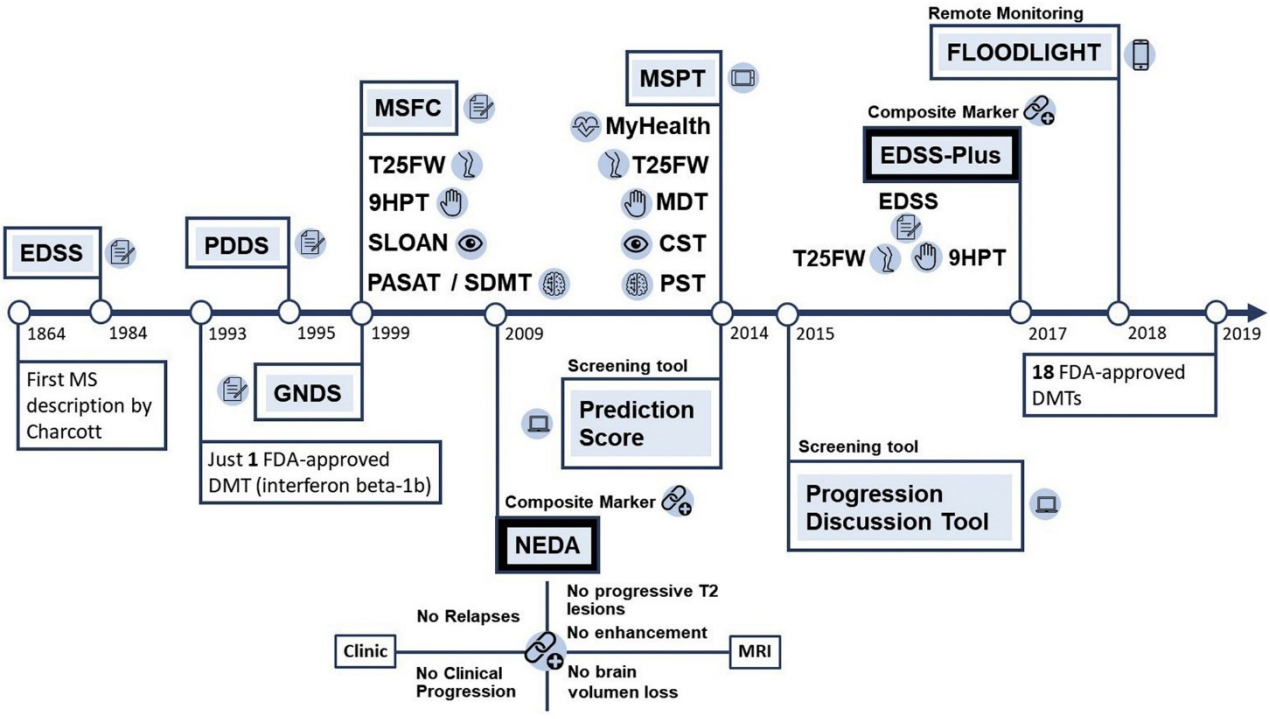
long-term perspective he or she should stay in a similar health condition. With the heterogeneity of MS symptoms, it becomes clear that thorough monitoring of disease activity is a crucial target in our attempts to make NEDA status a valid clinical outcome measure and thus to maintain the NEDA status of the person treated.

A nice overview of common clinical endpoints is provided in Figure 1.3 (Inojosa, Schriefer, & Ziemssen, 2020). However, this overview is far from complete. For decades, the two most common outcome measures used in MS research and clinical practice have been: 1) the observation of MS relapses and 2) the Expanded Disability Status Scale (EDSS), or before EDSS the Disability Status Scale (DSS) (Kurtzke, 1983).

EDSS is a 10-point scale based on neurological examination, with a score of 0 representing a person who is completely neurologically healthy and 10 representing a death from MS. The EDSS total score represents a sum of seven functional system subscores, representing various neurological domains (i.e., following subsystems: pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, cerebral, and ambulation) (Kurtzke, 1983).

FIGURE 1.3: CLINICAL OUTCOME MEASURES IN MULTIPLE SCLEROSIS (INOJOSA ET AL., 2020)

Since the first description of MS, several clinical outcome measures have emerged. However, due to the newer therapeutic options and technological developments, valid, responsive, and reliable methods should be further developed and applied in clinical practice.



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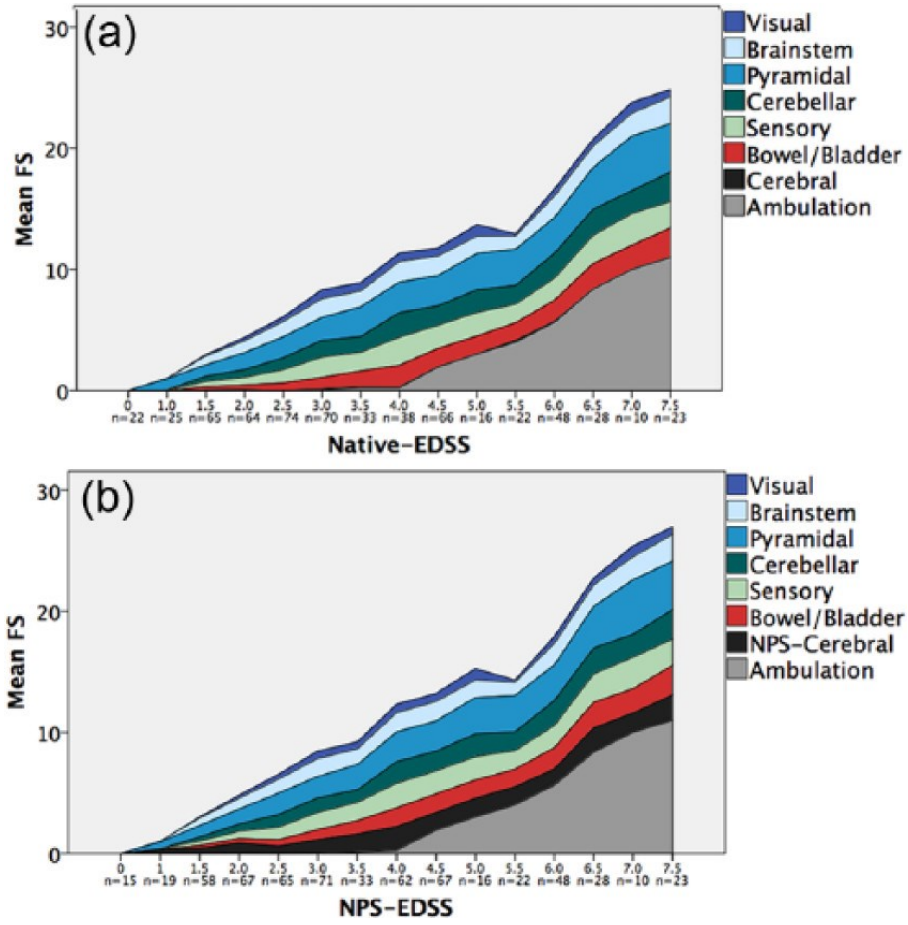
Although EDSS is an extensively used outcome measure in MS, approved and used also by numerous state regulators around the globe, it comes with various shortcomings that have been heavily discussed. First, it is

based on standard neurological examination, which is, to some degree, always subjective. Many attempts for better standardization were done, such as Neurostatus standardization and training; however, the core remains the same (Cohen, Reingold, Polman, & Wolinsky, 2012). But that is not the only weakness: EDSS is a nonlinear ordinal scale, which makes statistical analyses and their interpretation more difficult, total scores 4.0 – 7.5 are based primarily on the maximum walking distance of the patient, and some functional subsystems of the scale are poorly evaluated in a routine neurological examination (e.g., cognitive performance or sexual dysfunction) (Cohen et al., 2012; Sacca et al., 2017). Sacca et al. (2017) showed how the incorporation of a BICAMS neuropsychological battery can improve total EDSS scores and make the functional cerebral system more relevant part of the scale (Figure 1.4).

FIGURE 1.4: INCORPORATION OF BICAMS NEUROPSYCHOLOGICAL BATTERY INTO EDSS (SACCA ET AL., 2017)
Incorporation of neuropsychological assessment into the EDSS evaluation process (see NPS-EDSS) has a direct impact on the cerebral functional system, which becomes substantially less marginalized.



Reprinted from Multiple Sclerosis Journal, 23(9), Saccà, F., Costabile, T., Carotenuto, A., Lanzillo, R., Moccia, M., Pane, C., Russo, C. V., Barbarulo, A. M., Casertano, S., Rossi, F., Signoriello, E., Lus, G., & Brescia Morra, V., The EDSS integration with the Brief International Cognitive Assessment for Multiple Sclerosis and orientation tests, 1289-1296, 2017, with permission from Sage Publications.

It is no wonder that various attempts to find alternative clinical endpoints (which would be more reliable, would cover more MS symptoms, would rely mostly on quantitative objective assessment, and would be less rater-dependent) were made. These attempts included the creation of new clinical assessment batteries that incorporated measurement of cognition, motor symptoms, or vision (e.g., MSFC, 25-FWT, 9-HPT, BICAMS, MSPT, SLOAN), use of various patient reported outcomes (PRO) questionnaires, or a greater incorporation of selected paraclinical biomarkers (e.g. MRI, OCT, NfL measures) into routine clinical examination (Ralph H.B. Benedict et al., 2006; Cohen et al., 2012; Cutter, 1999; D'Amico, Haase, & Ziemssen, 2019; Giovannoni et al., 2017; Inojosa et al., 2020; Kalb et al., 2018; Nowinski, Miller, & Cella, 2017; S. M. Rao et al., 2020; Sacca et al., 2017; Srpova et al., 2021; Tomas Uher et al., 2021; Tomas Uher et al., 2020; T. Uher, Vaneckova, Krasensky, et al., 2017).

This brings us back to the NEDA, the concept of a composite endpoint used since 2009 (Eva Havrdova et al., 2009), which categorizes patients as disease activity free or as patients with signs of disease activity. The composite includes various clinical endpoints and biomarkers. According to their quantity, it is labeled NEDA-3, NEDA-4, or sometimes even NEDA-5 (Giovannoni et al., 2017; Inojosa et al., 2020). The classical status of NEDA-3 includes information on 1) relapse activity, 2) confirmed disability worsening, and 3) MRI-lesion activity (Giovannoni et al., 2017). NEDA-4 adds information on brain atrophy (Giovannoni et al., 2017; Inojosa et al., 2020) or cognition (Guevara et al., 2020; Stangel, Penner, Kallmann, Lukas, & Kieseier, 2015). NEDA-5 is mentioned in combination with NfL levels added as a fifth marker of disease progression (Håkansson et al., 2018; Inojosa et al., 2020). However, it must be noted that in many of the endpoints used longitudinally, we need to deal with measurement errors on the individual level. And although at the group level (where random measurement errors are suppressed), the marker looks like a very promising endpoint, it is much more difficult to use it at the individual level (e.g., brain atrophy, cognition) (L. B. Strober et al., 2022; T. Uher et al., 2021; Weinstock et al., 2021). I will cover this topic in the section aimed at longitudinal monitoring of cognitive functioning.

1.1.4 Clinico-Radiological Paradox

Although MRI measures such as dissemination of white matter lesions in space and time (their count, location, and volume), or brain atrophy measures such as total brain volume and its change are important tools of MS diagnostics and monitoring, they do not fully explain the heterogeneity of MS symptoms. This discrepancy between clinical manifestation of the disease and its radiological correlates as seen on MRI is described as a clinico-radiological paradox in MS (Barkhof, 2002).

There are various factors that may explain this paradox. Conventional MRI protocols and machines are not capable of imaging all the lesions in CNS, especially lesions in cortical grey matter (Geurts et al., 2005; Seewann et al., 2011), there may be microscopical abnormalities in a macroscopically normal appearing tissue (Barkhof, 2002; Granziera et al., 2021), or the influence of so-called cognitive reserve (Sumowski & Leavitt, 2013; Sumowski et al., 2014; Zahodne et al., 2013) and thus a masking effects of a cortical adaptation may play role (Barkhof, 2002). Furthermore, as mentioned in the previous section, both MRI and clinical assessment come with measurement errors and limited sensitivity, which could play some role in the explanation

of the paradox (Cohen et al., 2012; Inojosa et al., 2020; T. Uher et al., 2021). Not to mention the fact that regular assessment often misses some manifestations of MS such as cognition (Sacca et al., 2017), or spinal cord pathology (Andelova et al., 2019; Barkhof, 2002). Also, MRI is not able to differentiate histopathological differences such as those found by Lucchinetti et al. (2000), who pointed to four different histopathological lesion patterns.

Regarding the current state of the research, we are not completely sure what are the causes of the clinico-radiological paradox. But the best research and clinical practice is to improve all possibilities of disease monitoring, at the expenses we can bear, to have the most relevant information on the state of the disease, both radiological and clinical. In this matter, our team follows various paths. E.g., studying the possibilities of more comprehensive spinal cord monitoring (Andelova et al., 2019), researching the regular use of NfL levels as a biomarker (Srpova et al., 2021; Tomas Uher et al., 2021), or also studying the possibilities of regular monitoring of cognitive functioning in MS, as is further described in this dissertation.

1.2 Cognitive Impairment in MS

As Ralph Benedict (2020) pointed out, Charcot's early descriptions of people with MS, published in Lectures on the Diseases of the Nervous System in 1877, included notions of 'enfeeblement of memory' and 'concepts formed slowly', along with the classic MS triad of nystagmus, intention tremor, and ataxic dysarthria (Ralph H B Benedict, 2020). Although cognitive changes were known since the very beginnings of the modern medical approach to MS, they were for many decades an overlooked symptom of MS.

For example, medical textbooks from the 1980s estimated that the occurrence of 'intellectual' changes due to MS is approximately 5% (R. H. B. Benedict et al., 2017). This was probably based on observations made by Kurtzke, who described the involvement of cerebral (mentation) DSS subscale to be those of 5% (Kurtzke, 1970). But even before Kurtzke, the intellectual disorders due to MS were thought to be minimal and negligible (Cottrell & Wilson, 1926). Despite this fact, as I mentioned in the previous section, at the beginning of 1980s Poser's criteria signaled an increased interest in neuropsychology of MS, suggesting it as an additional diagnostic marker (Poser et al., 1983). Needless to say, the suggested use of cognitive impairment as an auxiliary diagnostic marker would probably, from the perspective of today, mean a quite an advanced state of the disease.

Importantly, there were two major changes that increased the focus on the neuropsychology of MS and pushed research in this field toward the current direction. This happened approximately three decades ago at the beginning of the 1990s, the time when the field of neuropsychology of MS, as we know it today, started.

The first change was introduced by the research of Stephen Rao, who constructed the first brief repeatable battery for neuropsychological evaluation in MS. The assessment battery is called simply the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB-N) (S. M. Rao, 1990; S. M. Rao, Leo, Bernardin, & Unverzagt, 1991). This allowed him to describe the prevalence of cognitive dysfunction in MS, that is, between 45% and 65% (S. M. Rao, 1995; S. M. Rao, Leo, Bernardin, et al., 1991), and to describe the low correlation between physical disability and cognitive dysfunction and the most commonly affected cognitive

domains, that is, slower processing speed and impaired retrieval from long-term memory (S. M. Rao, Leo, Bernardin, et al., 1991; S. M. Rao, Leo, & St Aubin-Faubert, 1989; S. M. Rao, St Aubin-Faubert, & Leo, 1989).

The second shift, as described by Benedict (2017), is highly interconnected with the first one. It describes the advances in brain imaging techniques, specifically the improvements achieved with the invention and spread of MRI. Regular use of magnetic resonance imaging in connection with neuropsychological tests allowed neuropsychologists to find the first neural correlates of cognitive dysfunction in MS, the total area of the white matter lesion on T2-weighted images (S. M. Rao, Leo, Haughton, Aubin-Faubert, & Bernardin, 1989). As Benedict (2017) argued, these first findings indicated that cognitive dysfunction in MS could be related to underlying brain pathologies related to MS rather than nonspecific conditions related to MS, such as fatigue, depression, or anxiety.

These were the first steps in our understanding of the neuropsychology of MS. The following lines will look at the current state of the field in detail.

1.2.1 MRI Correlates

The first findings of magnetic resonance correlates of neuropsychological dysfunction due to MS pointed out the total area of the white matter lesion on T2-weighted images (S. M. Rao, Leo, Haughton, et al., 1989). Since then, MRI techniques have advanced and new findings have emerged. However, at the general level, the total size of T2-weighted white matter lesions and total brain atrophy continue to reappearing as reliable volumetric predictors of cognitive impairment in MS (Deloire et al., 2011; Eijlers, Meijer, van Geest, Geurts, & Schoonheim, 2018; Mollison et al., 2017; Ouellette et al., 2018; T. Uher, Vaneckova, Sormani, et al., 2017). For example, Uher et al. (2017) suggested the combination of T2-weighted white matter lesions (>3.5 ml) and total brain atrophy (BPF <0.85) to show the best sensitivity/specificity ratio for the identification of cognitive impairment. However, the question whether the total volume of the lesion/atrophy (Nelson et al., 2011), or the location/pattern of lesions/atrophy (Eijlers, van Geest, et al., 2018; Charil et al., 2003; Martijn D. Steenwijk et al., 2016), may better explain cognitive impairment, is still ongoing. It is not hard to imagine that some combination of these MRI correlates may represent the final answer.

By looking at the MRI correlates in greater detail, we can identify three candidates (or their combination) that repeatedly show an association with cognitive impairment. Several studies pointed to a relationship between the smaller gray matter volume (cortical atrophy and deep gray matter volume) and cognitive changes in MS (Bernabéu-Sanz, Morales, Naranjo, & Sempere, 2021; Eijlers et al., 2019; Eijlers, Meijer, et al., 2018; Eijlers, van Geest, et al., 2018; Nelson et al., 2011; Martijn D. Steenwijk et al., 2016; M. D. Steenwijk et al., 2016; Welton, Kent, Constantinescu, Auer, & Dineen, 2015). However, there is an argument whether gray matter volume loss is not just an indirect downstream result of white matter pathology (Mühlau et al., 2013; M.M. Schoonheim & Geurts, 2019; Steenwijk et al., 2015). A specific candidate for a possible role in cognitive impairment due to MS is the thalamus and its atrophy or changes (R. H. Benedict et al., 2013; Bernabéu-Sanz et al., 2021; Bisecco et al., 2015; Eijlers, van Geest, et al., 2018; Houtchens et al., 2007). The third often mentioned MRI correlate of cognitive impairment is the hippocampus and its decreased volume or altered function (Eijlers, van Geest, et al., 2018; Geurts et al., 2007; Hulst et al., 2012; Sicotte et al., 2008).

As Eijlers et al. (2019; 2018) and other authors (Johnen et al., 2019; M.M. Schoonheim & Geurts, 2019) discussed, the order in which white matter integrity damage and cortical and deep gray matter atrophy occur in MS is currently a hot topic researched and discussed. Eijlers et al. (2018) argue that most studies showed that white matter and deep grey matter atrophy start early in the disease course and that cortical atrophy is more common in later stages of the disease. Therefore, they hypothesize that accumulation of damage to white matter integrity and deep gray matter atrophy are the primary drivers of cognitive decline in initial disease stages and that the later presence of cortical atrophy would potentially predispose to further cognitive decline in later stages of MS (Eijlers, van Geest, et al., 2018).

In this regard, as Johnen et al. (2019) pointed out, the above-mentioned process might explain the so called 'cognitive clinico-radiological paradox' (T. Uher et al., 2018). The cognitive clinico-radiological paradox is a term that describes the low correlation between cognitive and magnetic resonance measures in the early stages of the disease, in young patients, patients with low EDSS and patients with short duration of the disease, in contrast to higher correlations between cognitive and magnetic resonance measures in people with more severe or chronic disease (T. Uher et al., 2018). Already Rao et al. (1991) described similar differences as 'perplexing'. Also, the cognitive clinico-radiological paradox is to some extent comparable with the hypothesis of 'network collapse' (M. M. Schoonheim, Meijer, & Geurts, 2015). Uher et al. (2018) and similarly Schoonheim, Meijer, & Geurts (2015) argued that an accumulation of subclinical brain damage in MS can lead to quantitative brain damage later, that cognitive changes start to appear substantially since a certain threshold of an accumulated brain damage (see illustration in Figure 1.5). Whether the cognitive threshold might correspond to the shift between white matter integrity damage/deep gray matter atrophy and cortical atrophy (Johnen et al., 2019), remains to be answered.

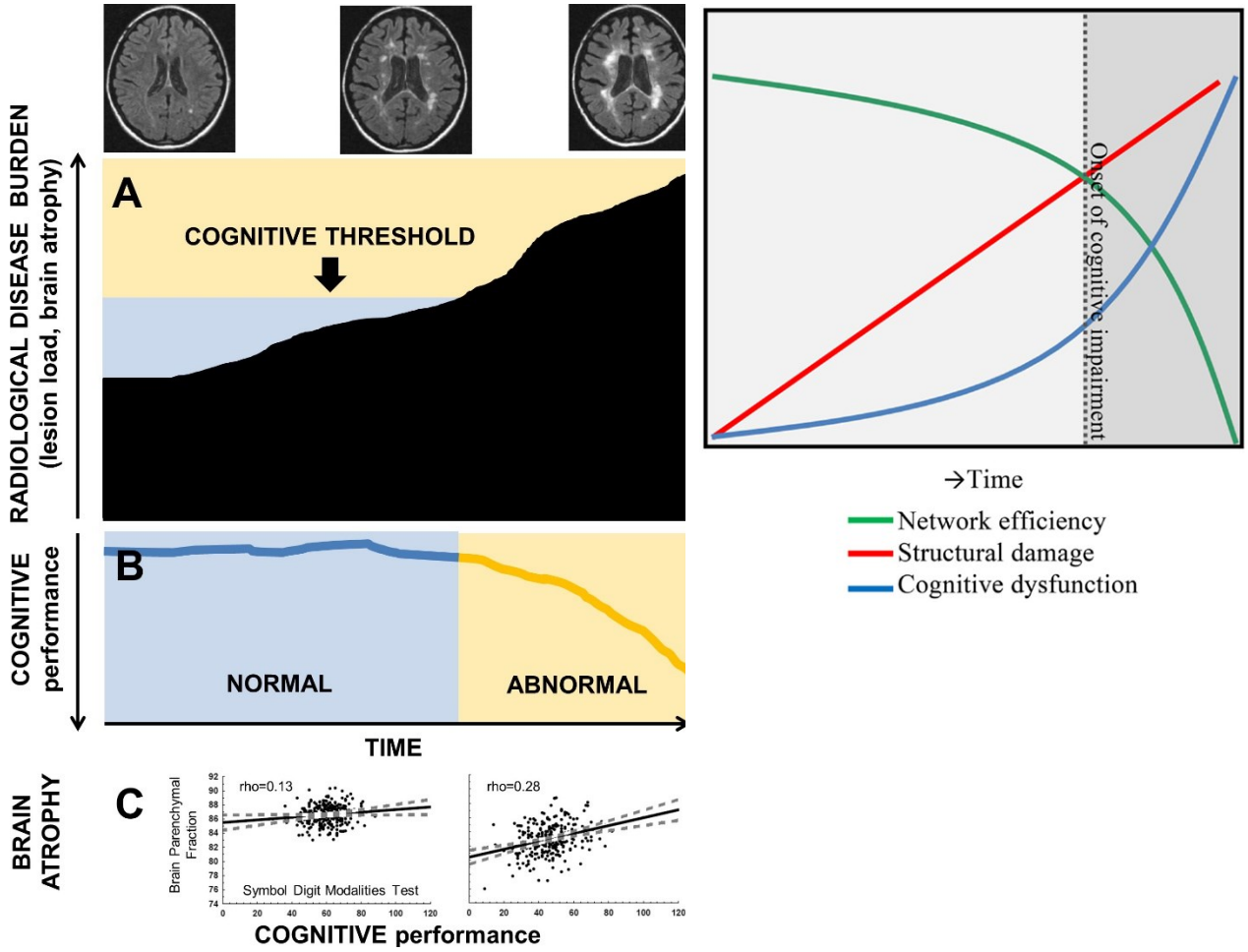
Parallel to volumetric studies, fMRI research continues to gain attention. Resting-state studies show at first sight a somewhat paradoxical finding of increased functional connectivity in cognitively impaired MS patients, in contrast to their cognitively preserved counterparts or healthy controls (Meijer et al., 2017; Meijer et al., 2018; Tona et al., 2014). This finding is explained by altered functional network activities, possibly indicating maladaptive processes (Meijer et al., 2018), or as an adaptive mechanism to the underlying structural pathology (Filippi et al., 2010). The first explanation could seem to be in contrast to the functional reorganization hypothesis (M. M. Schoonheim et al., 2015), and also in contrast to the similar theory of a certain cognitive threshold (T. Uher et al., 2018), in which it would be expected that patients with more severe structural damage would show decreased functional connectivity (Meijer et al., 2017; M. M. Schoonheim et al., 2015). Not to mention the completely contrary results of decreased connectivity in cognitively impaired patients (D'Ambrosio et al., 2020). Jandric et al. (2021) summarized that increased functional connectivity could reflect compensatory mechanisms after structural damage, and decreased functional connectivity could be evidence of network breakdown. One of the few comparative studies found that structural neuronal damage plays a key role in the severity of cognitive impairment; with functional damage having only a smaller predictive value in predicting decreased cognitive performance (Meijer et al., 2018). In any case, this discussion of the fMRI results suggests that this area of research still needs further attention.

With an increasing number of types of DMD treatment, the question of early identification of patients at the highest risk of developing cognitive deterioration, with the aim of preserving their cognitive capacity before they reach the cognitive threshold, begins to belong among urgent priorities for cognition research in

MS. Research on cognition in MS currently faces many shortcomings, such as insufficient scope and frequency of neuropsychological examination. Neuropsychological assessment is very often represented only by screening batteries or single tests, which may not fully differentiate between various cognitive profiles and thus possibly also between various disease subtypes (see the following sections).

FIGURE 1.5: THEORY OF THE COGNITIVE CLINICO-RADIOLOGICAL PARADOX [LEFT] (T. UHER ET AL., 2018) AND HYPOTHESIS OF NETWORK COLLAPSE LEADING TO COGNITIVE IMPAIRMENT [RIGHT] (M. M. SCHOONHEIM ET AL., 2015)

Two theories explain a similar phenomenon: cognitive impairment becomes apparent since a certain threshold of accumulated structural damage to the brain.



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Left: Uher, T., Krasensky, J., Sobisek, L., Blahova Dusankova, J., Seidl, Z., Kubala Havrdova, E., Sormani, M. P., Horakova, D., Kalincik, T., & Vaneckova, M. (2017). Cognitive clinico-radiological paradox in early stages of multiple sclerosis. Annals of clinical and translational neurology, 5(1), 81–91. doi.org/10.1002/acn3.512.

Right: Schoonheim, M. M., Meijer, K. A., & Geurts, J. J. (2015). Network collapse and cognitive impairment in multiple sclerosis. Frontiers in neurology, 6, 82.

1.2.2 Cognitive Profile

The prevalence of cognitive impairment in MS usually varies between 35% and 65% (R. H. B. Benedict et al., 2020; Patti et al., 2015; S. M. Rao, 1995). This wide range is caused by the different criteria for cognitive impairment used, the different research settings, and also by the varying prevalence among different subtypes of MS disease, with the prevalence in CIS patients being the smallest and in SP-MS and PP-MS the highest (R. H. B. Benedict et al., 2020; Ruano et al., 2017). Another possible explanation for this wide range in reported prevalence of cognitive impairment could be advances in MS treatment. Harel et al. (2019) argues that most of the prevalence studies cited, such as Rao (1991), were conducted in patients who were not treated with DMD or who started being treated with DMD later in their disease course. Their research shows that in a population of patients with RR-MS and SP-MS, treated with DMD, the prevalence of cognitive impairment can drop to 25% (Harel et al., 2019). The positive effect of DMD on cognitive performance is supported by the meta-analysis of current evidence (Landmeyer et al., 2020). However, we lack enough randomized controlled trials and trials with longer follow-ups in multiple cognitive domains to further differentiate the contribution of particular treatment types or to have enough evidence supporting treatment change due to cognitive deterioration (Amato & Krupp, 2020).

As already briefly mentioned, cognitive impairment or worsening can affect people of all subtypes of MS (Ruano et al., 2017). This is also true for people in the early stages of the disease. Cognitive impairment was documented not only in people with CIS (Hyncicova et al., 2017; Potagas et al., 2008; Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007; T. Uher et al., 2014), but also in the population with RIS (Lebrun et al., 2010), or in pediatric-onset MS (Amato, Krupp, Charvet, Penner, & Till, 2016). In a Norwegian population of men who underwent a conscription examination, it was found that lower cognitive performance, measured by general intelligence scales, can be found even in the preclinical phase of MS. Recruits who later developed MS scored on average 6 IQ points lower than matched controls (Cortese et al., 2016).

Concerning the typically impaired cognitive domains in MS, the typical cognitive profile was probably first outlined by Charcot, as already mentioned (Ralph H B Benedict, 2020). These first observations of 'enfeeblement of memory' and 'concepts formed slowly' were confirmed by the current neuropsychological findings. Deficits in cognitive processing speed, learning, and episodic memory are the most common among people with MS (Ralph H.B. Benedict et al., 2006; S. M. Rao, Leo, Bernardin, et al., 1991). Secondarily, we also see deficits in executive functioning, verbal fluency, and visuospatial functions (Ralph H.B. Benedict et al., 2006; Deloire et al., 2011). From a clinical perspective, many patients also report mild to severe wordfinding and multitasking difficulties, but these are rarely investigated (Sumowski et al., 2018). Most probably, due to the poor operationalization of these difficulties and thus the lack of specific and sensitive neuropsychological instruments that would be validated to measure such difficulties in daily practice. However, even here the situation seems to be slowly changing, and the hypothesis of word finding difficulty as an MS symptom was recently supported and a measure designed to assess it (Brandstadter et al., 2020).

Although the cognitive domains affected by MS are well described on the general group level, many questions, especially on the individual level, are still without a definitive answer. Sumowski et al. (2018) summarized it briefly: *'Conclusions about direct links between decline in speed, memory, or any function independent of*

premorbid ability or disease-related mediators (e.g., cerebral atrophy) are premature and potentially misleading (i.e., may encourage unfounded expectations, e.g., that treatment of one function leads to improvement in correlated functions).' The typical cognitive profile of a MS patient with cognitive impairment is not specific and much of the cognitive problems people experience with MS are rather mild; defined by group differences in comparison to healthy controls, or operationalized as worse performance compared to the premorbid level (Sumowski et al., 2018). Not to mention that some forms of cognitive deterioration in MS might be represented only by a lower practice/learning effect (Sormani et al., 2019). Only a small proportion of people with MS reach severe forms of cognitive impairment that could be marked as dementia (the exact prevalence of such cases is not well described, and the term dementia is not used very often in the field of MS) (Westervelt, 2015). Additionally, we need to bear in mind that the so-called cognitive domains are still only theoretical concepts, though supported by decades of continuous research in neuroscience and thus reified. Importantly, we cannot fully distinguish from one cognitive domain to the other; tests very often measure more functions at once (L. Strober et al., 2019), making any final interpretation of the typical 'cognitive profile' of a person with MS more problematic. To put it briefly: The individual diagnostic process of cognitive impairment due to MS is difficult, often dependent on knowledge of the premorbid state of cognition and must closely cooperate with other results of medical evaluation.

TABLE 1.2: COGNITIVE PHENOTYPES IN MS AS PROPOSED BY DE MEO ET AL. (2021)

Phenotype	Prevalence	Tests Affected	MRI Correlates
Preserved Cognition	19.4%	-	Lower Mean Thalamic Volume
Mild-Verbal Memory / Semantic Fluency	29.9%	SRT*, WLG**	Decreased Mean Hippocampal Volume
Mild-Multidomain	19.5%	SRT**, SCWT*, SDMT**, PASAT*	Decreased Mean Cortical Gray Matter Volume
Severe-Executive/Attention	13.8%	SRT**, SCWT***, SDMT**, PASAT***, WLG**	Higher Mean T2-hyperintense lesion volume
Severe-Multidomain	17.5%	SRT**, SPART**, SCWT**, SDMT***, PASAT***, WLG***	Extensive Brain Damage

*Note: *Group Mean Z-Score < -0.5, *Group Mean Z-Score < -1.0, ***Group Mean Z-Score < -2.0; SRT: Selective Reminding Test, SPART: 10/36 Spatial Recall Test, SCWT: Stroop Color and Word Test, SDMT: Symbol Digit Modalities Test, PASAT: Paced Auditory Serial Addition Test, WLG: Word List Generation (in this case semantic key) [WLG is interchangeable term for COWAT test].*

Cognitive domains affected by cognitive deterioration due to MS were well described. Research on cognitive phenotypes in MS is much scarcer. Probably because it requires: 1) large sample sizes, 2) neuropsychological batteries covering all important domains, and 3) samples representing all important MS subtypes and disease phases. Therefore, it is not surprising that relatively few studies on cognitive phenotypes in MS were conducted (De Meo et al., 2021; Johnen et al., 2017; Victoria M. Leavitt, Tosto, & Riley, 2018; Podda et al.,

2021). The most comprehensive results were presented by De Meo et al. (2021) who based the five distinct proposed cognitive phenotypes on a large multicentric Italian sample, used a complex neuropsychological battery (i.e., BRB-N & SCWT), included a control group of healthy individuals, and correlated the proposed phenotypes with MRI volumetry. The five cognitive phenotypes are presented in Table 1.2.

Patients with the preserved cognition and mild–verbal memory/semantic fluency phenotypes had similar age and disease duration, but they were younger and had a shorter disease duration in comparison with patients with the other phenotypes. Patients with the severe–multidomain phenotype had greater physical disability compared to other phenotypes. Patients with normal cognition had lower physical disability compared to the others. Furthermore, patients with the Severe-Executive/Attention phenotype had the highest Fatigue Severity Scale (FSS) scores (De Meo et al., 2021).

De Meo et al. (2021) also presented the prevalence of the five proposed cognitive phenotypes in various subtypes of MS. The results are presented in Table 1.3. Each cognitive phenotype can be present in each MS subtype. The Preserved Cognition and Mild-Verbal Memory / Semantic Fluency phenotypes showed a similar pattern with the highest prevalence in Early RR-MS and the lowest prevalence in SP-MS. On the other hand, the other three phenotypes showed a completely opposite direction of prevalence distribution, with the highest prevalence in SP-MS. Interestingly, but not surprisingly, PP-MS did not follow the patterns mentioned above and showed its unique prevalence distribution, with relatively few people with preserved cognition and the most with the Mild-Verbal Memory / Semantic Fluency phenotype.

Surprisingly, people with MS with the Preserved Cognition phenotype showed a lower mean thalamic volume on MRI compared to healthy controls. As I have discussed in the MRI Correlates section, this structure was found to correspond to cognitive issues due to MS, especially in the early stages of the disease. De Meo et al. (2021) speculate that even this group may experience cognitive changes, such as mild word finding or multitasking issues, which were not assessed and thus described (De Meo et al., 2021).

TABLE 1.3: COGNITIVE PHENOTYPES BY DE MEO ET AL. (2021), PREVALENCE IN MS SUBTYPES

Phenotype	Early RR-MS	Late RR-MS	SP-MS	PP-MS
Preserved Cognition	25%	19%	5%	7%
Mild-Verbal Memory / Semantic Fluency	38%	27%	15%	36%
Mild-Multidomain	14%	22%	25%	16%
Severe-Executive/Attention	11%	14%	19%	20%
Severe-Multidomain	12%	18%	36%	21%

Note: RR-MS: Relapsing-Remitting MS, SP-MS: Secondary-Progressive MS, PP-MS: Primary-Progressive

It is worth noting that De Meo et al. (2021) did not find the information processing speed to form one distinct phenotype. At first sight, that might be surprising, given the presented evidence of information processing speed being the most affected cognitive domain (R. H. B. Benedict et al., 2020; Ralph H.B. Benedict et al., 2006; S. M. Rao, Leo, Bernardin, et al., 1991) and the Symbol Digit Modalities Test (SDMT), commonly

perceived as an 'information processing speed test', being the most sensitive and accurate test to detect cognitive impairment due to MS (R. H. Benedict et al., 2017; L. Strober et al., 2019). In this regard, we see that both commonly used 'information processing speed' tests, SDMT and PASAT, contributed to three out of four phenotypes showing cognitive impairment, with the exception of the Mild-Verbal Memory / Semantic Fluency Phenotype (De Meo et al., 2021). Thus, these findings correspond to the previous results showing SDMT and PASAT as sensitive outcomes in MS. The fact that other cognitive domains are affected together with 'information processing speed' is not surprising. In fact, even calling SDMT (or PASAT) a simple 'information processing speed test' is an oversimplification (Costa, Genova, DeLuca, & Chiaravalloti, 2017; V. M. Leavitt, 2021; Sandry et al., 2021). The construct of 'information processing speed' is rarely defined in studies, actually it probably consists of more subconstructs (Costa et al., 2017), the slowdown in processing speed is always associated with some other domain in which the person is slower (V. M. Leavitt, 2021), and SDMT itself has been shown to be a sensitive test in MS, but nonspecific, with lexical access speed, memory, and information processing speed independently contributing to its performance (Sandry et al., 2021).

1.2.3 Neuropsychological Batteries in MS

Neuropsychological batteries can be categorized as fixed or flexible. The fixed batteries consist of a fixed set of neuropsychological tests that can be used for a general neuropsychological examination. Examples of well-known fixed neuropsychological test batteries are the Halstead-Reitan battery (Reitan & Wolfson, 1985), Luria-Nebraska neuropsychological battery (Golden, Purisch, & Hammeke, 1985), or in a Czech language environment the Neuropsychological Battery of the Prague Psychiatric Center (Preiss et al., 2012). The advantages of fixed batteries are obvious: such batteries are standardized, offer good normative data, and by using such batteries it is easy to compare results and cognitive profiles across various diagnostic units. On the other hand, such batteries are very often time-consuming, offer low flexibility, and thus they are used less and less often (especially the extremely long complex batteries). Flexible batteries represent the opposite. Flexible batteries offer a flexible approach, in which neuropsychologist chooses tests according to his/her professional knowledge, based on the individual patient or based on the diagnosis of the patient. It offers flexibility and saves time, but it prevents comparison on the level of typical cognitive profiles (Russell, Russell, & Hill, 2005). In the American cultural environment, the discussion of whether to choose flexible or fixed batteries was also influenced by forensic neuropsychology and legal practice in courtrooms (Bigler, 2007; Heilbronner et al., 2010; Larrabee, 2008; Reed, 1996)

In last decades, there has been a trend to shorten the neuropsychological examination. Lengthy batteries are more and more often substituted by shorter and less time-consuming variants when possible, e.g., the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998), Mattis Dementia Rating Scale (DRS-2) (Jurica, Leitten, & Mattis, 2001) or in the Czech environment the recently published Short Neuropsychological Battery (Straková, Věchetová, Dvořáková, Orlíková, & Preiss, 2020). At the same time, repetitive longitudinal neuropsychological examination becomes a standard across various types of disease, which puts pressure on neuropsychologists to standardize their assessments and support their decision making using high-quality psychometric and normative data (Heilbronner

et al., 2010). In this environment, the flexible batteries based on the common diagnosis seem to be a good compromise between standardization and flexibility. Such batteries are based on a preselected set of tests, and thus it is possible to conduct psychometric research on such a battery, to create robust normative datasets for it, and to conduct standardized and comparable testing of patients across the same disease type. On the other hand, it is a set of tests preselected specifically with the monitoring of a concrete disease in mind. Because of that, tests that are usually not sensitive on the neuropsychological examination of that disease are skipped, and thus the battery is shorter and better accepted by both patients and administrators. Examples of such batteries can be MATRICS in Schizophrenia (Nuechterlein et al., 2008), UDS for Alzheimer's disease (Weintraub et al., 2009), EpiTrack in Epilepsy (Lutz & Helmstaedter, 2005), or in MS MACFIMS and BICAMS (R. H. Benedict, Amato, et al., 2012; Ralph H.B. Benedict et al., 2006; Ralph H.B. Benedict et al., 2002).

TABLE 1.4: MACFIMS AND BICAMS BATTERIES FOR COGNITIVE ASSESSMENT IN MS

Test	Domain	MACFIMS	BICAMS
Controlled Oral Word Association Test (COWAT)	Language / Executive Function	X	
Judgment of Line Orientation Test (JLO)	Visuo-Spatial Processing	X	
California Verbal Learning Test, Second Edition (CVLT-II)	Verbal Learning and Memory	X	X[1]
Brief Visuospatial Memory Test—Revised (BVMT-R)	Non-Verbal Learning and Memory	X	X[1]
Symbol Digit Modalities Test (SDMT)	Processing Speed and Working Memory	X	X
Paced Auditory Serial Addition Test (PASAT)	Processing Speed and Working Memory	X[2]	
Delis-Kaplan Executive Function System Sorting Test (D-KEFS ST)	Executive Function	X[3]	

[1]The delayed recall and recognition trials are not administered as part of BICAMS battery, only the immediate learning and memory trial is administered in BICAMS; [2]Both versions (with 3 and 2 second intervals) are administered as part of MACFIMS battery; [3]It is allowed to administer the free sorting condition alone, to reduce total testing time.
Note: As part of the MACFIMS battery in a clinical setting, it is also recommended to do/administer: 1) Clinical Interview, 2) Depression Scale (HADS, BDI-II), 3) Visual/Sensory/Motor confound measures as appropriate (e.g., 9-HPT, Visual Acuity, 25-FWT), 4) Measure of Premorbid Abilities (NART, CRT).

Historically, various batteries for neuropsychological assessment of people with MS were proposed, e.g., Neuropsychological Screening Battery (NSB) (Franklin, Heaton, Nelson, Filley, & Seibert, 1988), or the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB-N) (S. M. Rao, 1990; S. M. Rao, Leo, Bernardin, et al., 1991), but the current standard is represented by the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery for a complex neuropsychological screening (Ralph H.B.

Benedict et al., 2006; Ralph H.B. Benedict et al., 2002) and the Brief International Cognitive Assessment for MS (BICAMS) battery for a brief screening (R. H. Benedict, Amato, et al., 2012). The overview of both batteries and their subtests is presented in Table 1.4.

Both batteries include tests covering the cognitive domains most frequently impaired in MS (see Table 1.4). Batteries were created based on a consensus of expert committees that tried to develop a more comprehensive batteries than the previously used Rao's BRB-N. The MACFIMS battery is a more complex of the two batteries, with tests covering basically all commonly MS-related cognitive domains. BICAMS is a shorter battery, based on a selection of the most sensitive methods from the MACFIMS battery. BICAMS is intended for a brief screening, and thus it includes only a cognitive processing speed test (i.e., SDMT) and two tests covering learning and memory of verbal and nonverbal material. Both these tests (i.e., CVLT-II, BVMT-R) are shortened, the delayed recall and recognition tasks are skipped in BICAMS. Administration of MACFIMS takes approximately between 60 and 90 minutes; administration of BICAMS takes approximately 15 to 25 minutes. Impairment for a single test was defined in both batteries as a Z-Score < -1.5. Neuropsychological impairment was defined as a defect in two or more measures for MACFIMS and in one or more measures for BICAMS. MACFIMS must be administered by a qualified neuropsychologist or clinical psychologist, BICAMS can also be administered by other, for this purpose trained, clinical personnel (R. H. Benedict, Amato, et al., 2012; Ralph H.B. Benedict et al., 2006; Ralph H.B. Benedict et al., 2002; Corfield & Langdon, 2018).

The MACFIMS battery was based on a consensus of experts solely from anglophone countries (Ralph H.B. Benedict et al., 2002) and some of its subtests lack validation or even translation in many other non-English languages, especially the methods subjected to copyright. This might also be one of the reasons why BRB-N battery was still used quite commonly in international clinical and pharmacological trials until recently. That was also one of the reasons, together with the need for a shorter battery, for creation of the BICAMS battery, based on a more internationally based consensus of experts from both English and non-English speaking countries (R. H. Benedict, Amato, et al., 2012; Corfield & Langdon, 2018).

In Czechia, both the MACFIMS and BICAMS batteries were validated (Dusankova, Kalincik, Havrdova, & Benedict, 2012), however, the real accessibility of some of the subtests remains scarce. Similarly to other countries, the situation with accessibility of BICAMS subtests is a bit easier. Both SDMT (Smith, 1982) and BVMT-R (R. Benedict, 1997) tests were not officially published in the Czech market, but are internationally easily obtainable. Czech normative data for BVMT-R have already been published (Havlík et al., 2020), but SDMT lacks its Czech normative study. The situation is a bit more difficult with CVLT-II (Bezdíček & Preiss, 2009). Following the recommendation of the international committee on BICAMS, it can be recommended to use RAVLT instead (R. H. Benedict, Amato, et al., 2012). The Czech version of RAVLT is easily accessible, well validated and with recent robust normative datasets (Bezdicek et al., 2014; Frydrychová, Kopeček, Bezdíček, & Štěpánková Georgi, 2018). Additionally, its alternative forms were found similar enough and therefore suitable for repetitive testing (Paštrnák, Sedláková, Dorazilová, & Rodriguez, 2018). It must be noted that CVLT-II is clinically somewhat superior to RAVLT because, based on its semantic categories subscores, it follows the principles of the Edith Kaplan Boston Process Approach to neuropsychological assessment more closely (Kaplan, 1988). Therefore, we hope that one day it will be officially published on the Czech market as well. Until then, the use of RAVLT is more than a sufficient substitute, especially in the context of BICAMS, where usually only the total scores are analyzed.

Similar situation as with CVLT-II is with the D-KEFS ST subtests from the MACFIMS battery. D-KEFS ST is also not accessible in Czechia. Until its official translation and publication, it can be recommended to use the Czech version of the Wisconsin Card Sorting Test (WCST) instead (Grant, Berg, & Telecká, 2013). Again, needless to say, D-KEFS ST would be a better option for various reasons, including the Boston Process Approach perspective (Kaplan, 1988). The remaining tests in BICAMS and MACFIMS batteries include JLO, PASAT, and COWAT. JLO and PASAT were never officially published in Czechia, but both are easily available locally, or internationally easily obtainable; however, we lack decent local normative studies on both tests. The Czech version of COWAT is easily available and validated. It should be used in the Czech language in its KPS form. Local normative data for the older population are available (Nikolai et al., 2015).

Although BICAMS is already a brief battery covering the most often impaired cognitive domains in MS, it still requires valuable time. In routine clinical practice with its limited financial and personal resources, there is a growing demand for even shorter neuropsychological examinations, especially in cases of routine neuropsychological screening, such as the recently proposed annual screening of cognitive functioning in MS (Kalb et al., 2018). Therefore, the possible use of a single sensitive test as a neuropsychological screening measure, used to identify MS patients in need of further testing, is often discussed. Already in 1999, the Multiple Sclerosis Functional Composite (MSFC) included only a single test of cognitive functioning (i.e., PASAT) (Jill S. Fischer, Jak, Kniker, Rudick, & Cutter, 2001; J. S. Fischer, Rudick, Cutter, & Reingold, 1999; S. M. Rao, 1990). This trend continues, only the PASAT test (S. M. Rao, 1990) was gradually replaced by the SDMT oral version (Smith, 1982) as the gold standard for cognitive screening in MS (R. H. Benedict et al., 2017; Costa et al., 2017; Drake et al., 2010; López-Góngora, Querol, & Escartín, 2015; Sonder, Burggraaff, Knol, Polman, & Uitdehaag, 2014). The SDMT was not only shown to be more sensitive than PASAT, but also better accepted by patients (Walker et al., 2012). Additionally, some of the previous disadvantages of the SDMT have been overcome over the last ten years. Alternative equivalent forms were proposed (R. H. Benedict, Smerbeck, et al., 2012) and new normative data for the oral version, which do not require previous administration of the written version, were published (L. Strober et al., 2019). The administration of the SDMT orally is recommended because oral administration with MS patients minimizes confounding events due to motor weakness or incoordination (Ralph H.B. Benedict et al., 2002). Therefore, administration of the similar but inversed Digit Symbol Substitution Test from the WAIS-III or WAIS-IV batteries cannot be recommended.

In near future we can expect a growing interest in digitalization of neuropsychological examination., especially in the context of neuropsychological and MS functional screening. Actually, digitalization has already begun. New methods such as CSCT, MSPT, PST, Floodlight, or MSReactor have been introduced in recent years (Merlo, Darby, Kalincik, Butzkueven, & Van Der Walt, 2019; Montalban et al., 2021; Stephen M Rao, 2018; S. M. Rao et al., 2020; S. M. Rao et al., 2017; Rudick et al., 2014; A. Ruet, Deloire, Charre-Morin, Hamel, & Brochet, 2013; C. M. Wojcik et al., 2019), and many other methods are yet to come. The electronic tests could offer metrics that are missing from their paper-based counterparts, these tests could be incorporated into other daily-used mobile apps and thus process the assessment on background of regular daily activities, or increase the ecological validity otherwise, e.g., by using virtual reality (VR) and thus create a more immersive lifelike situational testing (Plechatá, Hejtmánek, & Fajnerová, 2021; Aurélie Ruet & Brochet, 2020). Self-administration and rapid computer-based evaluation could also minimize the need for trained clinical professionals. But it comes also with disadvantages such as lengthy standardization processes of the

new methods, possible privacy issues, or issues which were thought to be already solved – the new electronic version of the SDMT test, the Processing Speed Test (PST) (S. M. Rao et al., 2020), intended for use among the MS population, does not include voice recognition, and thus the use of hand is needed again, after years when the orally administered SDMT was thought to be the blueprint of a quick cognitive screening in MS.

1.2.4 Neuropsychological Monitoring in a Clinical Setting

In previous sections, I have outlined how cognitive performance is related to neurodegenerative processes in the brain due to MS, described that ongoing disease activity can further affect and deteriorate cognition, but also noted that modern DMD treatments may possibly slow cognitive deterioration, and mentioned that the results of neuropsychological examination could serve as one of markers of disease activity due to MS, some thought to be even early markers of the disease activity (Kalb et al., 2018). All this brings us to the possibilities of neuropsychological monitoring of cognition in patients with MS in regular clinical setting.

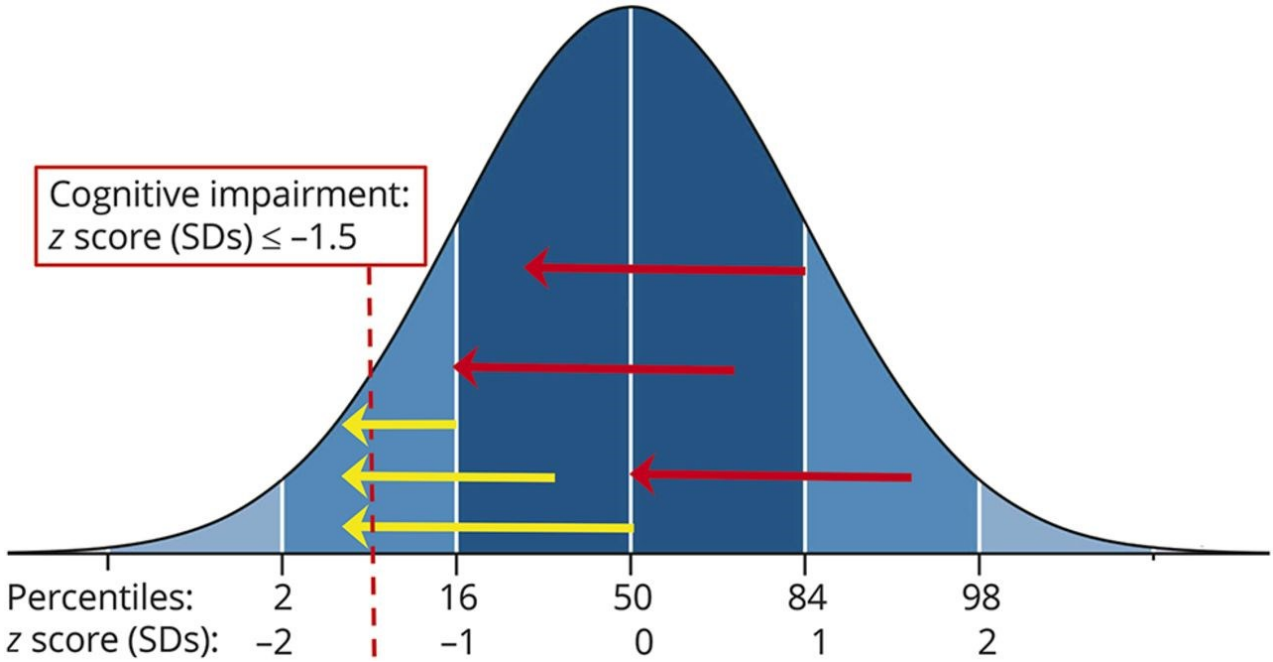
Standards currently promoted for cognitive screening and management of MS were proposed by the experts committee of the National MS Society in 2018 in the United States (Kalb et al., 2018). The main standard that was outlined based on the current evidence was the recommendation of annual cognitive screening in all MS patients (8 years of age and older), ideally since the onset of the disease (Kalb et al., 2018).

The need for annual cognitive screening comes from attempts to detect cognitive deterioration as early as possible. In this matter, Sumowski et al. (2018) correctly pointed out that cognitive deterioration starts much earlier than at the threshold of cognitive impairment; usually set at the Z-Score of the -1.5, below the mean of equivalent normative population. At the point of crossing the cognitive impairment threshold, cognitive deterioration has probably already been present for some time, and its detection has come late. But to spot the cognitive deterioration earlier, we need the knowledge of the cognitive performance at the beginning of the disease, and ideally a regular monitoring of the annual change in cognitive performance thereafter. That can help us serve the purpose of early detection, this way we can detect cognitive changes even before the threshold for cognitive impairment is reached (Sumowski et al., 2018). This principle is illustrated in Figure 1.6.

The recommended minimum for annual screening, proposed by the standards (Kalb et al., 2018), should be SDMT (Smith, 1982) or other equivalent well-validated information processing-speed tests such as PST (S. M. Rao et al., 2020; S. M. Rao et al., 2017) or CSCT (A. Ruet et al., 2013). Screening for depression should also be added (Kalb et al., 2018). In case of time for a more comprehensive battery, BICAMS, BRB-N, or MACFIMS are recommended (Kalb et al., 2018). However, the official distribution of the BRB-N battery has been stopped (R. H. B. Benedict et al., 2020). The more comprehensive evaluation performed by the clinical neuropsychologist should be applied in cases of positive screening for cognitive deficit or deterioration, in patients with subjective cognitive complaints, in children who experience unexpected decline in academic or behavioral functioning, in people who apply for state social security/disability benefits, or in people who seek cognitive remediation (Kalb et al., 2018; Stephen M Rao, 2018).

FIGURE 1.6: COGNITIVE DECLINE FROM PREVIOUS FUNCTIONING (SUMOWSKI ET AL., 2018)

The prevalence of cognitive impairment due to MS typically varies between 35% and 65%. The threshold for the diagnosis of cognitive impairment is usually set at -1.5 SD below the mean of a comparable normative sample. In this figure, the patients represented by the yellow lines crossed the cognitive impairment cut-off point. However, with knowledge of premorbid cognitive performance, it is possible to spot cognitive decline even before the cutoff point for cognitive impairment is reached (red lines).

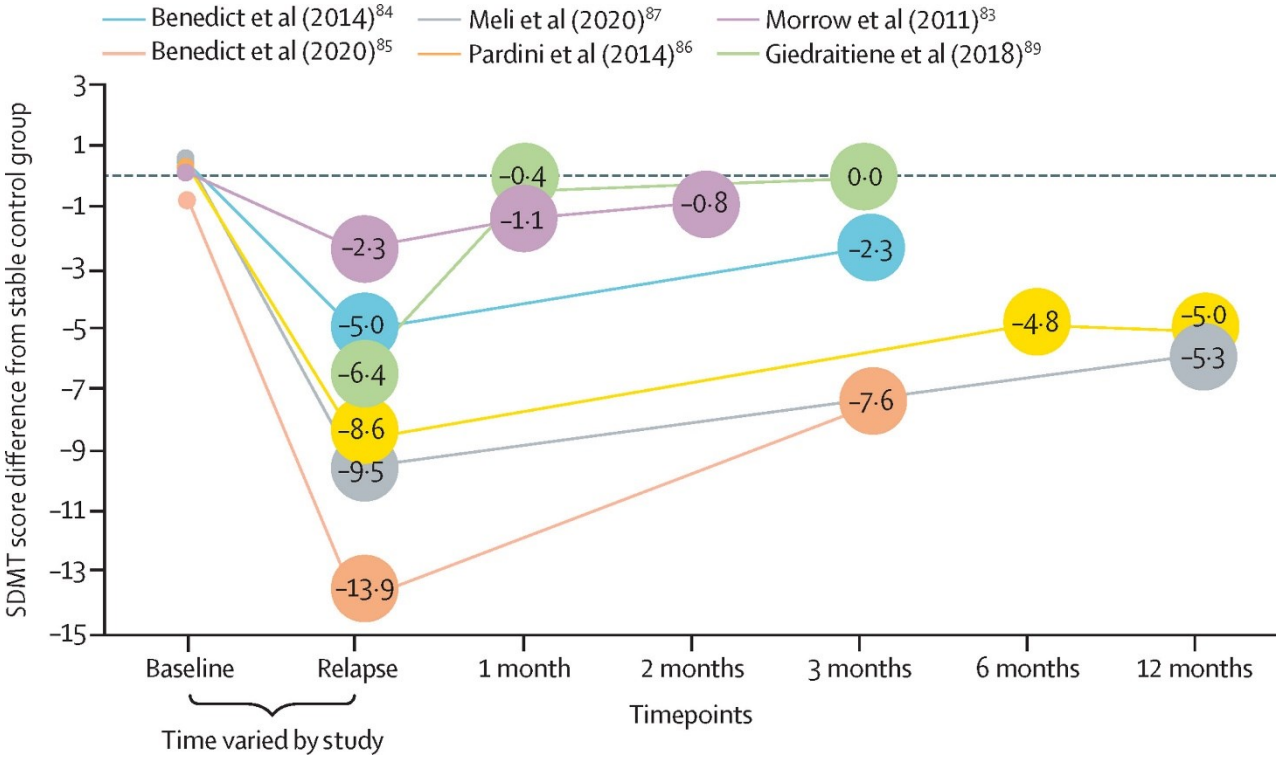


Reprinted from: Sumowski, J. F., Benedict, R., Enzinger, C., Filippi, M., Geurts, J. J., Hamalainen, P., ... & Rao, S. (2018). Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology, 90(6), 278-288, with permission from Wolters Kluwer Health, Inc.

I have already explained how cognition follows the course of the disease and that at the group level it seems to be an essential marker of disease activity and disease severity. As Figure 1.7 shows, a drop in cognitive performance also follows the presence of MS-related relapse, the acute activity of the disease. The drop is the most prominent at the time of the relapse, with later partial (or complete) improvement, as multiple studies show (R. H. Benedict et al., 2014; R. H. Benedict et al., 2020; R. H. B. Benedict et al., 2020; Giedraitiene, Kaubrys, & Kizlaitiene, 2018; Meli et al., 2020; S. A. Morrow, Jurgensen, Forrestal, Munchauer, & Benedict, 2011; M. Pardini et al., 2014). Additionally, the hypotheses of the so-called isolated cognitive relapse are also discussed (Baldwin & Morrow, 2021; Matteo Pardini, 2021; Aurélie Ruet, 2021). This phenomenon describes a possible relapse of the disease manifested solely in the drop in cognitive performance. The observation of isolated cognitive relapse was supported by concurrent MRI activity, with specifically only fronto-parietal gadolinium enhancing (gd+) lesions being correlated with isolated cognitive decline in MS (Meli et al., 2020; M. Pardini et al., 2014). However, other authors have questioned the validity of this concept. The argument goes that the so-called isolated cognitive relapse was only shown by two or three studies and that it needs to be researched more thoroughly (Baldwin & Morrow, 2021).

FIGURE 1.7: SDMT DECLINE AND RECOVERY CURVES DURING A COGNITIVE RELAPSE (R. H. B. BENEDICT ET AL., 2020)

Lines showing SDMT total score difference of patients with cognitive relapse from stable control group. Blue: (R. H. Benedict et al., 2014); Grey: (Meli et al., 2020), Violet: (S. A. Morrow et al., 2011), Apricot: (R. H. Benedict et al., 2020), Yellow: (M. Pardini et al., 2014), Green: (Giedraitiene et al., 2018).



Reprinted from The Lancet Neurology, 19(10), Benedict, R. H. B., Amato, M. P., DeLuca, J., & Geurts, J., Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues, 860-871, 2020, with permission from Elsevier.

Mentioning the existence of cognitive relapses, the important and a bit controversial topic is whether cognitive decline should lead to the possibility of a treatment change (Amato, 2018). As I have already discussed, cognitive deterioration is interconnected with the progression of brain atrophy (Eijlers et al., 2019; Ouellette et al., 2018). If disease activity is not stopped early, it can cause irreversible neuronal damage, which can add an additional burden to the disease and have severe consequences. Even a minor decline in cognitive performance could have a negative effect on personal and professional life, especially in professions where high cognitive performance is vital (Sumowski et al., 2018). Additionally, advanced cognitive impairment in MS is well described to lead to various personal and professional problems, such as loss of employment (R. H. Benedict et al., 2005; S. M. Rao, Leo, Ellington, et al., 1991; Aurélie Ruet et al., 2013; L. Strober, Chiaravalloti, Moore, & DeLuca, 2014). Furthermore, with the evidence that DMD treatment has a positive effect on cognitive performance (Landmeyer et al., 2020), and therefore generally speaking it appears to be prevent cognitive decline, it is no wonder that various authors argue that the detection of progressing cognitive decline should lead to a change in DMD treatment (Weinstock-Guttman, Eckert, & Benedict, 2018). However, Emilio

Portaccio (2018) correctly points to the uncertainties in the neuropsychological diagnostic process at the individual level. Most studies on cognition in MS were cross-sectional and based on observed group differences. Much is still unknown to make decisions about potentially harmful second-line treatment based solely on alleged cognitive decline (Portaccio, 2018). Also, as Amato & Krupp (2020) argue, we need more long-term double-blinded large-scale studies that would check the relationship between various DMD treatments and cognitive domains, before we start making decision on escalation of the treatment solely on cognitive outcomes (Amato & Krupp, 2020). However, current evidence seems sufficient for the use of cognitive outcomes as auxiliary markers in decision making about DMD treatment, together with other classical markers of disease activity.

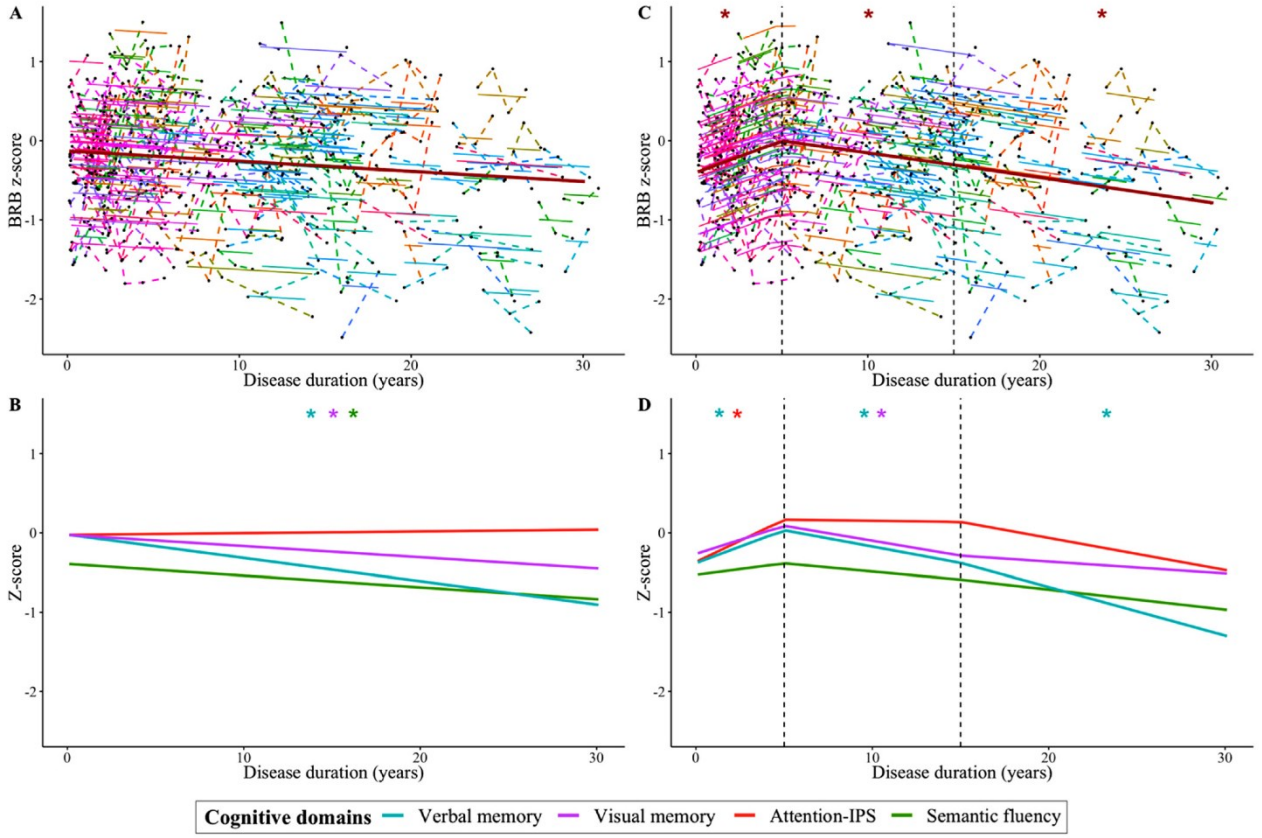
Speaking of the neuropsychological diagnostic uncertainties and differential diagnosis, we need to consider various factors affecting the neuropsychological assessment and its results. The acute cognitive decline due to MS relapses and the progressive cognitive decline due to neurodegenerative processes in MS are not the only factors that can cause the observed drop in scores on neuropsychological examination. Generally speaking, such factors that we need to evaluate in differential diagnosis can include emotional disturbances and personality disorders, psychotic disturbances, depression, or even malingering (Lezak, Howieson, Bigler, & Tranel, 2012).

Specifically in MS, the most notable comorbidities include affective disorders such as primary/secondary depression and anxiety, which have been shown to be much more prevalent in people with MS than in the general population (Boeschoten et al., 2017; Anthony Feinstein, 2011). For differential diagnostic purposes, the finding that depression most likely relates to attentional and information processing speed processes and, on the other hand, anxiety is related to non-verbal memory, is essential (Peter A. Arnett, Higginson, Voss, Bender, et al., 1999; Peter A. Arnett, Higginson, Voss, Wright, et al., 1999; V. M. Leavitt et al., 2020). Also, especially in connection with cognitive monitoring, possible vascular issues are notable, as they can show a similar cognitive manifestation to MS (Sanai et al., 2016; Schmidt, Enzinger, Ropele, Schmidt, & Fazekas, 2006). With the increasing life expectancy of people with MS, which has become almost similar to the life expectancy of the healthy population, it raises the importance of the differential diagnosis of neurodegenerative diseases in the elderly population with MS (Sanai et al., 2016). For example, the most common neurodegenerative disease of the elderly, Alzheimer's disease, seems to be unique in recognition problems that we do not see in people with MS-related cognitive impairment (Muller et al., 2013). Regarding the differential neuropsychological diagnosis in MS, it is important to note that various classical symptoms can affect the neuropsychological examination, for example, MS-related sight problems, hand dexterity problems, extreme fatigue, etc. (Ralph H.B. Benedict et al., 2006; Dejan Jakimovski et al., 2021; Krupp et al., 2010). Furthermore, many of the neuropsychological methods are influenced by various factors and measure multiple cognitive domains (V. M. Leavitt, 2021; Sandry et al., 2021). Under such circumstances, it is necessary to collect all the necessary assessment-related information, in as much detail as possible, and it can be extremely challenging to make final decision on the origin of the issues. Therefore, it might be reasonable to opt out of the final differential diagnosis and just describe the cognitive problems observed. However, the closer we get to the origins of the observed issues, the closer to the successful treatment, remediation, or adaptation we are (V. M. Leavitt, 2021; V. M. Leavitt et al., 2020).

Speaking of the much-needed detail, there are quite a few studies that cover cognition throughout the course of the disease, specifically looking at specific cognitive domains. Existing research supports evidence from cross-sectional studies that information processing speed and verbal memory in combination with word generation are the cognitive domains that drive cognitive deterioration in MS (Damasceno, Pimentel-Silva, Damasceno, & Cendes, 2020; Lopez-Soley et al., 2021; C. Wojcik et al., 2021). But there are some discrepancies: Wojcik et al. (2021) found SDMT to be the first test to show signs of cognitive deterioration, followed by PASAT, CVLT-II/BVMT-R (interchangeable order), and D-KEFS being the last. On the contrary, Lopez-Soley et al. (2021) reported that verbal memory is the first cognitive domain to decline in MS, followed by attention – processing speed (see Figure 1.8).

FIGURE 1.8: DYNAMICS OF COGNITIVE PERFORMANCE IN MS AS THE DISEASE PROGRESSES (LOPEZ-SOLEY ET AL., 2021)

A: General tendency of cognitive deterioration over 30 years since the disease onset; B: Tendency of cognitive deterioration divided into three periods (0-5, 5-15, 15-30 years since disease onset); C & D: Similar to A & B but particular cognitive domains analyzed separately (i.e., Verbal Memory, Visual Memory, Attention - Information Processing Speed (IPS), Semantic Fluency.



The figure is distributed under Creative-Commons License (CC BY 4.0). Source: Lopez-Soley, E., Martinez-Heras, E., Andorra, M., Solanes, A., Radua, J., Montejo, C., . . . Llufriu, S. (2021). Dynamics and Predictors of Cognitive Impairment along the Disease Course in Multiple Sclerosis. Journal of Personalized Medicine, 11(11), 1107. doi:10.3390/jpm11111107

This discrepancy remains to be answered. It could have several explanations; first of all Wojcik et al. (2021) analyzed concrete tests, Lopez-Soley et al. (2021) focused on joint cognitive domains. Also, the sensitive SDMT is not a simple information processing speed (V. M. Leavitt, 2021), Memory, IPS and Rapid Automatized Naming (lexical access speed) jointly and uniquely contribute to SDMT (Sandry et al., 2021), thus those at the first sight contrary results do not need to be in contrast when analyzed carefully. Also, in future studies, it might be helpful to follow the proposed cognitive phenotypes in MS (De Meo et al., 2021), rather than to analyze single tests or cognitive domains separately. And, more importantly, Lopez-Soley et al. (2021) mentioned the lower educational level of their sample. The observed difference could arise from this methodological difference, with the possible implication that people with lower cognitive reserve can face a different course of cognitive deterioration.

1.2.5 Serial Neuropsychological Assessment

Serial monitoring of cognitive functions has become more and more common in neuropsychological clinical practice (Heilbronner et al., 2010). However, various issues arise from the repetitive assessment, starting with the need for alternative equivalent versions of the test to prevent practice and learning effects (see example in Figure 1.9), and ending with the issues connected with the interpretation of the difference between the two or more follow-up assessment results. The reason why interpretation is not an easy process is that these scores are *'comprised of systematic (ability- and procedure-related) variance and error variance attributable to specific factors affecting the examinee, examiner, environment, and context of each individual testing session'* (Heilbronner et al., 2010). These issues are not new, clinical psychology and neuropsychology had to deal with such questions for decades throughout the whole existence of these fields. Therefore, it is quite surprising that topics such as clinically meaningful change, reliable change, standardized regression-based change (SRB), and reliable change index (RCI) have gained attention in research on cognitive monitoring in MS only recently (Heilbronner et al., 2010; S. A. Morrow et al., 2010; Portaccio, 2018; L. B. Strober et al., 2022; Weinstock et al., 2021)

The issue with the clinical evaluation of the reliable change is that it is always going to be an expert-based decision made by a clinical neuropsychologist with enough experience and backed up by current research evidence. From this perspective, any recommended cut-off value will always be just one of the auxiliary guidelines and not a rule which should be followed blindly. There will always be some space for uncertainty in such a decision-making, same as in any other diagnostic processes. This is reflected in the official position of the American Academy of Clinical Neuropsychology on serial neuropsychological experiments and its recommendations; see Table 1.5 (Heilbronner et al., 2010). The American Academy of Clinical Neuropsychology also proposed the Reliable Change Index (RCI) and Standardized Regression-Based Change (SRB) as the most recommended methods of reliable change assessment (Heilbronner et al., 2010).

TABLE 1.5: RECOMMENDATIONS OF THE AMERICAN ACADEMY OF CLINICAL NEUROPSYCHOLOGY ON SERIAL NEUROPSYCHOLOGICAL ASSESSMENT (HEILBRONNER ET AL., 2010)

1 Neuropsychologists who perform a repeat examination should address the potential influence of test practice effects, and may choose to report specifically how these effects were estimated or otherwise taken into consideration in interpreting the data and reaching conclusions. Rather than viewing repeat testing as primarily a confound, sound neuropsychological practice is best served when neuropsychologists consider change as a measurable construct to be used to inform the clinical descriptive and diagnostic process. Consideration may be given to the standard error of measurement from a test manual, empirical findings on the expected magnitudes of score increases over a particular interval, or other relevant research on test operating characteristics for the instruments employed in the neuropsychologist's battery.

2 Neuropsychologists remain up-to-date on research addressing test–retest effects, when available and relevant. Empirical data can clarify which tests are most vulnerable to practice effects, as well as which clinical samples tend to be more or less likely to display to such effects.

3 Neuropsychologists should be familiar with the concept and statistical methods related to reliable change indices (RCI) and regression-based approaches to change measurement and their associated risks and benefits when attempting to account for practice effects.

4 There is an obvious need for more data on normal change trajectories for all types of measures with all types of demographic variables and patient groups. This is especially salient in pediatric neuropsychological assessments where cognitive development, practice, and recovery can become potentially confounded in repeated assessments. Because of the inherent neurobiological and contextual change that is particularly relevant to both early development and aging, repeat assessment is often essential in identifying atypical maturational progression and in planning and evaluating treatment across different developmental stages of the lifespan.

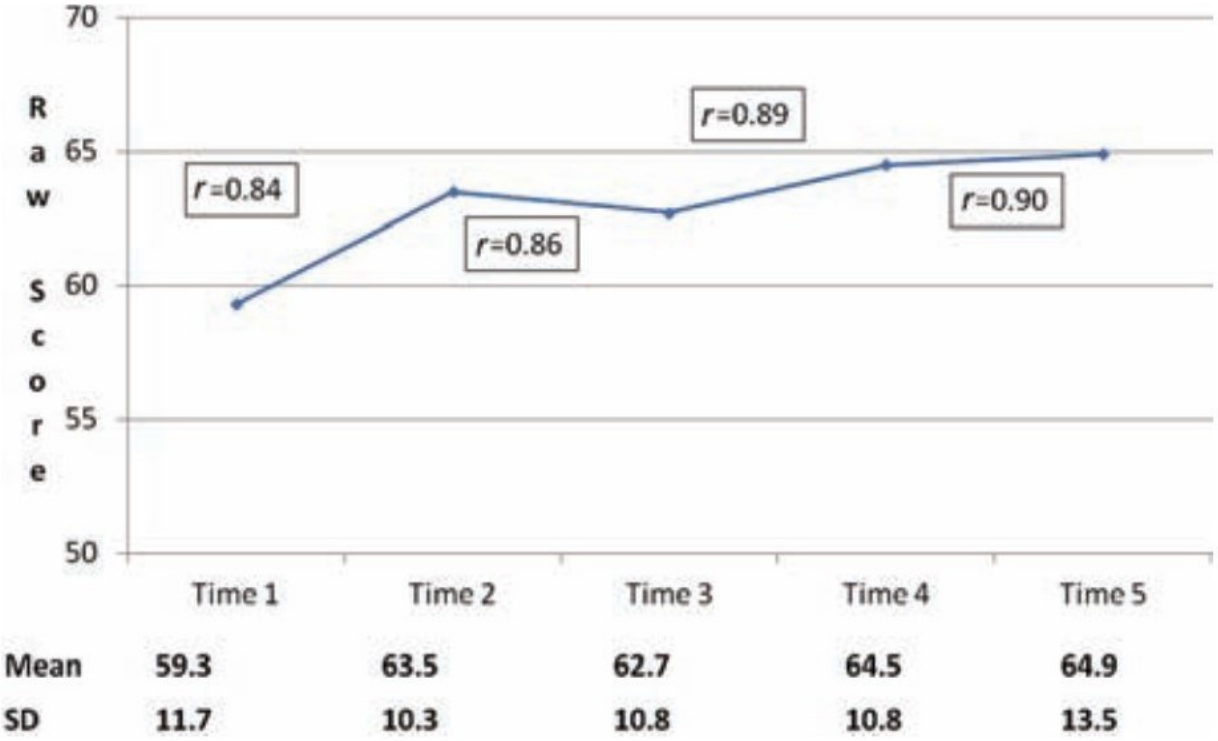
5 In a forensic context, neuropsychologists acting as experts should be aware of the relevant factors affecting change as in clinical settings. More data and extra test information (e.g., effort) should be considered in forensic settings to assist in the interpretation of test–retest findings.

6 There are no empirical data allowing the development of clinical guidelines regarding minimum test–retest intervals in clinical or forensic settings. In a forensic context, if confronted by an opposing expert who advocates for fixed retesting intervals, the neuropsychologist should be prepared to educate the court (or referral source) on the state of the art and science. Measurement of practice effects represents valuable data bearing on a person's capacity for learning and adaptation. Making clinical sense out of practice effects requires interpretation just as much as any single score. Neuropsychologists are qualified to interpret the significance of test–retest differences, and are especially equipped by virtue of their knowledge of test operating characteristics to understand the many variables contributing to test–retest change over time.

There are many methods by which the change between two scores can be interpreted. On the general level, several psychometric approaches are commonly applied, most notably Classical Test Theory (CTT) or Item Response Theory (IRT) (Jabrayilov, Emons, & Sijtsma, 2016). It is out of the scope of this text to provide a complete overview of these concepts. Although IRT seems to be superior and with its possibilities of adaptive testing could find great use in neuropsychology, the following lines will describe the interpretation of a score change from the perspective of CTT, which is probably the most widely used approach in current clinical practice.

FIGURE 1.9: LEARNING/PRACTICE EFFECT FOR SDMT IN HEALTHY PARTICIPANTS, IN A CASE EQUIVALENT ALTERNATIVE VERSIONS ARE ADMINISTERED (R. H. BENEDICT, SMERBECK, ET AL., 2012)

The average time between each timepoint was approximately one week.



Reprinted from Multiple Sclerosis Journal, 18(9), Benedict, R. H., Smerbeck, A., Parikh, R., Rodgers, J., Cadavid, D., & Erlanger, D., Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: implications for multiple sclerosis clinical trials, 1320-1325, 2012, with permission from Sage Publications.

To simplify the topic of a meaningful change, the most commonly we can encounter the following two approaches: 1) Anchor-based methods, 2) or Distribution-based methods of interpretation of the score change (Crosby, Kolotkin, & Williams, 2003).

Anchor-based methods provide a criterium of a meaningful change based on cross-sectional or longitudinal research-derived comparisons related to some meaningful real-world outcome, for example, based on

change in disease-related outcome or prognosis of future events (Crosby et al., 2003). In the field of cognition in MS, the most common example of this approach is the clinically meaningful change of 4-points decline in SDMT (S. A. Morrow et al., 2010). Morrow et al. (2010) found that deterioration in vocational status is related to a decrease of 4 points in the SDMT total score. Another criterium used is the average drop in the SDMT total score seen in MS relapses, this again suggested the criterium of the 4-point decline in the SDMT or a 10% change as a clinically meaningful drop in performance (R. H. Benedict et al., 2017).

Distribution-based approaches to determining clinically meaningful change are based on the statistical characteristics of the obtained sample (Crosby et al., 2003). These include, among others, the methods recommended by the American Academy of Clinical Neuropsychology (i.e., RCI and SRB). These approaches were also recommended for use in the field of MS (Kalb et al., 2018). However, until recently, they have not received significant research attention in the field of MS. Information on their use in clinical practice is unknown; however, any skilled clinical neuropsychologist should be familiar with the RCI.[1] In the last year, two research papers covering the topic of RCI (and SRB) in MS-related cognitive assessment were published (L. B. Strober et al., 2022; Weinstock et al., 2021). Additionally, it is noteworthy that longitudinal SRB trajectories of some neuropsychological tests used in MS cognitive batteries have been published already in 2009 (Attix et al., 2009).

Both, the anchor-based (e.g., 4-points clinically meaningful change) and the distribution-based approaches (i.e., RCI/SRB), come with advantages and disadvantages. Sound practice reflects their combination. The anchor-based approach, e.g., the 4-point meaningful decline in the SDMT total score, is a valid and useful observation showing the ecological validity; however, such criteria are derived from large-sample studies which naturally suppress the variance connected with random errors of measurement. With the assumption that the random error of measurement is always present in the individual assessment (Heilbronner et al., 2010; Lord & Novick, 1968), this criterium tells us what the hypothetically meaningful change in an ideal situation without any measurement errors is, but such ideal measurement cannot be practically achieved in clinical practice (or in any real-world situation). Also, anchor-based cut-offs are valid only in the connection with the criterium used, for example related to employment status deterioration or related to MS relapse. It is always a matter of clinical decision whether it is the valid criterium of change which can be generalized to the individual situation. Most importantly, very often we are not able to derive such a criterium: In the field of MS, the clinically meaningful change criterium has been derived until now only for a single test – SDMT (S. A. Morrow et al., 2010). Finally, the criterium we use should try to follow the theoretical framework of cognitive deterioration for the given test / cognitive domain / cognitive phenotype. This principle should be emphasized especially in connection with the recommended percentage change criterium, i.e., 10% decline in the SDMT (R. H. Benedict et al., 2017; Kalb et al., 2018). Such a criterion is intuitive but highly influenced by the mathematical functioning of the percentage score, which is dependent on the initial value entered. This practically means that for a person with above-average performance (e.g., SDMT total score = 90) the clinically meaningful change of 10% is much larger (i.e., 9 points decline) than for a person with a below-

[1] There are various online calculators which makes the process easy even for people unfamiliar with the necessary equations, e.g. the psychometric calculator PsychoCalc (https://begavett.shinyapps.io/PsychoCalc/), based on Hinton-Bayre's (2010) RCI overview.

average performance (e.g., SDMT total score = 30). In such a person, the clinically meaningful decline would be only 3 points on SDMT. We lack data that such a mathematical approach based on percentage change would be ecologically valid and would follow our theoretical understanding of cognitive decline. From my perspective, it seems highly unlikely.

The answer to some of the shortcomings of anchor-based approaches might be sought in distribution-based approaches. These approaches are in the field of clinical neuropsychology represented mainly by RCI and SRB (Heilbronner et al., 2010). These approaches are not new and in various forms have been used for decades: The two classics that introduced methods connected with RCI were written by Harold Gulliksen in 1950 (Gulliksen, 2013) and by Lord & Novick (1968), who extended and revised Gulliksen's work. In the Czech language, these two classics were recently reminded and presented by Cígler & Šmíra (2015). More recent overviews or methodological papers on RCI or SRB were published by Hinton-Bayre (2010), Chelune et al. (1993), or Maassen et al. (2009). There are various approaches to RCI to choose from; the most commonly used are those described by Jacobsen & Truax (1991), by Iverson (2001), or classically by Gulliksen, Lord & Novick (Gulliksen, 2013; Hsu, 1995; Lord & Novick, 1968). The recently published papers on RCI in MS (L. B. Strober et al., 2022; Weinstock et al., 2021) used the RCI approaches proposed by Jacobsen & Truax (1991) and Iverson (2001). Strober et al. (2022) also provided data on SRB. These two recent articles suggested the range between 8 and 12 points as a reliable change in SDMT scores (L. B. Strober et al., 2022; Weinstock et al., 2021). However, these findings cannot be generalized and the RCI/SRB should always be calculated individually, as it depends on the distribution and confidence interval applied.

The main assumptions of both RCI and SRB stem from the CTT. SRB is a bit newer and more precise approach derived from the research on functioning of a test in a repetitive examination; it uses normative longitudinal trajectories. Based on such normative longitudinal data, the approach proposes regression formulas with which we can calculate the probability of the observed score change compared to the normative longitudinal trajectories, with various covariates included and controlled for in the equation. The approach is well described by Maassen, Bossema, & Brand (2009). For the use in MS population it was introduced by Strober et al. (2022).

The RCI is a more classical approach, based on the following CTT assumptions (Gulliksen, 2013; Lord & Novick, 1968): 1) The observed score consists of the true score we want to measure and of a random error; 2) If the variables are normally distributed, the same applies for their variances; 3) The true score variance (reliability) is then defined as being equal to the covariance between parallel measurements; 4) This means that the error score variance is equal to the product of the observed score variance and one minus the correlation between parallel measurements. This can be mathematically expressed as Formula 1, which represents the concept of the Standard Error of Measurement (SEM), as is commonly applied in psychological measurement practice (Gulliksen, 2013; Lord & Novick, 1968). In Formula 1 σ_e represents SEM, σ_x represents the standard deviation observed, and r_{xx} represents the reliability index.

$$\sigma_e = \sigma_x \sqrt{1 - r_{xx'}} \quad \textbf{(1)}$$

Although there are many variants of the RCI approach, the basic RCI formula can be simplified to Formula 2, where the observed change between two measurements for the person *i* at the baseline *X* and at the follow-up *Y* is corrected for the test-retest effects *P*, according to the chosen method (some authors use a basic correction as proposed in this formula, others suggest replacing the baseline total score by a true score estimate based on knowledge of a populational mean). This result is then divided by SEM (adapted for the two measurement scenario), usually with confidence interval constructed around it (in this example multiplied by a z-score corresponding to the confidence interval chosen). Again, there are various approaches to the calculation of SEM in the two measurement scenario, e.g. some authors choose to use the so-called Standard Error of Difference (Iverson, 2001), others use the Standard Error of Prediction (Lord & Novick, 1968), with many other approaches unmentioned as it is out of the scope of this paper (see Hinton-Bayre, 2010). In a case the RCI index is greater than 1, it represents a reliable change in scores. The change in the score represented by the RCI index of less than 1 is probably produced by a random error of measurement. Please note that Formula 2 is simplified for illustration purposes only, it should not be used for real calculations. For this purpose, choose one of the existing RCI methodologies (e.g., Hinton-Bayre, 2010; Iverson, 2001; Jacobson & Truax, 1991; Lord & Novick, 1968)

$$RCI = \frac{\left(Y_i - X_i\right) - P_i}{SEM \times (\pm z)} \quad \textbf{(2)}$$

Even this approach has several disadvantages. When we compare the reliable change of 8 to 12 points on the SDMT (L. B. Strober et al., 2022; Weinstock et al., 2021) with the clinically meaningful change of 4 points (S. A. Morrow et al., 2010), we need to conclude that the RCI/SRB sensitivity in the detection of cognitive decline is low; it is highly likely that it produces many false negative observations. However, the specificity will be acceptable and depending on the confidence interval applied. It can be concluded that RCI is a clinically conservative criterion. In this matter, SRB will be a little bit more precise choice, but still rather conservative. Another, and more important, disadvantage is the fact that the result is directly dependable on the information on distribution (e.g., on reliability, variance, normative mean, etc.) we input in the equation. This might be accurate for individuals with average performance but can be skewed for individuals with extreme performance at the edges of the distribution, or for persons whose performance does not follow the norm, whatever the cause might be. The good news is that we can always do research on test performance in people with extreme (low or high) outcomes, although it might be a lengthy approach and often methodologically challenging. But it is completely in line with the recommendation for good practice in serial neuropsychological assessment: *"'Neuropsychologists remain up-to-date on research addressing test–retest effects."* and: *"Consideration may be given to (…) empirical findings on the expected magnitudes of score increases over a particular interval, or other relevant research on test operating characteristics for the instruments employed in the neuropsychologist's battery'* (Heilbronner et al., 2010).

1.2.6 Treatment

The most discussed approaches to the treatment of cognitive impairment in MS are: 1) DMD treatment, 2) restorative cognitive training, and 3) compensatory techniques of cognitive rehabilitation. The fourth option, the treatment of comorbidities related to cognitive deterioration (i.e., mainly depression and anxiety), is also an important approach, but usually overlooked.

In previous sections I have already discussed the promises of DMD treatment in stopping or slowing cognitive deterioration (Harel et al., 2019; Landmeyer et al., 2020; Weinstock-Guttman et al., 2018), with the drawback of insufficient research background to make evidence-based decisions about treatment change due to cognitive decline at the individual level (Amato, 2018; Amato & Krupp, 2020; R. H. B. Benedict et al., 2020; Portaccio, 2018). Although it is probable that the modern treatment aids also cognition, neuropsychological monitoring is going to stay, at the best, as an auxiliary marker of a recommended treatment change at this moment.

The other two popular approaches to the treatment of cognitive impairment in MS are cognitive rehabilitation. These include restorative techniques aimed at improving deteriorated cognitive functions and compensatory techniques which try to set up compensatory strategies to help the patient with his or her tasks affected by decreased cognitive functioning (R. H. B. Benedict et al., 2020; Chen, Chiaravalloti, & Deluca, 2021).

Restorative techniques are most frequently represented by various methods of cognitive training / remediation, very often based on computerized training programs (Chen et al., 2021), such as RehaCom, Attention Process Training III (APT-III), or in Czechia distributed Happy Neuron or Mentem.cz. These programs focus on almost all cognitive domains related to cognitive impairment due to MS. Furthermore, in recent years, virtual reality (VR) remediation programs have gained attention (Plechatá et al., 2021). Restorative rehabilitation techniques can also apply non-computerized 'real-world' cognitively stimulating activities such as music therapy (Impellizzeri et al., 2020), exercise / physical activities (Sandroff, Motl, Scudder, & Deluca, 2016), or can be combined with psychotherapy (Martínez-González & Piqueras, 2015).

Regarding restorative methods of cognitive rehabilitation, the often-discussed issue of such techniques is the generalizability of results outside of the program/assessment environment. In recent years, many new methodologically well-designed randomized studies have appeared and supported the effects of computerized cognitive training in MS. A recent metanalysis included 20 randomized control trials and found an overall moderate effect size of computerized cognitive training on key cognitive domains in MS (i.e., attention, information processing speed, executive functions, verbal and visuospatial memory. However, the evidence for working memory, fatigue, and psychosocial and daily functioning was ambiguous; and most importantly, the cognitive effects waned without further training (Lampit et al., 2019). This might suggest that the transfer of such programs to daily living might be limited; however, this topic needs further research attention, studies aimed at diverse populations over longer periods of time, to find out who might benefit from such programs the most (Lampit et al., 2019). For example, it has been suggested that people with low white matter destruction and high cognitive reserve might benefit from cognitive training more than people with more advanced MS and low cognitive reserve (Fuchs et al., 2020). However, cognitive trainings for people with

progressive variants of MS are also tested, although with inconclusive results (Janssen, Boster, Lee, Patterson, & Prakash, 2015; Messinis et al., 2020).

From a subjective perspective, cognitive training seems to work. The patients' perspective summarized in qualitative studies is generally positive, with patients reporting that they benefited from such programs in various ways (Klein, Drummond, Mhizha-Murira, Mansford, & Das Nair, 2019). The basic assumption about the functioning of such training programs stems from the theory of the protective factor of cognitive reserve in cognition, against the burden of MS disease (Chiaravalloti, Genova, & DeLuca, 2015; Sumowski & Leavitt, 2013; Sumowski et al., 2014), with theoretical explanation of this framework in concepts of *neural reserve* and *neural compensation* (Stern, 2005). However, as has been explained above, it is still questionable whether such computerized training programs can individually support increase in cognitive reserve associated capabilities in a long-term perspective. The emphasis on combination of training with other activities such as psychotherapy or physical activity and the extreme emphasis on ecological validity and maximum individualization of the cognitive training seem to be promising approaches to restorative cognitive training, with the promise of potentially high ecological validity and longer maintenance of the results (Martínez-González & Piqueras, 2015).

Although it does not have the promising restorative potential, compensatory strategies for cognitive rehabilitation also have a huge impact on the quality of life of MS patients. These approaches emphasize behavioral therapies that should provide people with skills needed to compensate for cognitive deterioration. Such strategies include complex approaches with elaborated methodologies such as the modified Story Memory Technique (Chiaravalloti, Moore, Nikelshpur, & Deluca, 2013), but also include various well-established therapeutically recommended strategies such as different kinds of internal or external aids, mnemonics, mental reviews, mental imagery, goal attainment trainings, attention-focus techniques or self-generated learning techniques (R. H. B. Benedict et al., 2020; Mousavi, Zare, Etemadifar, & Taher Neshatdoost, 2018).

The last option of a possible treatment of cognitive impairment in MS stands a little bit aside. It emphasizes the possibility that cognitive deterioration is not always a direct consequence of neuronal degeneration due to MS, but a symptom of another comorbidity. Treatment of such a comorbidity could possibly ease the deterioration in cognition (V. M. Leavitt et al., 2020; Whitehouse et al., 2019). This could be the case particularly in depression and other affective disorders that show a much higher prevalence in MS patients than in the general population (Boeschoten et al., 2017; Anthony Feinstein, 2011; A. Feinstein, Magalhaes, Richard, Audet, & Moore, 2014). However, reports on the effects of depression on cognitive functioning are contradictory (Lezak et al., 2012). In MS, depression and other affective disorders have been shown to be related to objective cognitive functioning (Peter A. Arnett, Higginson, Voss, Bender, et al., 1999; Peter A. Arnett, Higginson, Voss, Wright, et al., 1999; Sarah A. Morrow, Rosehart, & Pantazopoulos, 2016; Whitehouse et al., 2019). On the other hand, quite commonly, research has also shown that depression manifests itself only in subjective cognitive functioning and that objective cognitive functioning seems to be unrelated to depressive symptoms in MS (D'Hooghe et al., 2020; Kinsinger, Lattie, & Mohr, 2010; Pravatà et al., 2017). These contradictory observations could be explained by the severity of depression: only patients with vegetative symptoms showed impaired cognition, contradictory to patients with psychological depressive symptomatology (Palmer et al., 1996); but it could also be also explained by more complex changes in cognition: people with depression showed worsened memory, but especially to emotionally positive stimuli, and not to neutral or

negative stimuli (Burt, Zembar, & Niederehe, 1995); or potentially the changes in cognition and depression can just cooccur, having different neuronal substrates (Pravatà et al., 2017). In this matter, an interesting finding was presented by Julian, Merluzzi & Mohr (2007) who showed that in responders to depression treatment (by antidepressants or psychotherapy) the subjective cognitive deterioration was driven by the objective cognitive performance, whereas in non-responders to depression treatment the subjective cognitive impairment was best explained by the depressive symptomatology (Julian et al., 2007). In summary, both groups (i.e., patients with depression or cognitive impairment) are heterogeneous and the findings cannot be generalized. However, there are suggestions that the treatment of depression could improve cognitive functioning in some of the patients or at least improve their subjective cognitive functioning and therefore quality of life. Future research needs to look at the mechanism of the complex mood-cognition interrelationship in MS and clarify these connections in a global perspective, and also taking into account the differences between the primary and secondary depressive symptomatology.

The field of MS-related cognitive treatment starts to produce promising research findings, showing the perspective of improved quality of life in people suffering from cognitive deterioration. However, the spectrum of symptoms, possible causes, and solutions is so heterogeneous that it is impossible to provide easy methodologies or solutions. Any treatment of cognitive impairment in MS should be highly individualized.

2. AIMS AND HYPOTHESES

The first main aim of this thesis is to describe the subgroup of people with MS who show signs of cognitive deterioration without corresponding MS activity, as measured by standard disease activity markers such as MS relapses or EDSS worsening; so called isolated cognitive relapses or isolated cognitive decline.

This thesis aims to describe the prevalence of such isolated cognitive decline, monitor cognitive outcomes in people with MS experiencing cognitive deterioration, and put isolated cognitive decline in context with current knowledge on disease progression. The thesis will compare the course of MS of patients with isolated cognitive decline with patients who show signs of disease activity on standard neurological or radiological progression markers of MS.

As a second objective, the thesis aims to identify or standardize methods that can improve the quality of the diagnostic process of cognitive deterioration in MS and isolated cognitive decline.

Supplementary to the main two topics, with its third aim, the thesis will explore several topics highly interconnected with cognitive deterioration: the concept of subjective cognitive decline, the workability of MS patients, and volumetric MRI markers that can predict future cognitive deterioration.

Furthermore, with its fourth aim, the thesis will evaluate compensatory and rehabilitation strategies used to cope with cognitive deterioration in MS (e.g., neurorehabilitation, cognitive training, influence of the patient's environment, or his/her daily life activities, on cognitive deterioration).

This thesis has three main hypotheses:

1. People with MS experience isolated cognitive decline throughout their disease course.
2. Isolated cognitive decline is a phenomenon related to disease activity, particularly to structural neuronal changes due to MS, and therefore should be accompanied by the radiological activity of the disease.
3. Neuropsychological assessment could provide, through the concept of isolated cognitive decline, novel insights into disease activity that would be missed by conventional monitoring techniques.

Study 1: *Isolated Cognitive Decline in Neurologically Stable Patients with Multiple Sclerosis*
[2020 Clarivate IF: 3.706]

This study covers the main aim of this thesis. It provides information on the prevalence of isolated cognitive decline in MS, its correlates, predictors, and describes in detail the population of people with MS experiencing isolated cognitive decline. The study is based on 3-year longitudinal data from the Grant Quantitative (GQ) study.

Study 2: *The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years*

[2020 Clarivate IF: 4.339]

This study investigated the relationship between early neurofilament levels and cognitive performance after 9-years. The relationship was weak; neurofilament levels at the beginning of the disease are not a very promising predictor of future cognitive performance. This article covers the second and third aim of this thesis, the intended identification of methods that can improve the quality of the diagnostic process of cognitive deterioration in MS, and the intended research on topics that might be highly interconnected with cognitive deterioration in MS.

Study 3: *Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study*

[2020 Clarivate IF: 1.961]

This study elaborates on the second and third objectives of this thesis. It describes a very interesting relationship between a slowed articulation rate and a slowed information processing speed in people with MS. It postulates the question of whether the cognitive outcome measures of information processing speed could be influenced by motor symptoms such as slowed articulation rate.

Study 4: *Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients*

[2020 Clarivate IF: 3.181]

This study looked in detail at one of the topics highly interconnected with cognitive impairment due to MS: the employment status of people with MS and its possible loss due to the burden of the disease. Using Cox proportional-hazard models on the 12-year longitudinal data from the ASA study, we identified baseline brain atrophy and lesion load as significant predictors of worsening employment status in MS patients after 12-years of follow-up.

Study 5: *A Pilot Study of Applicability of a New Program for Cognitive Rehabilitation in Persons with Multiple Sclerosis*

[2020 Clarivate IF: N/A]

This feasibility study with its pilot test of a 6-weeks long cognitive rehabilitation tablet-based program covered the fourth supplementary goal of the thesis – the evaluation of compensatory and rehabilitation strategies of cognitive impairment in MS. The program was found to be suitable for further research and use in the MS population. However, the design of the feasibility study did not allow us to independently evaluate its benefits for the treatment of cognitive impairment in MS.

Study 6: *Brain MRI disease burden does not explain sex differences in cognitive performance of patients with multiple sclerosis*

[Submitted to *Multiple Sclerosis and Related Disorders* (Submission ID: MSARD-S-22-00401)]

This study has not yet been published. The submitted research paper is based on data from the Grant Quantitative (GQ) study. The second and third objectives of this thesis are elaborated. The article explores

sex differences in cognitive performance among the MS population. We specifically examined whether the observed sex differences in cognitive performance might be partially explained by brain MRI measures. It seems that the sex differences are independent of the disease burden, thus MS does not deepen the sex differences in cognitive performance observed already in healthy cohorts. Additionally, we found that subjective cognitive performance is not related to objective performance, but to affective symptoms.

3. METHODS

The following studies presented in the results section of this thesis are based on data collected in the Department of Neurology and the Center of Clinical Neuroscience of the General University Hospital in Prague and the 1st Faculty of Medicine of Charles University in Prague. The samples in the following studies consist mostly of MS patients or healthy volunteers who participated in projects carried out at the MS center of the Department of Neurology.

The studies presented in the results section followed various methodological approaches and analyzed diverse datasets based on various research projects from different periods of time. Therefore, the methodology of each study is briefly presented in the results section as part of the study summary.

4. RESULTS

The results section summarizes findings from six original research papers. The presentation of results is accompanied by a short summary of the objectives and methods applied in the presented articles.

4.1 Study 1

Motyl, J., Friedova, L., Vaneckova, M., Krasensky, J., Lorincz, B., Blahova Dusankova, J., Andelova, M., Fuchs, T. A., Kubala Havrdova, E., Benedict, R. H. B., Horakova, D., & Uher, T. (2021). Isolated Cognitive Decline in Neurologically Stable Patients with Multiple Sclerosis. *Diagnostics, 11*(3), 464.

4.1.1 Aim

The purpose of this study was to investigate the proportion of MS patients with isolated cognitive decline. The secondary objective was to describe the characteristics of patients with an increased risk of isolated cognitive decline. These goals stem from previous work on isolated cognitive relapses (Meli et al., 2020; Matteo Pardini, 2021; M. Pardini et al., 2014) and from the recommended annual screening of cognitive functions in people with MS (Kalb et al., 2018). The objective was to provide new information on annual cognitive screening, to show its possible benefits in everyday clinical practice.

4.1.2 Methods

This study investigated a large sample (N=1091) of MS patients from the Grant Quantitative (GQ) study (T. Uher et al., 2018; T. Uher, Vaneckova, Sormani, et al., 2017) over a two-year follow-up, revisiting older observational data collected between 2012 and 2015. The main analysis included 1091 participants with available data on EDSS, relapses, demographic information, and SDMT test performed at the beginning of the study and at the follow-up time point after one year. Additionally, the confirmatory analysis was conducted in the second year of follow-up.

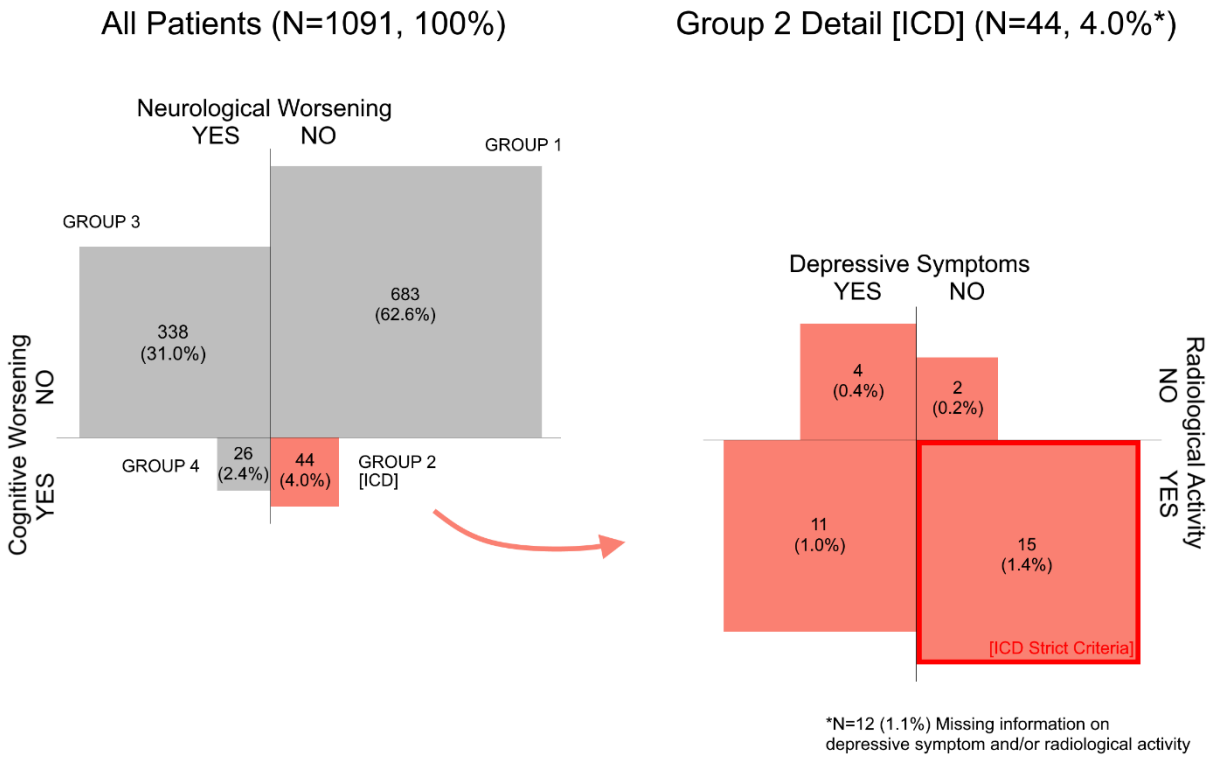
Based on an annual evaluation of the change in SDMT [Lord-Novick RCI (Lord & Novick, 1968)] and the neurological activity of the disease (EDSS worsening, new relapses), we divided our sample into four groups: Group 1: Both neurologically and cognitively stable, Group 2: Neurologically stable but cognitively worsening, Group 3: Cognitively stable but neurologically worsening, Group 4: Both neurologically and cognitively worsening over the one-year follow-up. Co-occurring MRI activity and depressive symptoms were analyzed.

We tested group differences (using the One-Way ANOVA (Fischer), Kruskal-Wallis H test, and the Chi-squared test), we evaluated predictors of isolated cognitive decline within the neurologically stable group (by binomial logistic regression with Group 1 and Group 2 used as dependent variables).

4.1.3 Results

Overall, 6.4% of MS patients experienced cognitive decline during 1-year follow-up (decline in SDMT test) and 4.0% experienced isolated cognitive decline without the corresponding clinical activity (see Figure 4.1). The vast majority of cognitively worsening patients showed concomitant progression in other neurological and radiological measures: only in 6 patients (i.e., 0.6% of the total sample) the isolated cognitive decline without corresponding radiological activity was observed. The results were confirmed in the confirmatory analysis with 7.3% of patients cognitively declining and 4.7% experiencing isolated cognitive decline in the second year of follow-up.

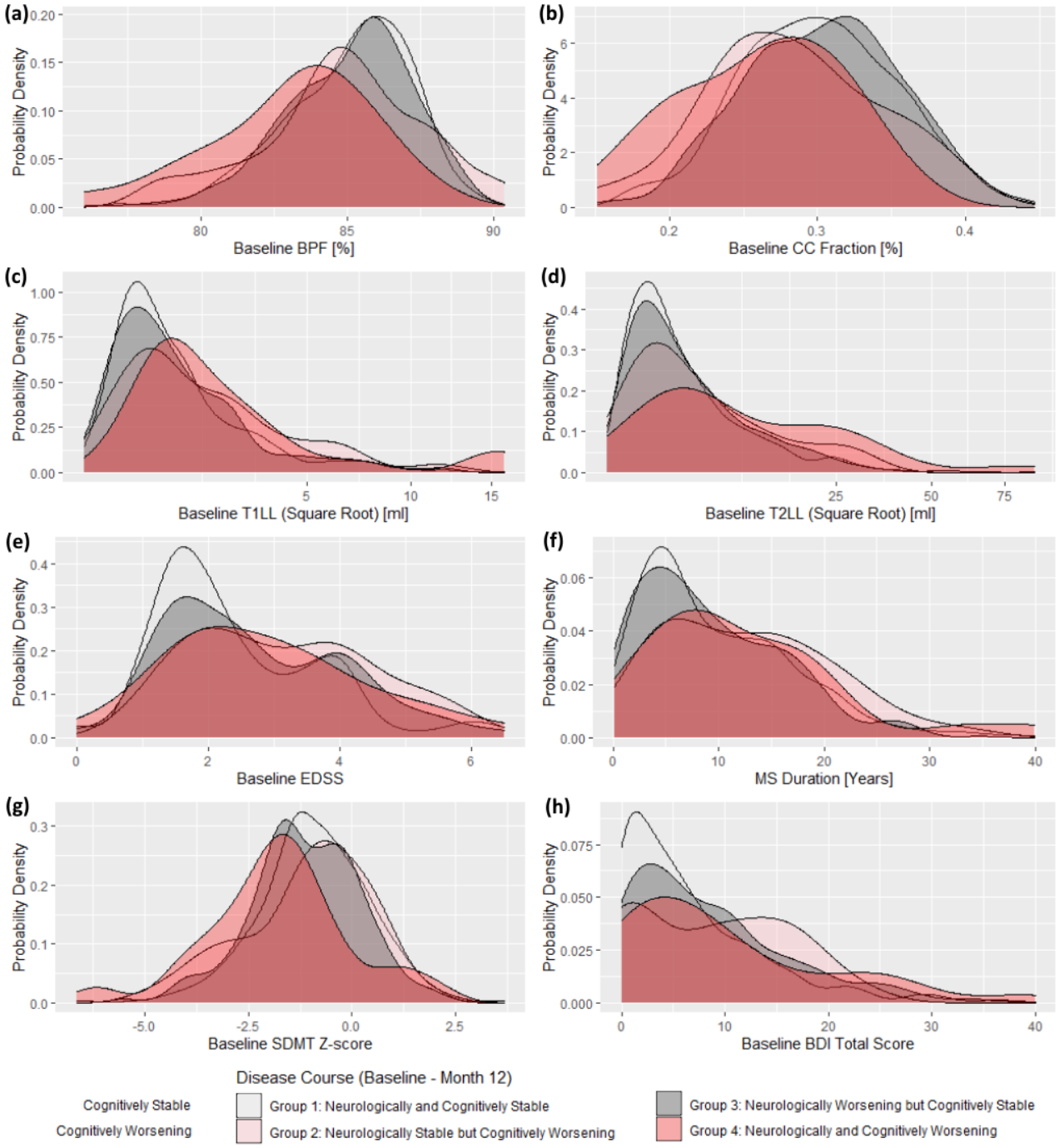
FIGURE 4.1: NEUROPSYCHOLOGICAL AND NEUROLOGICAL EVALUATION BETWEEN BASELINE AND MONTH 12.



Regarding group differences, cognitively worsening groups showed a trend to score worse than cognitively stable groups on a majority of important baseline cross-sectional disease severity markers, such as higher baseline T1 and T2 lesion load, lower BPF and lower corpus callosum fraction scores (see Figure 4.2). Additional analysis of patients without cognitive impairment at baseline revealed no differences in disease severity between completely stable patients and patients with cognitive worsening (with normal baseline cognitive performance). To put it in brief, we found that the differences between cognitively worsening and cognitively stable groups are driven especially by patients who were already cognitively impaired at the start of the study (see Figure 4.3).

FIGURE 4.2: BETWEEN-GROUP DIFFERENCES IN BASELINE RADIOLOGICAL (A – D), NEUROLOGICAL (E, F), AND NEUROPSYCHOLOGICAL (G, H) SCORES SHOWED ON PROBABILITY DENSITY PLOTS

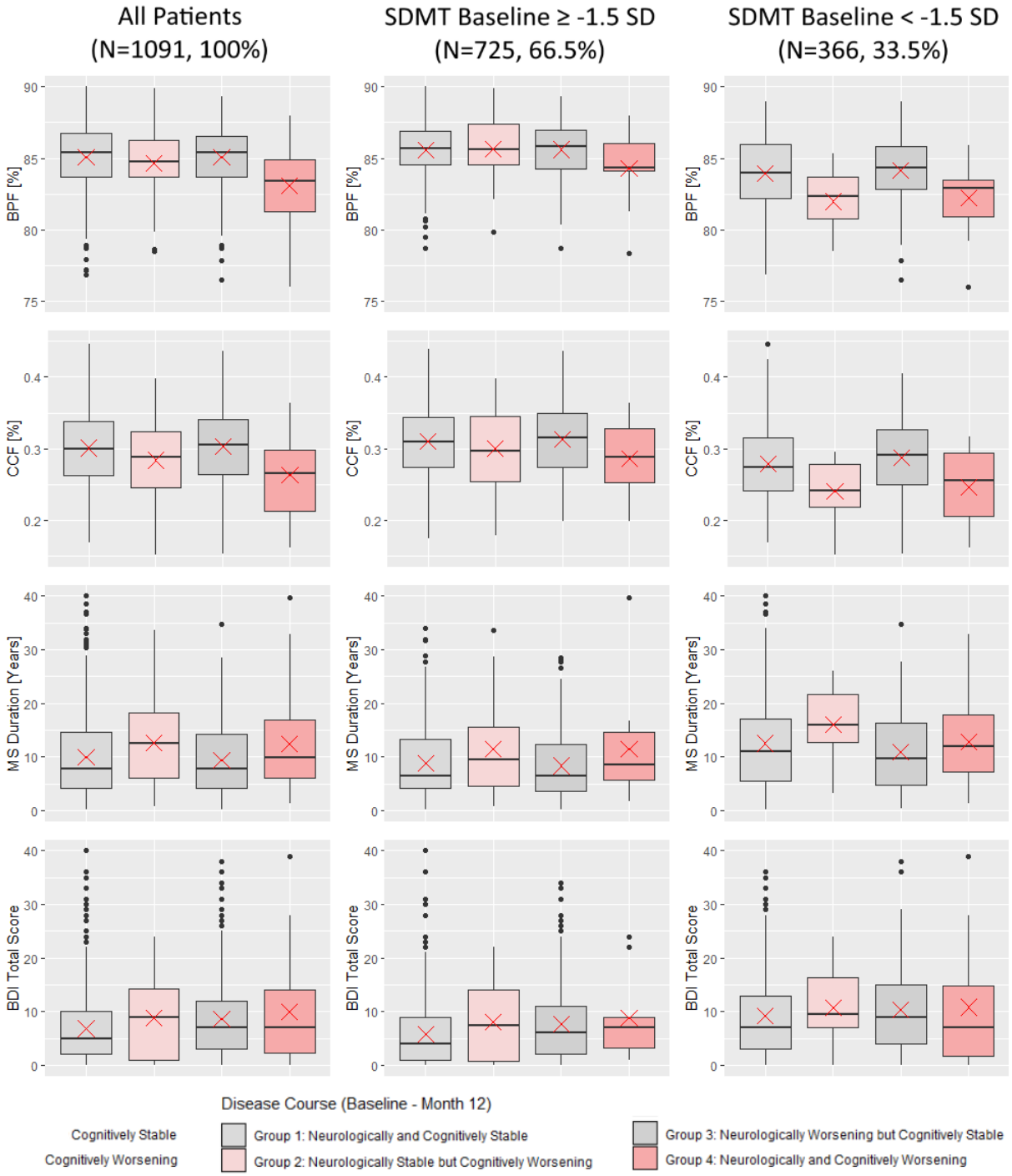
An example of the similar trend of worse baseline disease markers in both cognitively worsening groups (red), in contrast to both cognitively stable groups (grey).



Note: BPF = Brain parenchymal fraction, CC = Corpus callosum, T1LL = T1 Lesion Load, T2LL = T2 Lesion Load, EDSS = Expanded Disability Status Scale, SDMT = Symbol Digit Modalities Test, BDI = Beck Depression Inventory.

FIGURE 4.3: BETWEEN-GROUP DIFFERENCES IN BASELINE RADIOLOGICAL, NEUROLOGICAL, AND NEUROPSYCHOLOGICAL SCORES, DEPENDENT ON BASELINE STATE OF COGNITIVE PERFORMANCE

Left: All Patients; Middle: Population of patients with normal SDMT performance at baseline; Right: Patients with slowed tempo on SDMT at baseline.



Note: BPF = Brain parenchymal fraction, CCF = Corpus callosum fraction, BDI = Beck Depression Inventory. The red cross shows the mean value.

We did not find any strong baseline predictors of an upcoming cognitive decline (see Table 4.1). Differences between groups found in the primary analyses were caused mainly by people who were already cognitively impaired. The percentages of total variance explained by the investigated predictors were relatively low and the results were not confirmed in the confirmatory analysis.

TABLE 4.1: RESULTS OF BINARY LOGISTIC REGRESSION, MEMBERSHIP OF GROUP 1 AND GROUP 2 AS A DEPENDENT VARIABLE (BASELINE – MONTH 12)

	B (SE)	Odds Ratio	95% CI	p-value
Intercept	-21.067 (9.822)	7.09^{-10}	3.09^{-18}-0.163	0.032*
MS Duration	0.033 (0.027)	1.033	0.981-1.089	0.218
Baseline EDSS	0.336 (0.159)	1.399	1.026-1.909	0.034*
Baseline BPF	0.210 (0.115)	1.233	0.984-1.545	0.069
Baseline T1Lesion Volume (Square Root)	0.487 (0.360)	1.627	0.803-3.295	0.176
Baseline CCF	-4.125(4.170)	0.016	4.56^{-6}-57.311	0.323
Baseline SDMT Z-score	0.206 (0.154)	1.229	0.909-1.662	0.181

Note: BPF = Brain parenchymal fraction, CCF = corpus callosum fraction; R^2 = 0.022 (Cox & Snell), 0.062 (Nagelkerke), 0.051 (McFadden). Model χ^2 = 13.8(6), p = 0.032.
Predictors selected from the pool of variables that show meaningful differences (see Table 1), based on the results of Omnibus Likelihood Ration Test (p<0.7) and on the VIF statistics preventing collinearity issues.
** p < 0.05, ** p < 0.01, *** p < 0.001*

4.1.4 Manuscript Contribution

I designed and conducted the whole analysis. This also included cleaning up the previous dataset, clinical re-evaluation of the cognitive impairment in all patients using more precise improved normative dataset, and application of conservative clinical RCI methodology to assess the significance of annual cognitive change at the individual level (Cígler & Šmíra, 2015; Lord & Novick, 1968). Additionally, I also coordinated the evaluation of new or enlarged T2 lesions on MRI. And most importantly, I conducted the final statistical analysis, prepared the figures, and was the main author who wrote and finalized the manuscript.

4.2 Study 2

Friedova, L., **Motyl, J.**, Srpova, B., Oechtering, J., Barro, C., Vodehnalova, K., Andelova, M., Noskova, L., Fialova, L., Kubala Havrdova, E., Horakova, D., Benedict, R. H. B., Kuhle, J., & Uher, T. (2020). The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years. *Multiple sclerosis and related disorders*, *46*, 102534.

4.2.1 Aim

Previous research on the relationship between NfL (a new promising biomarker of disease activity in MS) and cognition was inconclusive. Therefore, the main objective of this study was to investigate the predictive value of NfL levels in newly diagnosed MS patients for the development of cognitive decline after long-term follow-up. The study was carried out with the aim of improving the early identification of patients at increased risk of cognitive decline. This topic is clinically highly relevant, because it might help identify patients who benefit from more intensive cognitive monitoring or from early high-efficacy DMD treatment.

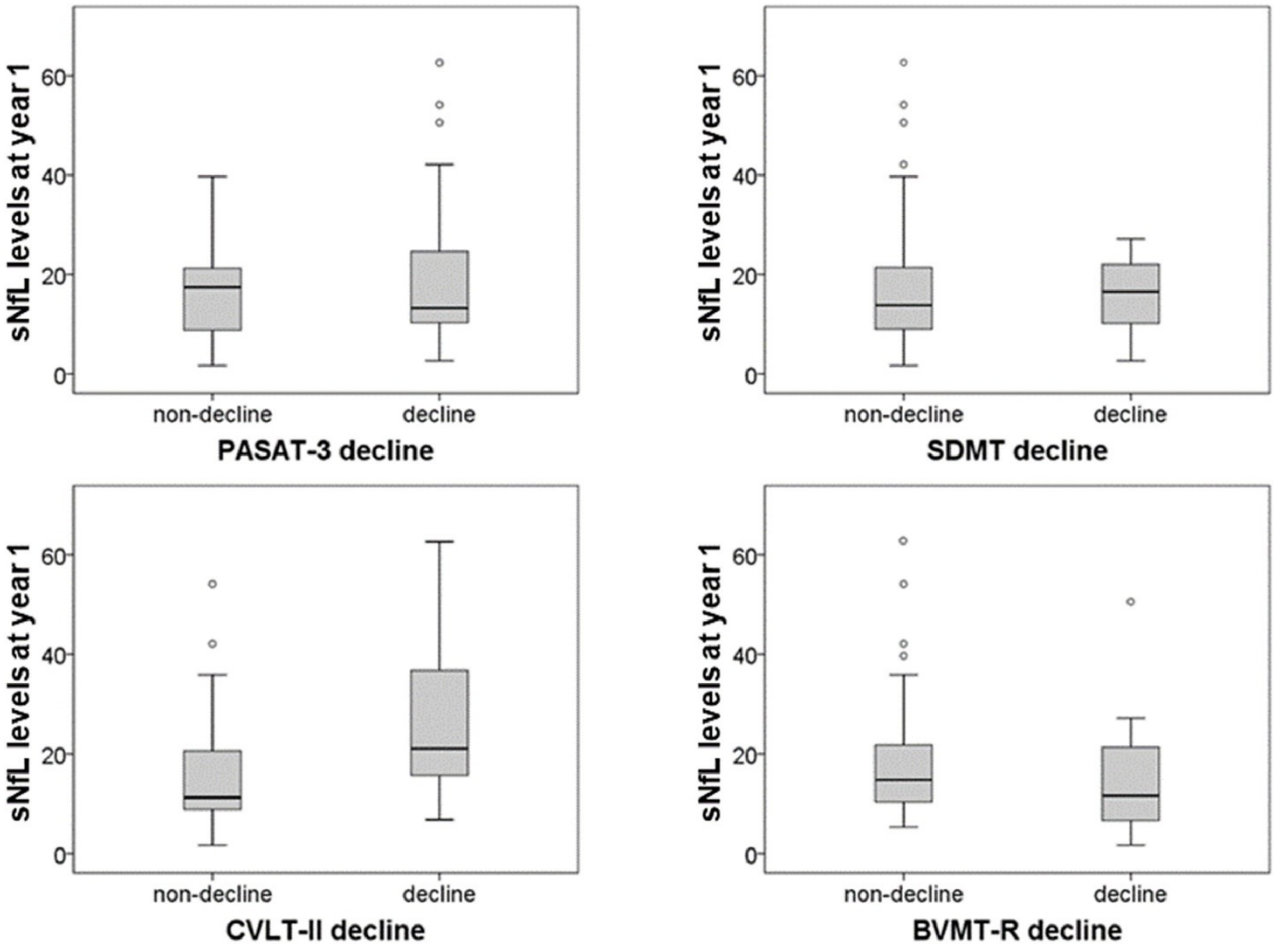
4.2.2 Methods

We analyzed 58 individuals from the total sample of 220 MS patients who participated in the SET study (Study of Early Interferon beta-1a Treatment) (Kalincik et al., 2012). The patients, originally diagnosed with CIS according to the McDonald 2005 criteria, were enrolled between October 2005 and July 2009. The 58 patients included in this study underwent a cognitive evaluation at all required timepoints (baseline, year 1, year 9) and had available analysis of neurofilament light chain levels in serum (sNfL) at year 1. The patients were neuropsychologically tested using the BICAMS battery and the PASAT test. We analyzed the association of cognition with average sNfL or CSF-NfL levels within the first 2 years. 1) Patients were divided into two groups using the 90th percentile cut-off as the definition of pathological sNfL levels; 2) Cognitive decline was defined as a categorical variable of the absence or presence of a decrease in a raw score of each neuropsychological test between baseline and follow-up. Logistic and linear regression measures were used to test the relationship between early pathological sNfL levels, early MRI outcomes, and cognitive outcomes after 9 years of follow-up.

4.2.3 Results

We did not observe associations among early neurofilament light chain levels in serum (sNfL) at the screening or in year 1 and cross-sectional or longitudinal cognitive measures (i.e., BICAMS and PASAT in year 1, 2, or 9) (see Figure 4.4). Additionally, we did not observe an association between average sNfL levels within the first 2 years of follow-up (with or without screening levels) and cross-sectional or longitudinal cognitive measures (in year 1, 2 a 9).

FIGURE 4.4: BOX PLOTS CORRESPONDING TO SNFL LEVELS IN YEAR 1 (PG/ML) STRATIFIED BY ABSOLUTE DECLINE IN COGNITIVE TESTS OVER THE 9 YEARS



Note: sNFL = neurofilament light chain levels in serum, PASAT-3 = Paced Auditory Serial Addition Task (3 seconds interval), SDMT = Symbol Digit Modalities Test, CVLT-II = California Verbal Learning Test, 2nd Edition, BVMT-R = Brief Visuospatial Memory Test Revised.

Reprinted from Multiple Sclerosis and Related Disorders, 46, Friedova, L., Motyl, J., Srpova, B., Oechtering, J., Barro, C., Vodehnalova, K., Andelova, M., Noskova, L., Fialova, L., Kubala Havrdova, E., Horakova, D., Benedict, R. H. B., Kuhle, J., & Uher, T., The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years, 102534, 2020, with permission from Elsevier.

There was an exception of a trend for the association between higher sNfL levels in the screening and lower CVLT-II scores in year 1 (rho = -0.31, unadjusted p = 0.028). sNfL levels above the 90th percentile in year 1 were associated with a greater risk of CVLT-II decline over 9 years compared to patients with lower sNfL levels [odds ratio (OR) 15.8; 95% CI 1.7–147.0; p = 0.015; q = 0.060 after the Benjami-Hochberg procedure]. We did not observe other relationships between sNfL levels in year 1 and the increased risk of cognitive decline in other neuropsychological tests over the 9 years follow-up. Furthermore, higher sNfL levels were not

associated with an increased risk of cognitive decline, defined as a composite measure (an average z-score of all cognitive tests). Similar trends were observed for CSF-NfL levels.

4.2.4 Manuscript Contribution

I was one of the two main investigators (together with Mgr. Lucie Friedová) who coordinated and collected neuropsychological (that is BICAMS, PASAT & PROs questionnaires) and other paraclinical measures (that is 25-FWT, 9-HPT) in the follow-up of the SET study between 2017 and 2018. This provided the basis for the longitudinal analysis in this article. Additionally, I was involved in the final manuscript editing and consulted the methodology how to approach the evaluation of cognitive decline in the manuscript.

4.3 Study 3

Friedova, L., Rusz, J., **Motyl, J.**, Srpova, B., Vodehnalova, K., Andelova, M., Novotna, K., Novotny, M., Ruzickova, H., Tykalova, T., Kubala Havrdova, E., Horakova, D., & Uher, T. (2019). Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study. *Journal of Clinical Neuroscience*, *65*, 28-33.

4.3.1 Aim

Impairment in information processing speed tests is relatively common among people with MS. Similarly, speech impairment is widespread in this population as well, but the relationship between speech and cognitive impairment has not been well described. Although, many of the neuropsychological tests used are speech-dependent. Our objective was to describe the relationship between articulation rate characteristics and information processing speed and to investigate the potential role of objective speech analysis for the detection of cognitive decline in MS.

4.3.2 Methods

Of the original 141 patients with MS (Rusz et al., 2018), 122 completed all necessary measures, including EDSS, speech, and neuropsychological examination (SDMT, PASAT, BDI-II). The average time between each examination was 6 ± 13 days. All patients were relapse-free for at least 30 days prior to testing.

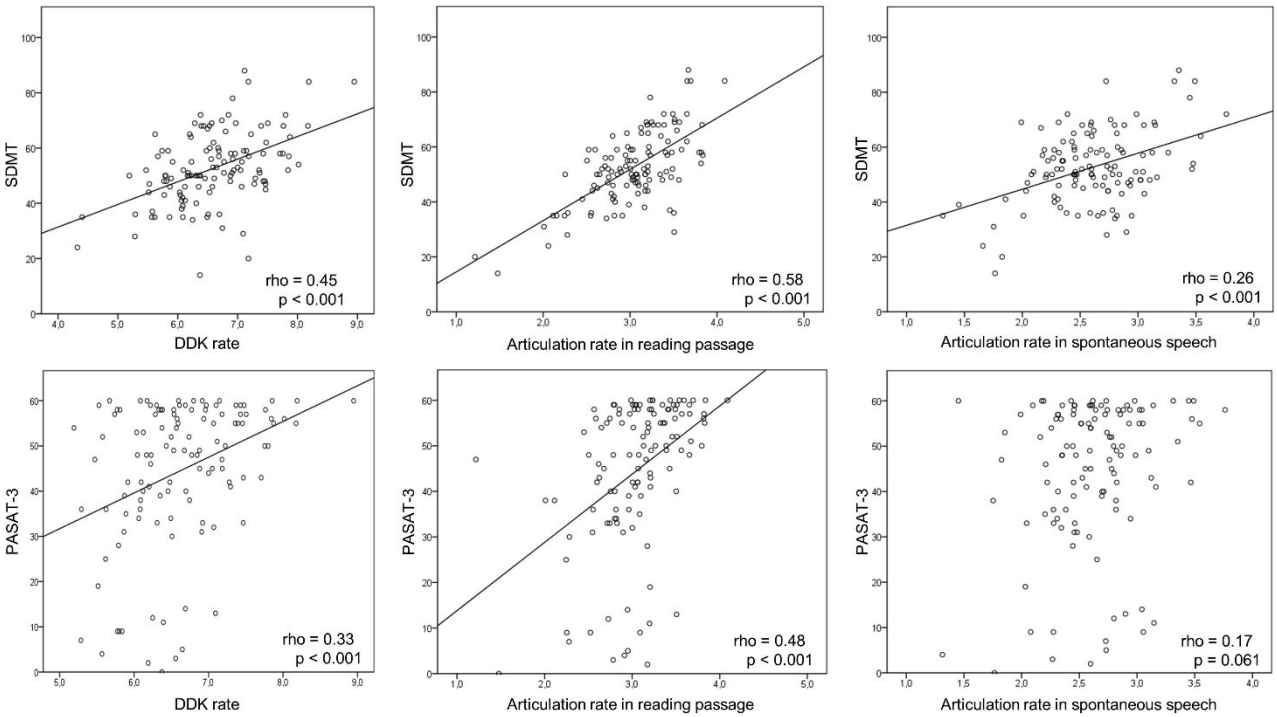
Acoustic articulation rate assessment consisted of the following tasks: tasks of 1) fast /pa/-/ta/-/ka/ syllable repetition at least seven times per one breath as steadily and accurately as possible (oral diadochokinesis), 2) reading a short paragraph of standardized text composed of 80 words, and 3) a monologue for approximately 90 s on a given topic (i.e., hobbies, job). Based on these three tasks, a quantitative acoustic vocal evaluation of speech dimensions related to diadochokinetic and articulatory rate characteristics was performed: 1) the diadochokinetic rate (DDK rate) was calculated as the number of syllable vocalizations per second; 2) the articulation rate in reading passage (ARR) and 3) articulation rate in spontaneous speech (ARS) was calculated as the number of words per second after removing periods of silence exceeding 60 ms.

The relationship between cognitive and speech characteristics was tested using Spearman's correlation. Additionally, linear regression analyzes were used to investigate the association between articulation and cognitive measures. The ROC curve (Receiver Operating Characteristics) was constructed and Area under the ROC Curve (AUC) was computed to assess the predictive accuracy of the articulation measures to detect abnormal information processing speed.

4.3.3 Results

A strong correlation was observed between the ARR and the SDMT (rho = 0.58, p < 0.001) and PASAT (rho = 0.48, p < 0.001) (see Figure 4.5). Additionally, slower DDK rates were found to be associated with a decrease in SDMT (rho = 0.45, p < 0.001) and PASAT (rho = 0.33, p < 0.001) scores. A weaker association was detected between ARS and SDMT (rho = 0.26, p < 0.001). However, in contrast, no relationship was observed between ARS and PASAT scores (rho = 0.17; p = 0.061).

FIGURE 4.5: ASSOCIATIONS BETWEEN ARTICULATION RATE CHARACTERISTICS AND INFORMATION PROCESSING SPEED



Note: DKK = diadochokinetic rate, SDMT = Symbol Digit Modalities Test, PASAT-3 = Paced Auditory Serial Addition Task (3-second interval).

Reprinted from Journal of Clinical Neuroscience, 65, Friedova, L., Rusz, J., Motyl, J., Srpova, B., Vodehnalova, K., Andelova, M., Novotna, K., Novotny, M., Ruzickova, H., Tykalova, T., Kubala Havrdova, E., Horakova, D., & Uher, T., Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study, 28-33, 2019, with permission from Elsevier.

If we compare all the speech metrics, ARR explained the most variance of SDMT (44%, $R^2 = 0.44$). In the model adjusted for sex, age, and DMD treatment status, the full model could explain 51% ($R^2 = 0.51$) of the variance in SDMT. An increase in ARR by one word per second would theoretically be associated with an increase in the total SDMT score by 18.66 points (95% CI 14.89–22.45) and the PASAT score by 14.66 points (95% CI 8.92–20.39).

Both ARR and DKK were found moderately suitable for discrimination between cognitively impaired and unimpaired patients (in information processing speed), with the AUC in DKK reaching 0.75 for SDMT and 0.75 for PASAT (0.77 for both measures combined), and with the AUC in ARR reaching 0.75 for SDMT and 0.78 for PASAT (0.79 for both measures combined). Cognitive impairment cut-off values for DKK rate (syllables/sec) in the range between < 6.7 and < 6.9, and for the ARR rate (words/sec) in the range between < 3.0 and < 3.2, were proposed and compared.

4.3.4 Manuscript Contribution

My main input to this article was in the statistical analysis section. I consulted the chosen approach to analysis, discussed the results from ROC and AUC analyses, and cooperated with the first author Mgr. Lucie Friedová on conclusions we drew based on the observed sensitivities and specificities of the automatic speech measurement methods. Finally, I was involved in the editing and proof-reading of the manuscript.

4.4 Study 4

Kadrnozkova, L., Vaneckova, M., Sobisek, L., Benova, B., Kucerova, K., **Motyl, J.**, Andelova, M., Novotna, K., Lizrova Preiningerova, J., Krasensky, J., Havrdova, E., Horakova, D., & Uher, T. (2018). Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients. *Journal of the neurological sciences, 388*, 87-93.

4.4.1 Aim

Cognitive performance decline is known to be related to a worsening employment status due to MS (R. H. Benedict et al., 2005; S. M. Rao, Leo, Ellington, et al., 1991; Aurélie Ruet et al., 2013; L. Strober et al., 2014), but reliable predictors of employment status change are lacking. Also, MS is frequently diagnosed in the most productive years of adulthood and therefore changes in cognition and employment status are perceived as even more destructive. The aim of this study was to identify early clinical and MRI markers of worsening employment status in MS patients at 12-year follow-up.

4.4.2 Methods

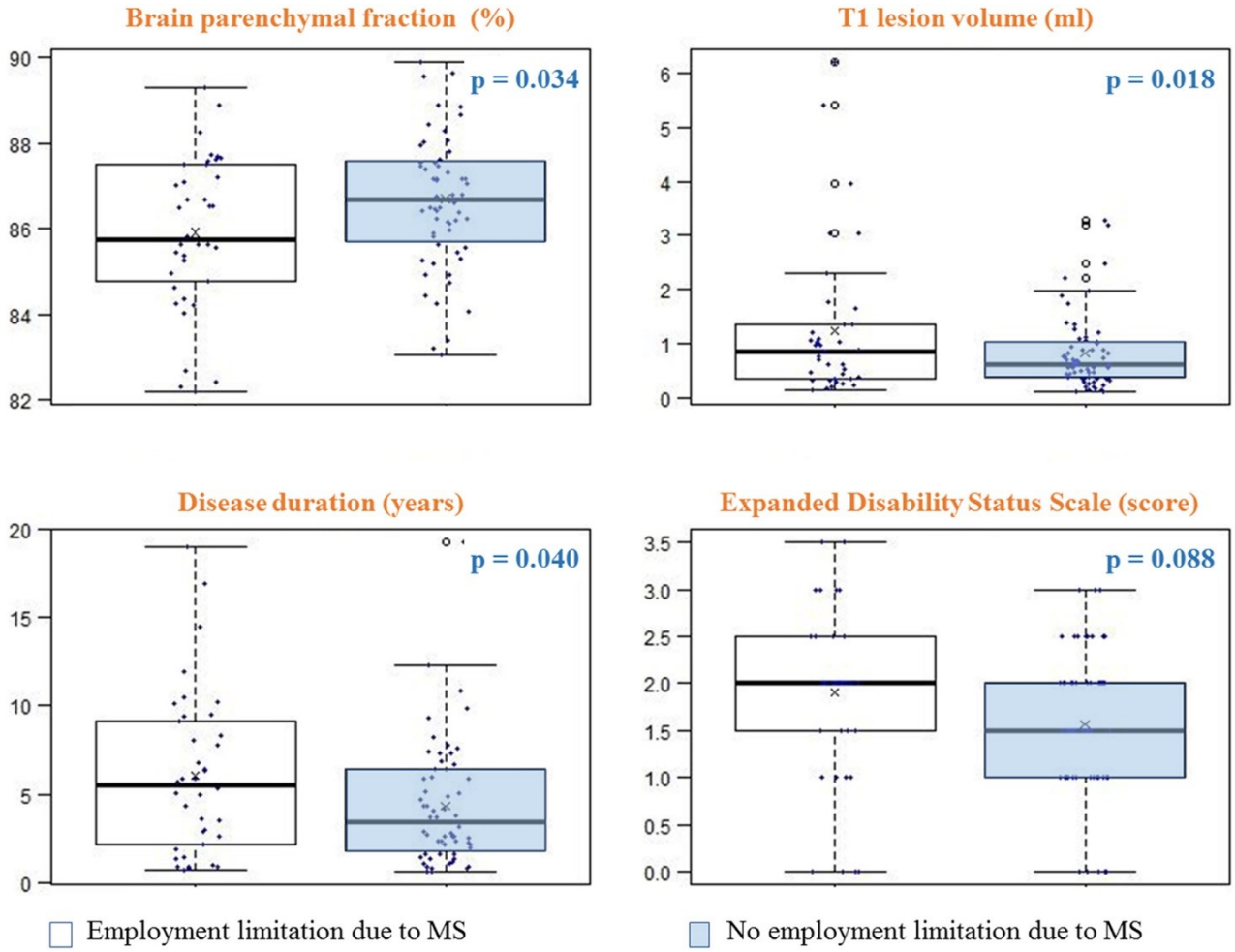
A total of 145 patients with MS, of the originally 181 patients enrolled in 1999 in the Avonex-Steroids-Azathioprine (ASA) study (E Havrdova et al., 2009), were included in this analysis. These patients had all the necessary longitudinal follow-up data (complete 12-year clinical, MRI, and employment monitoring) and did not show any signs of comorbidity or worsening employment status due to other reason than MS. Employment status and hours worked were monitored during regular clinical examinations (every 3 months) for 12 years. For the current analysis the employment status of patients was divided into 4 groups: 1) No employment limitation due to MS, 2) Employment limitation due to MS, 3) Employment limitation due to other reason (e.g., caregiver), 4) Employment limitation due to significant comorbid condition. The outcome of this study was the worsening of the employment status over the 12-year follow-up, defined as a transition from the first category to the second category. Cox proportional hazard models were used to find associations between predictors at baseline or at 12 months, and a worsening employment status during the 12-year follow-up period.

4.4.3 Results

After 12 years of follow-up, 60 (41%) patients worked full-time without limitation due to MS, a total of 71 (49%) were unemployed or worked part-time due to MS, and 14 patients (10%) were unemployed or worked part-time due to another reason (e.g., caregiver). At 12-year follow-up, only 60 patients who worked without limitations due to MS at baseline maintained full ability to work. 38 patients changed their working status to unemployed or working part-time due to MS.

The duration of the disease was the only baseline clinical predictor of the worsening of employment status over 12 years [HR = 1.10, 95% confidence interval (95% CI) 1.03–1.18; Nagelkerke's R^2 = 0.06; p = 0.040]. The EDSS score and the annualized rate of relapse during the first 12 months were not significant predictors of the worsening of the employment status. When we also consider baseline MRI parameters, both the higher T1 lesion load (HR = 1.53, 95% CI 1.16–2.02; R^2 = 0.07; p = 0.018), and the higher T2 lesion load (HR = 1.09, 95% CI 1.02–1.17; R^2 = 0.05; p = 0.034), plus the lower BPF (HR = 0.78, 95% CI 0.65–0.95; R^2 = 0.06; p = 0.034) were significant individual predictors of the worsening of employment status after 12 years of follow-up (see Figure 4.6).

FIGURE 4.6: BEST INDIVIDUAL BASELINE PREDICTORS OF EMPLOYMENT STATUS WORSENING AFTER 12 YEARS OF FOLLOW-UP



Reprinted from Journal of Neurological Sciences, 399, Kadrnozkova, L., Vaneckova, M., Sobisek, L., Benova, B., Kucerova, K., Motyl, J., Andelova, M., Novotna, K., Lizrova Preiningerova, J., Krasensky, J., Havrdova, E., Horakova, D., & Uher, T., Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients, 87-93, 2018, with permission from Elsevier.

To put it briefly in an example, an extra milliliter of T1 lesion load was associated with a later 53% greater risk of worsening employment status. Additionally, a reduction in BPF by 1% resulted in the risk of worsening employment status after 12 years to increase by 22%.

Multivariate Cox models showed that the best individual predictors explained 5 to 7% (R^2 = 0.05 to 0.07) of the variability of worsening of employment status over 12 years, their combination (that is, the combination of BPF and T1 lesion load) explained 9% of the variability, and the multivariate model adjusted by sex, age, educational level and EDSS explained 20% (R^2 = 0.20) of the worsening of variability of the employment status.

4.4.4 Manuscript Contribution

In this article, I contributed at the level of data collection and curation. I was part of the team that finalized the employment status data throughout the 12-year period. This included preparation of the dataset and verification of collected information on employment status (through database search, or via phone call with individual research participants).

4.5 Study 5

Novotná, K., Janatová, M., Kadrnožková, L., Holeňová, M., **Motýl, J**., Horáková, D., & Kubala Havrdová, E. (2018). Pilotní studie využitelnosti nového programu pro kognitivní rehabilitaci osob s roztroušenou sklerózou. *Rehabilitace a fyzikální lékařství, 25*(3).

4.5.1 Aim

The objective of this study was to provide data on the feasibility of a new computer-based cognitive rehabilitation training intended for MS patients.

4.5.2 Methods

A cognitive rehabilitation program intended for the restorative training called Kote was used. The program was developed in cooperation of the 1st Faculty of Medicine of Charles University with the Faculty of Biomedical Engineering of the Czech Technical University in Prague. The program consisted of 9 optional difficulty training games aimed at training of various cognitive domains such as reaction time, information processing speed, working memory, and others.

Four MS patients underwent a 6-week long program of cognitive rehabilitation with at least 1 or 2 sessions of cognitive training per week. The patients completed a complex neuropsychological battery prior and after the cognitive training program (alternative versions of the tests were administered where possible). They also completed selected PRO questionnaires and a survey to report their experiences with the computer-based program and cognitive training. Training experience and the neuropsychological outcomes were analyzed to provide the first data on the feasibility of the new cognitive training program.

4.5.3 Results

The pilot feasibility study included 4 MS patients (2 men and 2 women) with a mean age of 40 years (± 8.6). All four patients had a higher neurological deficit with an EDSS range between 5.0 and a 6.5 and longer duration of the disease (mean duration of the disease = 41 years, ± 8.6). Two participants had previous experience with other cognitive training methods. All participants evaluated the training program as beneficial and would like to train more often and for a longer period. The most popular tasks were N-Back Task, Pair Matching, and Visuospatial Training. The participant perceived negatively insufficient settings of the task difficulty. This feedback was shared with the programmers of the cognitive training program.

Neuropsychological outcomes before and after cognitive training are presented in Table 4.2. Given the small sample size and lack of a control group, these results are purely illustrative.

TABLE 4.2: RESULTS OF THE NEUROPSYCHOLOGICAL ASSESSMENT PRIOR AND AFTER THE 6-WEEK COGNITIVE REHABILITATION PROGRAM

Neuropsychological Test	Baseline Mean (±SD)	Post-Training Mean (±SD)
SDMT	50.25 (±15.8)	50.75 (±14.8)
PASAT	40.5 (±13)	47.75 (±11.9)
CVLT-II	44.75 (±12.3)	45.75 (±12.3)
BVMT-R	23 (±7.3)	24.75 (±7.7)
COWAT (NKP)	47 (±13.6)	45.7 (±13.4)
COWAT (categorical)	49 (±15.8)	54 (±15.4)
JLO	28.5 (±1.1)	27.7 (±0.4)
Prague Stroop Test (interference)	1.8 (±0.2)	1.3 (±0.2)
MSNQ	15.75 (±5.1)	13.5 (±6.5)

Note: SDMT = Symbol Digit Modalities Test, PASAT = Paced Auditory Serial Addition Test (3 seconds), CVLT-II = California Verbal Learning Test, 2nd Edition, BVMT-R = Brief Visuospatial Memory Test, Revised, COWAT = Verbal Fluency Test (phonemic and semantic), JLO = Benton Judgement of Line Orientation, MSNQ = Multiple Sclerosis Neuropsychological Screening Questionnaire

4.5.4 Manuscript Contribution

Together with my colleague Mgr. Lucie Friedová, I participated in the neuropsychological assessment of cognitive training participants before and after the cognitive training program. I also contributed to the interpretation of the results of the neuropsychological assessment.

4.6 Study 6

Motyl, J., Friedova, L., Ganapathy Subramanian, R., Vaneckova, M., Fuchs, T. A., Krasensky, J., Blahova Dusankova, J., Kubala Havrdova, E., Horakova, D., Uher, T. (202_). Brain MRI disease burden does not explain sex differences in cognitive performance of patients with multiple sclerosis. [Submitted to *Multiple Sclerosis and Related Disorders* (Submission ID: MSARD-S-22-00401)]

4.6.1 Aim

The objective of this study was to investigate sex differences in cognitive performance of MS patients, in the context of brain pathology and disease burden. We wanted to explore whether sex differences in cognitive performance, which are also present in healthy samples, can be intensified by the brain pathology of patients with MS.

4.6.2 Methods

Data from the Grant Quantitative (GQ) study were analyzed. Of the 1,253 GQ study patients, 1,052 individuals with complete cognitive assessment and available volumetric MRI data at the beginning of the study were included in the analyzes. Neuropsychological data consisted of results from the BICAMS battery and the PASAT test. For statistical analyzes we applied linear or logistic regression analysis adjusted for sex, age, EDSS, education, depression, brain atrophy, lesion burden, and treatment status. In multivariate models, cognitive performance was treated as a dependent log transformed variable and sex as a categorical independent variable. The estimates for sex were exponentially back-transformed and represent a multiplicative effect on the geometric mean of the cognitive outcome and are denoted by βmult (Barro et al., 2018).

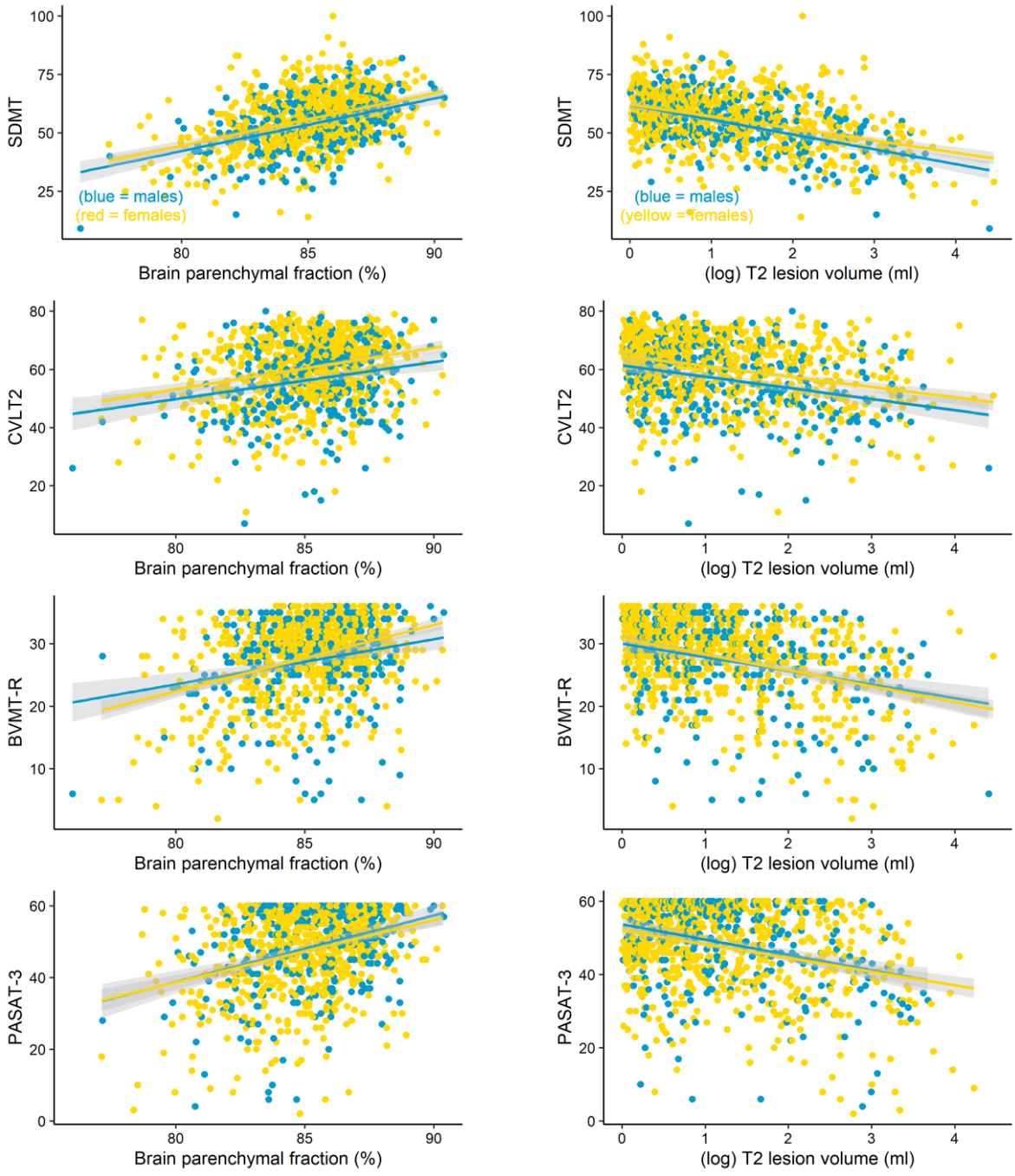
4.6.3 Results

Females had higher scores on the SDMT (median 57 vs. 54, d = 0.19) and the CVLT (median 63 vs. 57, d = 0.34), but not the BVMT-R scores (median 29 vs. 28, d = 0.09) or PASAT scores (median 50 vs. 51, d = 0.08). Paradoxically, women evaluated their cognitive performance as worse than males (median MSNQ score 15 vs 13, d = 0.021). Sex differences in cognitive performance (SDMT and CVLT) remained significant also after adjustment for potential confounders, such as age, EDSS, education, depression, brain atrophy (assessed by BPF), lesion burden (assessed by T2-LL), and treatment status. In multivariate models, females had 4.8% (95% CI: 2.1-7.6%) higher SDMT scores and 8.5% (95% CI: 5.4-11.7%) higher CVLT scores compared to males. BVMT-R and PASAT were similar between both sexes.

Females had a trend for a weaker negative correlation between T2-LL and SDMT (rho = -0.37 in females vs. -0.46 in men; interaction p = 0.038), the duration of the disease and CVLT (rho = -0.16 vs. -0.18; interaction p = 0.006) and between EDSS and BVMTR (rho = -0.28 vs. -0.32; interaction p = 0.014). On the other hand,

women had a trend for a stronger correlation between BPF and BVMT-R (Spearman´s rho = 0.21 vs. 0.31; interaction p = 0.016), depression and BVMT-R (rho = -0.13 vs. -0.09; interaction p = 0.038), age and PASAT-3 (rho = -0.22 vs. -0.11; interaction p = 0.037) and EDSS and PASAT (rho = -0.33 vs. -0.32; interaction p = 0.026). All these trends were not significant after correction for the false discovery rate (see Figure 4.7).

FIGURE 4.7: ASSOCIATIONS BETWEEN COGNITIVE MEASURES AND BPF (LEFT) OR T2-LL (RIGHT)



Note: Blue = males, yellow = females.

4.6.4 Manuscript Contribution

Together with my colleague Mgr. Lucie Friedová, we contributed equally to the manuscript. I took care of the finalization of the manuscript, worked closely on the theoretical sections of the article with Ranjani Ganapathy Subramanian, and coordinated the team of authors in the process of the preparation of the manuscript.

5. DISCUSSION

5.1 Study 1

One of the main objectives of this study was to observe the possibilities of an annual cognitive screening (Kalb et al., 2018) in the detection of people with potential cognitive decline, as assessed in a regular clinical environment. We decided to retrospectively analyze a large sample dataset which contains approximately more than a quarter of MS patients at our MS center. When we planned the study procedure, we decided not to use the proposed clinically meaningful 4-point decline in SDMT (S. A. Morrow et al., 2010), as we were skeptical about its usability on the individual level due to the unavoidable random error of measurement (Heilbronner et al., 2010). Our plan was to show the prevalence of cognitive decline in the annual clinical screening at the individual level, we did not want to proceed with another group-level comparison. Therefore, we decided to use the RCI methodology to evaluate significant cognitive decline, specifically the procedure proposed by Lord & Novick (Cígler & Šmíra, 2015; Lord & Novick, 1968). Additionally, we applied the strict confidence interval of 95% to receive very conservative estimates on the prevalence of cognitive decline.

We were aware that by using such criteria, the sensitivity of our assessment of cognitive change would be rather low, but we believed that for the application of regular cognitive screening in the clinical environment, with possible consequences, such as in decision making about possible DMD treatment change due to cognitive decline (Amato, 2018; Portaccio, 2018; Weinstock-Guttman et al., 2018), we needed conservative estimates first. We assume that after the method is well established and confirmed to be useful, the work on improving the sensitivity of the assessment can always take place. The approach to use the recommended RCI methodology (Heilbronner et al., 2010) to evaluate cognitive decline at the individual level was later confirmed to be legitimate by two methodological articles evaluating the RCI methodology in MS (L. B. Strober et al., 2022; Weinstock et al., 2021). It must be noted that using SRB equations would be even more precise (L. B. Strober et al., 2022), however, we did not have the needed longitudinal normative trajectories available at the time we conducted our study.

However, there are various approaches to the RCI calculation to choose from (Hinton-Bayre, 2010). The Lord & Novick RCI we applied (Cígler & Šmíra, 2015; Lord & Novick, 1968) is much more dependent on the normative dataset because it directly applies (accounting for the reliability of the method) the assumption of regression to the mean (Lord & Novick, 1968). This is probably the main difference from the RCI methodologies proposed to be used in the MS population a few months after our article has been published (L. B. Strober et al., 2022; Weinstock et al., 2021). Each of the approaches has its strengths and weaknesses. For example, the RCI methodology proposed by Iverson (Iverson, 2001; Weinstock et al., 2021) uses a useful approach of how to deal with the known practice effect of the test. On the other hand, the approach to RCI as proposed by Lord & Novick (1968) uses a normative dataset and possibly promises reliable evaluation of change between two timepoints with an undefined time interval in between, thus in a situation when we do not have information on possible practice effect. Additionally, regarding the evaluation of the information

on the usefulness of a combination of two baseline scores for the later more precise evaluation of a change in neuropsychological outcome seems very practical and easily applicable in clinical practice (Bruce et al., 2016).

Given that in most cases the cognitive changes were associated with other markers of clinical or radiological disease activity, it opens a question whether the annual screening of cognitive functioning in MS (Kalb et al., 2018) is cost-effective. In this regard, it should be noted that cognitive testing is not completed only to detect otherwise uncaptured disease activity. It can be carried out for its own purpose, for example, to identify patients who are experiencing significant cognitive decline as its own set of symptoms. Addressing these symptoms experienced by individual patients allows clinicians to tailor treatment to each individual person. Considering the impact cognitive decline can have on patients' quality of life (e.g., employment, relationships, basic functioning) (S. M. Rao, Leo, Ellington, et al., 1991; Aurélie Ruet et al., 2013), it might be beneficial to receive information on an ongoing cognitive decline also for the patient himself/herself, so he/she can prepare, or consider possible treatment or coping strategies (R. H. B. Benedict et al., 2020; Chen et al., 2021; Landmeyer et al., 2020).

Cognitive monitoring can certainly improve our disease activity monitoring, and thus decision-making. As I have mentioned in the theory, cognitive changes can be present even in early/mild/preclinical forms of MS and can present a risk factor for future disease course (Cortese et al., 2016; Hyncicova et al., 2017; T. Uher et al., 2014). Furthermore, in patients with low cognitive reserve, even small structural damages can result in irreversible cognitive deterioration (Eijlers et al., 2019; Eijlers, Meijer, et al., 2018; Fuchs et al., 2020; Sumowski et al., 2014; T. Uher et al., 2018). Therefore, it is essential to detect ongoing disease activity as early as possible. In this study, patients with cognitive worsening showed a trend for a higher disease burden at baseline in comparison to patients with stable cognition during follow-up. Also, cognitive decline did not affect the change in the total EDSS score. This corresponds to a general trend in which cognitive outcomes are clinically underestimated (Sacca et al., 2017). That can be harmful to the patient if the disease activity continues undetected. Although we saw the corresponding MRI activity in our study in almost all patients with isolated cognitive decline, it has been reported that more sophisticated nonconventional magnetic resonance imaging techniques may be needed to detect imaging correlates of disease activity associated with cognitive worsening (Eijlers, van Geest, et al., 2018; Rocca et al., 2015). Both the current and previous study (T. Uher et al., 2018) of our team suggested that patients with more severe MS pathology are more prone to cognitive decline. However, based on our current results, in people with less severe MS, cognitive decline might be a crucial measure suggesting ongoing disease activity, when only conventional MRI measures are applied. And for such patients, it might be the most beneficial to detect the ongoing disease activity soon; before they reach the cognitive threshold (M. M. Schoonheim et al., 2015; T. Uher et al., 2018).

Limitations. Our study had several limitations. Data from the GQ study we analyzed included three consecutive timepoints, although four timepoints would be beneficial to fully understand the personal longitudinal cognitive profiles. Four timepoints would allow us to set up practice and confirmation phases. Furthermore, it would be highly beneficial to compare various screening intervals in future potential analyses on the topic of regular cognitive screening in MS. Although we carefully reevaluated cognitive outcomes in all participants in the first phase of our analysis, our RCI evaluation was still based on a preliminary normative sample from the Czech MACFIMS validation study (Dusankova et al., 2012). Adequate local norms would make the

results more reliable. However, with the conservative confidence interval applied, I believe that the potential bias was minimized. Furthermore, it is important to mention that the Czech normative study on BICAMS battery is in preparation and is expected to be published soon (Motyl et al., 2019). The cognitive functions in this study were assessed by the SDMT. While the SDMT assesses the most frequently impaired cognitive domain in MS, processing speed, several domains such as episodic memory, executive functioning, visual-spatial functioning or phonemic fluency were not tested (R. H. B. Benedict et al., 2020). The analysed sample included patients with shorter disease duration and lower severity of the disease; therefore, I assume that the prevalence of cognitive impairment might be actually higher. Finally, even though we analyzed a large sample of patients (that is, N = 1091), the groups representing cognitively declining patients were relatively small. These numbers are too small to present any definitive answers; a more rigorous analysis would probably require a multicentric coordinated approach.

Conclusions. In the case of annual screening by the SDMT test, only a small proportion of patients experienced isolated cognitive decline detectable by rigorous criteria of RCI. In addition, most patients who experienced isolated cognitive decline showed concurrent MRI activity. This supported the relevance of the concept, however, it also showed that the annual screening by the SDMT test is useful especially in cases when we are interested in detection of cognitive symptoms of the disease per se. Patients with severe MS were more prone to cognitive decline, but based on the literature overview, I hypothesize that those patients with healthy cognition and mild MS symptoms might benefit the most from early detection of cognitive decline.

5.2 Study 2

In this study, we investigated the relationship between sNfL levels in the first two years of MS and cognitive outcomes in later stages of the disease; up to nine years of follow-up. We found only a trend for a weak association between sNfL levels at year 1 and episodic memory decline over 9 years. Importantly, this association was not observed for sNfL levels at baseline and at year 2. Also, we did not observe this relationship in the longitudinal mixed model analysis.

These results are consistent with other longitudinal studies investigating the relationship between sNfL levels and cognitive outcomes. Similarly to our findings, this relationship was weak or nonexisting (Chitnis et al., 2018; D. Jakimovski et al., 2020). Given these results, we can't exclude the possibility that our observation of the trend of the relationship between sNfL levels and episodic memory decline might be just a random false positive finding. This nonexistence of the relationship between early sNfL levels and cognitive performance could be explained accordingly with the theory of cognitive clinico-radiological paradox / cognitive network collapse (M. M. Schoonheim et al., 2015; T. Uher et al., 2018). Cognitive performance has previously been described to be not linearly connected with the disease burden, as measured by radiological or neurological paraclinical markers. Especially at the beginning of the disease, cognitive performance can remain intact, due to cognitive reserve or other factors related to neuronal adaptation (Sumowski et al., 2014), despite continuous neuronal degradation (T. Uher et al., 2018). This phenomenon can possibly also apply for sNfL levels.

Furthermore, sNfL is a marker of neuroaxonal degradation. On the other hand, cognitive deterioration in MS, especially in later stages of the disease stages marked by the cognitive threshold (T. Uher et al., 2018), is related to cortical gray matter atrophy (Bernabéu-Sanz et al., 2021; Eijlers et al., 2019; Eijlers, Meijer, et al., 2018; Eijlers, van Geest, et al., 2018; Nelson et al., 2011; Martijn D. Steenwijk et al., 2016; M. D. Steenwijk et al., 2016; Welton et al., 2015). In this light, it is not surprising to see a weak or non-existing relationship between early sNfL levels and cognitive outcomes after 9 years of follow-up.

However, it should be noted that some preliminary studies showed concurrent relationship between sNfL levels and cognitive outcomes (Kalatha et al., 2019; Mattioli et al., 2020; Quintana et al., 2018). Furthermore, the predictive value of sNfL levels in a short-term perspective of disease progression was well described, in opposite to long-term prognosis, where the results were inconclusive and controversial. sNfL levels have been shown to drop considerably in a case of successful DMD treatment (Bittner, Oh, Havrdová, Tintoré, & Zipp, 2021). Therefore, I would expect that the relationship between early sNfL levels and long-term cognitive outcomes will be weak (as was our finding) but that there will be a relationship between sNfL levels and cognitive performance at the same timepoint (we found only a weak relationship between baseline sNfL levels and year 1 memory/learning outcome). In this regard, it is important to mention that our participants had very low levels of disability even after 9 years of follow-up (median EDSS = 2.0). This was a homogeneous group of patients with an early start of interferon beta treatment. It might be that the relationship would be stronger if the burden of the disease in our sample was higher. Or maybe if we would use different methods of cognitive assessment that would provide much more adequate information on the relationship between sNfL levels and cognitive performance at the beginning of the disease. Very interesting would be to see data on tests measuring accurately word-finding difficulties (Brandstadter et al., 2020) or other issues we see often in early stages of the disease. In this sense, our finding of a trend between sNfL levels at baseline and word-learning / memory difficulties at year 1 could reflect the cognitive phenotype of 'mild-verbal memory / semantic fluency' as proposed by De Meo et al. (2021). This phenotype was described to be associated with verbal learning / memory issues and to be found in people in early stages of the disease (De Meo et al., 2021).

Finally, in future studies, it would be very interesting to see the use of sNfL levels as a possible validation marker of neuroaxonal damage associated with cognitive relapses. It would be especially interesting to see a study on isolated cognitive relapse using sNfL levels as a concurrent marker of disease activity. Some preliminary results supporting such use of sNfL already exist (Kuhle et al., 2019).

Limitations. The main limitation of our current study was the implementation of neuropsychological methods that cover only information processing speed and memory/learning functions. Although these are the cognitive domains most commonly affected by MS (R. H. B. Benedict et al., 2020), incorporation of a more complex neuropsychological battery such as MACFIMS would be beneficial. Regarding other neuropsychological methods, in such a cohort of patients with low disease burden, the most beneficial would probably be implementation of neuropsychological tests that cover word-finding or multitasking difficulties (Brandstadter et al., 2020).

Conclusions. In conclusion, although we found some trends for the association between high levels of sNfL at the onset of the disease and word-learning / memory difficulties over long-term follow-up, our results are

preliminary and do not provide convincing support of this relationship. It is yet to be answered whether associations between high sNfL levels and verbal learning / memory decline represent rather random false positive finding or whether such association will also be observed in other studies.

5.3 Study 3

Our study supported the relationship between the slowed articulation rate and cognitive impairment in MS. Speech and cognitive impairment are highly prevalent in MS, although their manifestation is rather mild. Both symptoms are often overlooked, although they can have a significant impact on quality of life, social functioning and employability (S. A. Morrow et al., 2010; Piacentini et al., 2014; S. M. Rao, Leo, Ellington, et al., 1991; Yorkston, Baylor, & Amtmann, 2014).

In a sample of 122 MS patients, we showed that an objective acoustic assessment can provide certain information about cognitive performance, specifically about information processing speed. This was proved for both the SDMT and PASAT tests. All speech measures applied were related to information processing speed, but the strongest relationship was observed between articulation rate in reading (ARR) and the SDMT and PASAT. The second task with an acceptable relationship to information processing speed was the diadochokinesis task (DKK). The DDK rate specifically measures the motor abilities of speech articulation and can reveal movement limitations, whereas ARR reflects a combination of speech-motor execution and cognitive linguistic processing. Therefore, it is not surprising that the relationship of information processing speed with ARR was found to be superior over DKK. On the other hand, the last speech measure, the spontaneous monologue (ARS), showed only a weak relationship with information processing speed.

These findings are consistent with previous research on this topic (Peter A. Arnett, Smith, Barwick, Benedict, & Ahlstrom, 2008; Rodgers, Tjaden, Feenaughty, Weinstock-Guttman, & Benedict, 2013). Regarding the relatively weak relationship between information processing speed and the spontaneous monologue, Rodgers et al. (2013) suggested that in the case of a self-chosen familiar topic, memory domain may play a role and thus the involvement of executive functions / information processing speed is lower than in the task involving reading of an unknown passage of text.

One of the important questions is the pathological process behind this relationship. It is not clear whether there is a causal relationship or whether it is just an epiphenomenon. In the causal pathway, phonatory motor dysfunction could cause a slowdown in articulation affecting performance in various time limited speech-based neuropsychological tests. Or vice versa: cognitive dysfunction might possibly cause a slowdown in speech production. However, it might be that we can't simply distinguish cognitive and phonatory / motor processes. A similar relationship was also found between cognitive functioning and basic motor functions in MS (Ralph H.B. Benedict et al., 2011). The authors of this study hypothesized that it is a concurrent relationship caused by shared neural networks involving prefrontal, frontal, and subcortical regions that mediate motor control and cognitive processing. (Ralph H.B. Benedict et al., 2011). However, I do not know of any study that would provide substantial information on this question without possible methodological issues. This is also the case with our study where we lacked neuropsychological methods that would be less dependent on phonatory or motor functioning.

Similar to the relationship between cognitive performance and motor / phonatory dysfunction is the question of influence of eye movements or other eye deficits on cognitive performance as a whole, or on concrete neuropsychological tests (Dejan Jakimovski et al., 2021; Nygaard et al., 2015; Pavisian, Patel, & Feinstein, 2019). Various OCT measures are associated with cognitive performance (Dejan Jakimovski et al., 2021) and saccadic eye movements may play a role in SDMT performance (Nygaard et al., 2015; Pavisian et al., 2019).

All of these findings open a space for well-planned research in the MS population that would carry out neuropsychological assessment of multiple cognitive domains, while controlling for subtle phonatory, motor, and eye impairments. Such primary research could answer an interesting question about the pathway of deterioration in certain neuropsychological tests, especially in SMDT, as this method is believed to be the most sensitive test of cognitive deterioration in MS. It would add interesting insight to previous neuropsychological research suggesting that SDMT covers multiple cognitive domains (V. M. Leavitt, 2021; Sandry et al., 2021).

Our study found that ARR and DKK rates can be used as a sensitive (80 – 95%) but not highly specific (40 – 69%) predictor of deterioration in information processing speed. As the finding, that a faster ARR by one word per second was associated with a 19 point higher raw SDMT score and approximately 15 point higher raw PASAT score, suggests, the differences in articulation rate are so subtle, they can't be measured otherwise than by the objective acoustic assessment. And given the cut-offs between 3.0 and 3.2 words per second for ARR (ranging in sensitivity between 82 and 96%), it is still questionable how to make such assessment valid in an individual assessment. Given these preliminary results, the implementation of this assessment into clinical practice still has a very long way to go. On the other hand, it promises the possibility of an automated first screening of cognitive functions, which could send people suggestive of cognitive deterioration further to complex neuropsychological examination. The promising factor is that an automated speech assessment can be implemented into daily used devices such as smartphones or various intelligent virtual assistants and thus provide the regular cognitive screening to virtually anyone (after solving inevitable legal issues connected with privacy and personal data protection).

Limitations. Our study has several limitations. It is not clear whether the relationship between cognitive performance and speech assessment is causal or represents an epiphenomenon. Furthermore, our study included only tests of information processing speed. In future studies, it would be beneficial to include assessment of other cognitive domains and to add tests that minimize motor and speech involvement.

Conclusions. We showed a strong relationship between slowed articulation rates and decline in information processing speed. Acoustic quantitative speech analysis was able to identify patients suggestive of cognitive deterioration. Objective acoustic speech analysis has the potential to provide regular cognitive screening to a wide public.

5.4 Study 4

Loss of employment is one of the severe socioeconomic and psychological consequences of MS. Not only for individual but also for the society as a whole (Blahova Dusankova et al., 2012; Havrdova et al., 2017; Hilt Pfleger et al., 2010a). The worsening in employability and possible downgrade in career aspirations is also closely related to cognitive performance (S. A. Morrow et al., 2010; Papathanasiou et al., 2015; S. M. Rao, Leo, Ellington, et al., 1991; L. Strober et al., 2014).

In the current study, we found that the only baseline clinical predictor of future employment status worsening after 12 years of follow-up was the baseline disease duration. Each additional year of MS duration at baseline increased the risk of worsening employment status after 12 years by 10%. When we also consider MRI evaluation, T1 and T2 lesion load, together with brain atrophy (BPF), are the strongest predictors of loss in employment status 12 years later. One extra milliliter of T1 lesion load was associated with a 53% higher risk of worsening employment status. Furthermore, a reduction in the brain parenchymal fraction by 1% resulted in the risk of worsening employment status increasing by 22%. The increase in T2 lesion load of 1 ml was related to an increased risk of worsening employment status by 9%.

We found that after 12 years of follow-up, 38 (26.2%) patients with MS worsened their employment status due to MS. This means that after 12 years, almost 50% of our sample showed worsened employment status due to MS. This is in line with previous data on the burden and cost of MS in Czechia, which showed that around 49% of people with MS were employed (Havrdova et al., 2017).

As mentioned in theory, the associations between physical disability, cognitive impairment, and employment status are well described (Honarmand, Akbar, Kou, & Feinstein, 2011; Moore et al., 2013; S. A. Morrow et al., 2010; Papathanasiou et al., 2015; S. M. Rao, Leo, Ellington, et al., 1991; L. Strober et al., 2014). Furthermore, the relationship between measures of brain atrophy or lesion burden and long-term disability is well established (T. Uher, Vaneckova, Sobisek, et al., 2017). However, only few studies investigated the combined association between MRI measures and employment status (Papathanasiou et al., 2015; Tauhid et al., 2015). It is noteworthy that Papathanasiou et al. (2015) investigated the complex relationship between the MRI measure, cognition, and employment status. They found the employment to be closely associated with corpus callosum and thalamic atrophy, and with memory and Trail Making Test B (TMT-B) results.

Interestingly, when we compare the current results with our previous study on predictors of cognitive impairment (T. Uher, Vaneckova, Sormani, et al., 2017), we see noteworthy parallels. BPF (BPF < 0.85) and T2 lesion load (T2-LL > 3.5 ml) were identified as the most accurate MRI markers of possible cognitive impairment (T. Uher, Vaneckova, Sormani, et al., 2017). In our current study we see, already at the baseline, that patients with a worsening of employment status due to MS after 12 years had lower BPF (M = 85.91, ±1.79) and a higher T2 lesion load (M = 2.20, ±5.20) at the baseline. This is getting close to the cognitive impairment cut-offs and suggests the mentioned association between loss of employment and cognitive impairment due to MS. Unfortunately, we did not have data on neuropsychological tests in the ASA study at baseline and therefore cognitive predictors could not be directly analyzed in this work.

Limitations. Our current study had several limitations. One of the main limits comes from the sample we analyzed. The ASA study includes RR-MS patients with relatively high disease activity before the study baseline. Additionally, all patients were treated with intramuscular interferon beta-1a alone or in combination with low-dose azathioprine or low-dose azathioprine and prednisone at the beginning of the study (E Havrdova et al., 2009). Therefore, the generalizability of our results on the whole RR-MS population is troublesome. In addition, more research is needed to support these results in other MS cohorts.

In the current study, we divided patients into two basic groups that represent patients without work limitations due to MS and patients who experienced work limitations or loss of work due to MS. This basic division was based merely on information about whether patients worked full-time/part-time/lost employment. In future studies, a more precise evaluation would be beneficial, e.g., taking into account also the total amount of hours in work, the total workload, or the skills needed for the current position.

The accuracy of the proposed model could be further improved by taking into consideration other important determinants of employment status, such as the above-described cognitive performance, or also symptoms of mood disorders, personality characteristics, or local unemployment rates.

Conclusions. With the growing recognition of employment status worsening as an important marker of quality of life in MS patients, and an important measure of the burden of the disease at a societal level, early identification of patients at risk of loss of employment due to MS might be of great importance to both patients and physicians. Our study suggested integrated clinical and MRI markers which could suggest a greater risk of future loss of employment or worsening of employment status due to MS. However, the suggested markers explained only a relatively low proportion of the variance of employment status worsening. Therefore, in order to improve the prediction of employment status worsening early in the course of the disease, future studies must also take into account other predictive factorer.

5.5 Study 5

Our new cognitive training program aimed at the restorative function of the training (R. H. B. Benedict et al., 2020; Chen et al., 2021). The aim of the program is to alleviate the burden caused by MS. This is an especially important factor as MS affects young adults in productive age, and one of the disabling consequences related to the cognitive deterioration due to MS is the worsening of employment status (S. A. Morrow et al., 2010; Papathanasiou et al., 2015; S. M. Rao, Leo, Ellington, et al., 1991; L. Strober et al., 2014).

The Kote program was used in the current pilot study. The program was developed in cooperation of the 1st Faculty of Medicine of Charles University with the Faculty of Biomedical Engineering of the Czech Technical University in Prague. The Kote program is tablet-based, with the potential to make cognitive training more accessible and thus more regular than with the use of standard computer-based training applications (Stuifbergen, Becker, Morgan, Morrison, & Perez, 2011). In our study, the program was well accepted, even two MS patients with upper extremity tremors did not experience difficulties while using tablet-based cognitive training. However, users would appreciate greater variety in training-difficulty settings. Also, when the program should be used independently at home, experience shows that instructions should be detailed

and double checked to determine whether they are understandable and accepted by users (Stuifbergen et al., 2011).

The current pilot study tested the program on a single sample of 4 participants without application of any control group paradigm. Therefore, we can't draw any conclusions from the neuropsychological assessment done before and after the training. Our patients felt that they benefited from the training which is in agreement with other subjective experiences with cognitive training (Klein et al., 2019).

In this regard, it is questionable whether the restorative cognitive training really objectively improves cognitive functions and quality of life in daily life activities, or whether the training effect is restricted to the particular training / assessment scenario. The basic assumption about the functioning of such training programs stems from the theory of the protective factor of cognitive reserve in cognition, against the burden of MS disease (Chiaravalloti et al., 2015; Sumowski & Leavitt, 2013; Sumowski et al., 2014). We see that people who are physically and intellectually active are more resilient to cognitive deterioration due to MS. The results of cognitive training are promising (R. H. B. Benedict et al., 2020; Chen et al., 2021; Lampit et al., 2019), but, on the other hand, it has been shown that results of the training wane without further continuation (Lampit et al., 2019), and the data on improvements in daily living are still inconclusive at best (Lampit et al., 2019; Lincoln et al., 2020).

Given these preliminary results and using the theory of cognitive reserve, the emphasis on the combination of training with other activities such as psychotherapy or physical activity and the extreme emphasis on ecological validity and maximum individualization of cognitive training seem to be more promising approaches to restorative cognitive training (Impellizzeri et al., 2020; Martínez-González & Piqueras, 2015; Sandroff et al., 2016). Such a complex individually planned approach resembling real-world cognitive stimuli could prove more successful in affecting daily-life activities in a long-term perspective. However, such complex training paradigms are difficult and expensive to study, especially in randomized control trials.

But this should definitely be the next step after the current pilot study, to use Kote in combination with other approaches to form a complex and more individualized training scenario.

Limitations. The main limitation of the current study is based on its pilot / feasibility research paradigm. The study was not blinded and no control group was established. The study was intended purely for the purpose of checking the feasibility of the new program and collecting the experiences of users of the cognitive training program. Therefore, no conclusions about objective functioning of the cognitive training program can be drawn. The next study of Kote should be conducted in a larger sample of MS patients, using randomized and blinded control and research groups.

Conclusions. The new Kote program intended for restorative cognitive training in the MS population is well-accepted and can be used in following studies on benefits of cognitive training in MS. The integration of the program into a more complex and individualized approach to cognitive rehabilitation is recommended.

5.6 Study 6

We found that women with MS had better information processing speeds and language learning and memory skills than men with MS. This is consistent with previous research showing better performance of females on verbal memory and learning tasks amongst healthy sample (Goretti et al., 2014). This is similar to what we have found in MS patients.. The same study also found that females had an average SDMT score of 5.1 points higher than men (Goretti et al., 2014), and some studies reported that the magnitude of the differences decreases with age (Roivainen, 2011), while others found that gender effects were most apparent between the third and sixth decades of life (L. B. Strober et al., 2020). However, in our study, we did not find clear associations (only trends, not significant after correction for the false discovery rate) between age and the magnitude of sex differences in cognitive performance.

We found that females had on average 2.2 points higher SDMT scores, and 4 points higher CVLT scores when compared to men. Despite this apparent difference between the sexes, the SDMT standard deviation for females was 11.8 and for males 11.0, and the CVLT standard deviation for females was 11.3 and for males 12.1. Hence, the mean differences were smaller than the standard deviation of each sex group. This means that the variability within the same sex is greater than the difference between the two sexes.

Despite the better cognitive performance, female patients tended to subjectively evaluate their own cognitive abilities worse than males and reported slightly more depressive symptoms than males, which is consistent with previous research (D'Hooghe et al., 2020). Given that mood, self-report of functioning, comorbidities, and sleep behaviors have been shown to contribute to subjective evaluation of cognitive performance (on MSNQ) (D'Hooghe et al., 2020; Obrien et al., 2007), this observation is not be surprising. Likewise, in our study, objective cognitive performance was not associated with subjective assessment of cognitive performance.. Based on our findings, we agree that subjective evaluation of cognitive performance as assessed by MSNQ correlates better with depression (e.g., affective state) than with objective cognitive functioning (D'Hooghe et al., 2020). These results suggest that the discrepancy between subjective evaluation of cognitive performance and objective cognitive measures appears to be higher in women compared to men. This may be of clinical relevance when indicating MS patients for cognitive screening or examination.

Male sex has been implicated as a risk factor for progression of cognitive disability in previous research, and male patients with low education or intelligence, early onset of MS, and evidence of cerebral gray matter atrophy appeared to be more susceptible to cognitive impairment, while those with higher levels of premorbid intelligence levels are better protected (Beatty & Aupperle, 2002; Ralph H. B. Benedict & Zivadinov, 2011; Savettieri et al., 2004). Our findings on a large data set suggest that MS disease burden did not have any additional relation to the differences between sexes in cognitive performance, as measured by BICAMS and PASAT. Although we found several trends in our data, all of these trends were not significant after correction for the false discovery rate. These findings thus seem to be rather false-positives, based solely on our large-sample size and the amount of multiple comparisons done in our analysis.

Limitations. One of the main limitations of this study is caused by the lack of a Czech normative study on BICAMS and PASAT. Adequate local norms would allow us to compare the observed sex differences in the

MS population with the differences in the healthy population. However, based on previous findings, we believe such analysis would not bring a major change to our interpretations. Furthermore, it is important to mention that the Czech normative study on BICAMS battery is in preparation (Motyl et al., 2019). Cognitive functions in this study were evaluated using the BICAMS battery and the PASAT test. While BICAMS assesses the most frequently impaired cognitive domains in MS (processing speed and learning and memory), several domains such as executive functioning,, visual-spatial functioning or phonemic fluency were not tested (R. H. B. Benedict et al., 2020). The analyzed sample included patients with a shorter disease duration and a lower severity of the disease, which could influence the results.

Conclusions. On a large sample of people with MS, we confirmed previous findings showing sex differences in processing speed and verbal learning capacity, with females scoring generally better in these tasks. However, sex differences in cognitive performance were smaller than the variability of scores within the same sex group. Sex differences in cognitive performance were not explained by brain pathology or neurological disability. We did not find enough support for the theory that MS disease can further increase these sex-related differences.

5.7 General Discussion

The results presented in this thesis supported the first two hypotheses. The first hypothesis suggested that people with MS experience isolated cognitive decline throughout their disease course. In the first study, I have described that approximately 4% of people with MS can experience isolated cognitive decline annually. The actual number is probably going to be even higher, because our results were based only on the SDMT test (information processing speed cognitive domain) and on a sample with relatively small disease burden.

I have shown that in most cases isolated cognitive decline is accompanied by concurrent radiological disease activity and thus I have supported my second hypothesis that isolated cognitive decline is a phenomenon related to disease activity, particularly structural neuronal changes due to MS, and therefore should be accompanied by the radiological activity of the disease. More than 81% of patients with MS experiencing isolated cognitive decline showed concurrent radiological activity (new or enlarged T2 lesions on brain MRI).

Interestingly, our data on depressive symptomatology did not show any suggestion that isolated cognitive decline would be more related to depression than to other factors related to MS burden. Unsurprisingly, the lowest depressive symptoms were seen in patients with no neurological or neuropsychological progression. The disease-progressing groups showed higher depressive symptoms, however, the level was comparable, with no significant differences between the neurologically or neuropsychologically worsening groups. Based on these preliminary results, it seems very probable that isolated cognitive decline is a factor related to disease severity / progression and not to a nonspecific affective symptomatology.

Hypothesis 3 stated that neuropsychological assessment could provide, through the concept of isolated cognitive decline, novel insights into disease activity that would be missed by conventional monitoring techniques. This hypothesis was only partially supported. We have seen isolated cognitive decline without concurrent relapses or worsening of EDSS in 4% of patients annually, but in most cases the isolated cognitive

decline was accompanied by radiological disease activity. Therefore, it can't be seen as a measure that could provide groundbreaking information on the disease course that would be missed otherwise. However, knowledge of the cognitive symptomatology may be beneficial on its own. It can help to better target the treatment, in uncertain cases it can provide additional background on the disease state, it can allow patients to adapt early to the possibility of cognitive deterioration, or techniques of cognitive training can be applied. Furthermore, based on our studies, we can't rule out the possibility that with more complex batteries or tests aimed at specific issues such as word-finding difficulties (Brandstadter et al., 2020), we would detect more cases without the corresponding MRI activity where cognitive decline could mark disease activity undetectable by standard MRI protocols.

The findings of the first study are also highly interconnected with the second and third objectives of this thesis. Based on our preliminary results presented at the IMSCOGS conference in 2017, the SDMT test appears to be the most sensitive method of the BICAMS battery to identify cognitive decline (Motyl et al., 2017). This is in agreement with other studies on this topic (R. H. B. Benedict et al., 2020; Kalb et al., 2018). In the first study, it was also shown that it can be used for the description of isolated cognitive decline in information processing speed. Additionally, study 1 suggested (and indirectly through data on employability also study 4) that people with generally worse disease parameters at the study baseline tend to experience cognitive decline (or worsening of employment status) with greater probability at follow-up timepoints. Especially potent MRI predictors of future cognitive decline (or worsening of employment status) were shown to be brain atrophy (BPF) and T1 or T2 lesion load. People who experienced cognitive deterioration in the annual assessment also had significantly longer duration of the disease and higher EDSS at the baseline. An association between these findings and the theory of cognitive threshold, and late cognitive deterioration connected with cortical gray matter atrophy, can be drawn (Eijlers et al., 2019; T. Uher et al., 2018).

However, it must be noted that when people without baseline cognitive impairment were analyzed separately (that is, the population in which it is the most essential to detect the progression of the disease soon), the baseline disease severity differences between cognitively worsening and cognitively stable samples disappeared. Based on this finding, I hypothesize that cognitive assessment might be especially crucial in this population with the lower disease burden, whose cognitive performance is still relatively intact, and maximum effort should be made to preserve cognition. Our ultimate goal (even though still far away) should be to detect and stop neuronal degradation and cognitive deterioration before the cognitive threshold is reached, before people get cognitively impaired. Or before they worsen their employment status, as study 4 has shown. Such achievement could help them maintain a high quality of their lives.

Predicting cognitive deterioration before the cognitive impairment is reached is not an easy task. This was highlighted by the second study which found that early levels of sNfL cannot predict long-term cognitive performance. However, there is still an assumption based on preliminary data that sNfL levels could be associated with current cognitive performance (Kuhle et al., 2019). If that would be confirmed, sNfL levels could, for example, serve as validation marker for the concept of (isolated) cognitive relapses in future studies (M. Pardini et al., 2014).

All this puts pressure on the neuropsychological diagnostic process of cognitive deterioration, to make it more reliable at the individual level, more accurate, and less costly. Various computer-based tests have recently been developed to provide a more effective screening of cognitive performance (Stephen M Rao, 2018),

however, the approach to develop methods which follow the first symptoms of cognitive deterioration in MS more precisely (Brandstadter et al., 2020) seems possibly even more promising, given the fact that our objective is to detect cognitive deterioration as early as possible. Our study 3 suggested an interesting marker of cognitive deterioration: the automated objective acoustic assessment. This could be a screening technic easily implementable to regular devices such as smartphones or virtual home assistants. It could provide regular cognitive monitoring on the background of other common activities in interaction with personal smart accessories. As our cut-off points suggest, such a screening would not be very specific and its accuracy could be a bit controversial, but a positive result from such a screening could serve as a sign suggesting patients for a more complex neuropsychological assessment.

With regard to the improvement of the diagnosis process of cognitive deterioration,, we have shown in the study 6 that normative data stratified by sex could further improve the diagnostic processes in neuropsychology of MS, especially in the SDMT test and in verbal learning and memory tasks such as CVLT. We have not seen any deepening of the sex-differences in cognitive performance based on brain pathology due to MS.

Regarding the treatment of cognitive deterioration, the situation is uncertain. On the group level, modern DMD treatment can protect patients from cognitive deterioration (Harel et al., 2019; Landmeyer et al., 2020), but the knowledge of the effects of particular drugs on specific cognitive domains and on the individual level is low, and therefore the escalation of DMD treatment due to cognitive deterioration is controversial (Amato, 2018; Amato & Krupp, 2020; Landmeyer et al., 2020; Portaccio, 2018; Weinstock-Guttman et al., 2018). However, prospectively, it seems to be the most promising approach in the suppression of cognitive deterioration due to MS. The results of cognitive training programs are at this moment better supported (R. H. B. Benedict et al., 2020; Chen et al., 2021) but its applicability to real-world activities outside the training program shows inconclusive results (Lampit et al., 2019; Lincoln et al., 2020). The fourth aim of this thesis is represented by study 5 where we pilot-tested a new program of tablet-based cognitive training. With minor improvements it proved to be usable in MS population. In future cognitive training programs, I would suggest combining it into individualized complex long-term training including also other activities such as physical exercise, psychotherapy / counseling, or offline intellectually enriching activities. (Martínez-González & Piqueras, 2015).

Limitations. The main limitations of this thesis are related to the fact that we still lack localized normative data for the neuropsychological batteries used in MS in Czechia. This is crucial for the individual evaluation and would make the conclusions on individual level more well-founded. However, the future looks bright in this case; I have already finalized the normative dataset in the research project GAUK 1154218 and the publication is in preparation (Motyl et al., 2019).

Another limitation stems from the retrospective analytical approach used in the first, second, and fourth study. Because of that, we had to deal during the analyses with various issues which would be naturally resolved in a newly collected dataset, where the most recent findings could be directly incorporated into the study methodology. In this sense, to some extent, retrospective analyses are always compromised by their outdated design. In our case, these issues included, for example, the data on depressive symptomatology collected by BDI instead of revised and more recommended BDI-II. Throughout my postgraduate education

we have continued with the prospective longitudinal data collection; however, the dataset has been finalized just recently and is yet to be analyzed.

Lord and Novick RCI methodology was used to reliably evaluate cognitive change at the individual level in the study 1. This approach was applied before the proposal of standardized regression-based change equations (SRB) for the SDMT was published earlier this year (L. B. Strober et al., 2022). This is a more precise approach and a much needed metric for the longitudinal evaluation we have aimed for. The use of proposed SRB equations would be a more appropriate methodology to choose from in such a situation. However, we still lack SRB validation in the Czech environment and we lack the equations for the entire neuropsychological battery used in MS (BICAMS, MACFIMS). Despite these limitations, I believe that the proposed RCI methodology is still a very well-founded approach that provided reliable results that will significantly improve the clinical practice of neuropsychological assessment in MS in Czechia.

5.8. Conclusions

Regular neuropsychological screening followed by complex neuropsychological assessment was shown to be beneficial in MS disease monitoring. Annual screening can provide clinicians new data on disease activity and can serve as a source for further decision-making about patient treatment and rehabilitation of the patient. In this research, patients with a higher burden of disease were shown to be more prone to cognitive deterioration; however, with the aim of early identification of an ongoing disease activity, neuropsychological screening in cognitively healthy individuals seems to be more beneficial.

Neuropsychological monitoring and treatment of MS face many obstacles. While on the group level, the associations and effects are well-documented, the individual diagnostic process remains challenging. The next steps in the research will probably include the development of more sensitive and cost-effective assessment methods, accompanied by the adoption of more accurate and reliable interpretation criteria of the results.

This thesis introduced conservative RCI methodology in the evaluation of an annual change in cognitive performance in MS, described the results of an annual cognitive screening in MS, and evaluated several predictors of cognitive deterioration and worsening of employment status. Finally, a new method of cognitive screening was proposed in MS, which could make cognitive screening automatic and widely available.

The field of neuropsychology in MS is rapidly evolving. During the last 30 years, neuropsychological research has completely changed the common view on cognitive impairment in MS. Although there are still many issues and controversies to investigate, neuropsychological diagnostics is becoming more and more common in MS clinics and centers, accompanied by comprehensive research-based guidelines. But despite all these research advances, some level of uncertainty remains. Therefore, expert-based decision making will probably remain part of daily practice in neuropsychological assessment in MS for the years to come.

6. SUMMARY

Neuropsychological assessment of cognitive functions in multiple sclerosis (MS) has been established as an important paraclinical marker of disease stability or progression in MS. It has been established as a standard outcome in MS and we can find it increasingly often as a standard procedure in the clinical practice of MS clinics and centers. Recent recommendations proposed an annual evaluation of cognitive functions in all MS patients as a standard of neuropsychological monitoring in MS. At least an annual screening of information processing speed by the SDMT test should be applied. The trend to diagnose possible disease progression as early as possible is clear. The objective is to allow clinicians to respond quickly, to allow them to stop disease progression as soon as possible.

The theoretical part of this thesis presents the current state of knowledge on cognitive impairment in MS, its correlates, predictors, and treatment possibilities. Furthermore, a comprehensive overview of neuropsychological assessment and diagnosis of cognitive deterioration in MS is presented. The highly relevant topics, such as the cutoff criteria of a meaningful change in individual neuropsychological examination, possibilities of treatment of cognitive deterioration, or the so-called isolated cognitive relapses, are discussed in particular detail.

The empirical part extends current knowledge in the field of MS. I present and discuss six original publications that follow these four main objectives: first, to describe the prevalence of isolated cognitive decline in MS and to put isolated cognitive decline in context with current knowledge on MS disease progression. Second, to identify methods that can improve the quality of the diagnostic process of cognitive deterioration in MS, and third, to explore the concept of subjective cognitive decline, the workability of MS patients, and volumetric MRI markers that can predict future cognitive deterioration. And the last objective is to evaluate compensatory and rehabilitation strategies used to cope with cognitive deterioration in MS.

In the empirical part, I have shown that more than 6% of MS patients can experience deterioration in information processing speed in the annual screening and 4% of MS patients experience isolated cognitive decline without concurrent EDSS or new MS related relapses. Patients with more severe MS are more prone to cognitive deterioration and worsening of employment status; however, patients in less severe phases of the disease might benefit more from annual screening more. An annual assessment can provide clinicians with new disease activity data and help further decide on the treatment and rehabilitation of MS patients. Furthermore, data on possible improvements of the diagnostic process of cognitive deterioration have been presented, including a pilot study on usability of automatic speech analysis in detection of cognitive deterioration, or suggesting the need for normative data stratified by sex.

The findings presented in this thesis have the potential to improve neuropsychological clinical practice in MS centers and clinics. Some results are waiting for future follow-up research; some findings are directly applicable. This thesis successfully applied the RCI methodology for the evaluation of a reliable annual change and proved that this decades-old psychometric approach is applicable for the detection of isolated cognitive decline in the annual neuropsychological screening.

7. SOUHRN

Neuropsychologické vyšetření kognitivních funkcí při onemocnění roztroušenou sklerózou (RS) je stále častěji standardem klinické evaluace progrese a stabilizace onemocnění RS. Sledování kognitivního výkonu je již samozřejmostí ve výzkumné praxi RS a čím dál častěji si nachází svou cestu i do klinické praxe RS center a klinik. Před nedávnem publikované odborné postupy vyšetření kognice u lidí s RS navrhly každoroční screening kognitivních funkcí u všech pacientů s RS jako standard jejich neuropsychologického monitoring. Navržen byl každoroční screening alespoň testem SDMT. Cílem je pokusit se zachytit možnou progresi onemocnění RS co nejdříve. To by umožnilo zdravotnickému personálu rychlou reakci v pokusu zastavit progresi onemocnění.

Teoretická část této práce se věnuje současnému stavu poznání v oblasti kognitivních potíží při RS, popisuje jejich koreláty a prediktory, představuje možnosti v léčbě. Práce také komplexně představuje současnou podobu vyšetření kognitivních funkcí u pacientů s RS a dále také proces diagnostiky kognitivní deteriorace. V tomto ohledu jsou rozebírána především témata klinicky významné změny výsledku v individuálním neuropsychologickém vyšetření, možnosti léčby kognitivního poklesu, nebo téma takzvaných izolovaných kognitivních relapsů.

Empirická část práce dále prohlubuje poznání v této oblasti. V této části prezentuji a diskutuji šest původních vědeckých publikací, které sledují čtyři hlavní cíle práce. Zaprvé: popsat prevalenci izolovaného poklesu kognitivního výkonu při RS a propojit tyto poznatky se současným poznáním o progresi onemocnění RS. Zadruhé, identifikovat metody, které mohou napomoci zlepšení kvality diagnostiky kognitivní deteriorace při RS. Zatřetí: prozkoumat koncept subjektivního kognitivního horšení, práceschopnost lidí s RS, a identifikovat volumetrické MRI prediktory horšení kognitivních funkcí. Posledním cílem je zhodnocení kompenzačních a rehabilitačních strategií užívaných při zvládání zhoršení kognitivního výkonu.

Ve výsledkové části ukazuji, že každoroční screeningové vyšetření rychlosti zpracování informací může odhalit více než 6 % pacientů s RS s významným zpomalením. Až 4 % pacientů pak zažijí izolované zhoršení výkonu kognice, které nedoprovází horšení EDSS nebo nové relapsy. Ke kognitivnímu poklesu jsou více náchylní pacienti s více pokročilým onemocněním, zároveň ale ukazuji, že pacienti ve včasných fázích onemocnění mohou z brzkého záchytu kognitivní deteriorace profitovat více. Bylo ukázáno, že každoroční screening kognitivních funkcí může zdravotníkům přinést nové informace o aktivitě a povaze onemocnění a může tak napomoci rozhodování o možné léčbě nebo rehabilitaci pacientů s RS. Dále pak byla prezentována data, která mohou sloužit ke zlepšení diagnostiky kognitivní deteriorace. Byly představeny výsledky pilotní studie automatické analýzy řeči, která by mohla sloužit ke screeningu kognice, nebo také výsledky o vhodnosti stratifikovaní normativních dat některých neuropsychologických testů na základě pohlaví.

Výsledky prezentované v této dizertaci mají potenciál zlepšit neuropsychologickou klinickou praxi v prostředí RS center a klinik. Některé výsledky čekají na své rozpracování návazným výzkumem, jiné jsou již přímo aplikovatelné. V této dizertaci byl také úspěšně aplikován RCI přístup k hodnocení významnosti změny výkonu při výročním kognitivním screeningu pacientů s RS. Bylo tak ukázáno, že tento desítky let starý psychometrický postup lze aplikovat i u dočasného výročního neuropsychologického screening pacientů s RS.

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9. List of Publications

9.1 Publications Related to the Thesis

PUBLISHED IN IMPACT FACTOR JOURNALS

Motyl, J., Friedova, L., Vaneckova, M., Krasensky, J., Lorincz, B., Blahova Dusankova, J., ... & Uher, T. (2021). Isolated Cognitive Decline in Neurologically Stable Patients with Multiple Sclerosis. *Diagnostics, 11*(3), 464. [**2020 Clarivate IF: 3.706**]

Friedova, L., **Motyl, J.**, Srpova, B., Oechtering, J., Barro, C., Vodehnalova, K., ... & Uher, T. (2020). The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years. *Multiple sclerosis and related disorders*, *46*, 102534. [**2020 Clarivate IF: 4.339**]

Friedova, L., Rusz, J., **Motyl, J.**, Srpova, B., Vodehnalova, K., Andelova, M., ... & Uher, T. (2019). Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study. *Journal of Clinical Neuroscience*, *65,* 28-33. [**2020 Clarivate IF: 1.961**]

Kadrnozkova, L., Vaneckova, M., Sobisek, L., Benova, B., Kucerova, K., **Motyl, J.**, ... & Uher, T. (2018). Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients. *Journal of the neurological sciences*, *388*, 87-93. [**2020 Clarivate IF: 3.181**]

PUBLISHED IN JOURNALS WITHOUT IMPACT FACTOR

Novotná, K., Janatová, M., Kadrnožková, L., Holeňová, M., **Motýl, J.**, Horáková, D., & Kubala Havrdová, E. (2018). Pilotní studie využitelnosti nového programu pro kognitivní rehabilitaci osob s roztroušenou sklerózou. *Rehabilitace a fyzikální lékařství*, *25*(3). [**2020 Clarivate IF: N/A**]

9.2 Publications Unrelated to the Thesis

PUBLISHED IN IMPACT FACTOR JOURNALS

Rusz, J., Vaneckova, M., Benova, B., Tykalova, T., Novotny, M., Ruzickova, H., Uher, T., Andelova, M., Novotna, K., Friedova, L., **Motyl, J**., … & Horakova, D. (2019). Brain volumetric correlates of dysarthria in multiple sclerosis. *Brain and language, 194*, 58-64. [**2020 Clarivate IF: 2.381**]

Andelova, M., Uher, T., Krasensky, J., Sobisek, L., Kusova, E., Srpova, B., Vodehnalova, K., Friedova, L., **Motyl, J.**, ... & Vaneckova, M. (2019). Additive effect of spinal cord volume, diffuse and focal cord pathology on disability in multiple sclerosis. *Frontiers in neurology, 820*. [**2020 Clarivate IF: 4.003**]

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PUBLISHED IN JOURNALS WITHOUT IMPACT FACTOR

Motýl, J., Friedová, L., Blahová Dušánková, J. (2019) Měření kognitivních schopností u pacientů s roztroušenou sklerózou. *Multiple Sclerosis News, 6*(2), 15-19. [**2020 Clarivate IF: N/A**]

10. SUPPLEMENT

1. **Motyl, J.**, Friedova, L., Vaneckova, M., Krasensky, J., Lorincz, B., Blahova Dusankova, J., ... & Uher, T. (2021). Isolated Cognitive Decline in Neurologically Stable Patients with Multiple Sclerosis. *Diagnostics, 11*(3), 464. [**2020 Clarivate IF: 3.706**]
2. Friedova, L., **Motyl, J.**, Srpova, B., Oechtering, J., Barro, C., Vodehnalova, K., ... & Uher, T. (2020). The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years. *Multiple sclerosis and related disorders*, *46*, 102534. [**2020 Clarivate IF: 4.339**]
3. Friedova, L., Rusz, J., **Motyl, J.**, Srpova, B., Vodehnalova, K., Andelova, M., ... & Uher, T. (2019). Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study. *Journal of Clinical Neuroscience*, *65,* 28-33. [**2020 Clarivate IF: 1.961**]
4. Kadrnozkova, L., Vaneckova, M., Sobisek, L., Benova, B., Kucerova, K., **Motyl, J.**, ... & Uher, T. (2018). Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year employment status in multiple sclerosis patients. *Journal of the neurological sciences*, *388*, 87-93. [**2020 Clarivate IF: 3.181**]
5. Novotná, K., Janatová, M., Kadrnožková, L., Holeňová, M., **Motýl, J.,** Horáková, D., & Kubala Havrdová, E. (2018). Pilotní studie využitelnosti nového programu pro kognitivní rehabilitaci osob s roztroušenou sklerózou. *Rehabilitace a fyzikální lékařství, 25*(3). [**2020 Clarivate IF: N/A**]
6. **Motyl, J.**, Friedova, L., Ganapathy Subramanian, R., Vaneckova, M., Fuchs, T. A., Krasensky, J., Blahova Dusankova, J., Kubala Havrdova, E., Horakova, D., Uher, T. (202_). Brain MRI disease burden does not explain sex differences in cognitive performance of patients with multiple sclerosis. [**Submitted to *Multiple Sclerosis and Related Disorders* (Submission ID: MSARD-S-22-00401)**]