CHARLES UNIVERSITY

1st Faculty of Medicine

Summary of the dissertation thesis


# Cognitive Deterioration in Otherwise Clinically Stable Patients with Multiple Sclerosis

# Progrese kognitivního deficitu u jinak klinicky stabilních pacientů s roztroušenou sklerózou

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

# Content

# 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 pro-posed 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, popisu-je 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. Za-třetí: 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

# 1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune neurodegenerative disease of the central nervous system (CNS). 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).

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 clinico-radiological paradox (Uher et al., 2018), characterized as a discrepancy between clinical or cognitive manifestations of the disease and its radiological correlates as seen on MRI.

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, to have the most relevant information on the state of the disease, both radiological and clinical.

Regular monitoring of cognitive functioning in MS is one of the possibilities how to improve the disease monitoring in clinical practice.

Problems of patients with MS connected with cognitive performance are known since the first modern findings about MS. Charcot's early descriptions of people with MS 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. This changed in the late 1980es.

Since then, the neuropsychological outcomes have become an intensively researched subject in MS research field and the neuropsychological assessment has been suggested as a standard procedure in regular MS disease course

monitoring (Ralph H. B. Benedict, Amato, DeLuca, & Geurts, 2020; Kalb et al., 2018).

The current research shows that cognitive impairment (CI) in MS is rather mild. The prevalence of cognitive impairment in MS is between 35% and 65% (Ralph H. B. Benedict et al., 2020; Patti et al., 2015; Rao, 1995). Cognitive impairment affects all MS subtypes and can be found even in very early phases of the disease (Cortese et al., 2016; Hyncicova et al., 2017; Ruano et al., 2017; Uher et al., 2014). Importantly, Association between cognitive impairment and physical disability is mild (Ralph H. B. Benedict et al., 2020; Rao, Leo, Bernardin, & Unverzagt, 1991). This is crucial for possibilities of disease activity and progression monitoring.

The most affected cognitive domains in MS are information processing speed and episodic memory and learning. Followed by executive dysfunction, or impairment of visuospatial functions (Ralph H. B. Benedict et al., 2020; Rao, Leo, Bernardin, et al., 1991). Considering the MRI correlates, cognitive impairment in MS is associated with white matter integrity damage and deep gray matter atrophy in early disease stages, and with cortical atrophy in an advanced MS (Eijlers et al., 2018).

Current recommendations on neuropsychological assessment in MS recommend to do a baseline cognitive screening at the disease onset, and to proceed with cognitive screening in MS annually, to detect cognitive deterioration as early as possible (Kalb et al., 2018; Sumowski et al., 2018). Interestingly, cognitive deterioration in MS can take a form of gradual cognitive decline or (isolated) cognitive relapses (Ralph H. B. Benedict et al., 2020; M. Pardini et al., 2014; Sumowski et al., 2018). Isolated cognitive relapses may not be accompanied by standard neurological clinical disease activity of MS (Meli et al., 2020; Matteo Pardini, 2021). Standard cognitive relapses are well-described (Ralph H. B. Benedict et al., 2020), however, concept of isolated cognitive relapses remains controversial (Baldwin & Morrow, 2021; Matteo Pardini, 2021; Ruet, 2021).

Regarding the treatment of cognitive deterioration, on a group level it has been shown that modern disease modifying drugs (DMD) treatment protects against cognitive deterioration, however, on the individual level, we lack enough data on applicability of concrete DMDs in specific cognitive issues, to

make any treatment decisions based solely on neuropsychological assessment (Landmeyer et al., 2020). On the other hand, cognitive rehabilitation/training is proved to be effective but the effects seem to wane early without continuation, and the effectiveness of the training, to improve quality of life and everyday life activities, seems to be questionable (Chen, Chiaravalloti, & Deluca, 2021; Lampit et al., 2019).

One of the current biggest challenges of research on cognition in MS is to provide data that would support diagnostic process in neuropsychological assessment in MS, that would help to provide more reliable results from the assessment on the individual level, and later the individualized treatment preventing further cognitive deterioration.

# 2. Aims and Hypotheses

This study has four main objectives: 1) to describe the subgroup of people with MS who show signs of cognitive deterioration without the corresponding MS activity; 2) to identify or standardize methods that can improve the quality of the diagnostic process of cognitive deterioration in MS in general and isolated cognitive decline in particular; 3) to 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; 4) to evaluate compensatory and rehabilitation strategies used to cope with cognitive deterioration in MS.

Three main hypotheses were proposed:

1. People with MS experience isolated cognitive decline throughout their disease course.
2. 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.

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.

# 3. Overview of the Studies

## 3.1 Study 1: Isolated Cognitive Decline in Neurologically Stable Patients with Multiple Sclerosis

**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. **[2020 Clarivate IF: 3.706]**

Study 1 investigated the proportion of MS patients with isolated cognitive decline and described the characteristics of patients with an increased risk of isolated cognitive decline. Provided new information on annual cognitive screening to show its possible benefits in everyday clinical practice.

**Methods.** This study investigated a large sample (N=1091) of MS patients with a two-year follow-up. Based on an annual evaluation of the change in the SDMT and the neurological activity of the disease, we divided our sample into four groups characterizing the sample by the presence of neuropsychological or neurological decline and analyzed differences between groups.

**Results.** Annually, 6.4% of the patients experienced cognitive decline and 4.0% experienced isolated cognitive decline without corresponding clinical activity. The vast majority of cognitively worsening patients showed concomitant

progression in other neurological and radiological measures. There were no differences in disease severity between completely stable patients and patients with cognitive worsening, but with normal cognition at baseline.

**Discussion.** When we planned the study procedure to study the possibilities of annual cognitive screening, we decided not to use the proposed clinically meaningful 4-point decline in SDMT (Morrow et al., 2010), as we were skeptical of its usability at the individual level due to the unavoidable random error of measurement (Heilbronner et al., 2010). With the help of Lord and Novick's reliable change index (RCI), we were able to receive conservative estimates on the prevalence of annual cognitive deterioration (Lord & Novick, 1968). It must be noted that using standardized regression-based change (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.

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.

In this study, patients with cognitive worsening showed a trend for a higher disease burden at baseline compared to patients with stable cognition during follow-up. Both the current and previous study (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 may be the most beneficial to detect ongoing disease activity soon; before they reach the cognitive threshold (Schoonheim, Meijer, & Geurts, 2015; Uher et al., 2018).

**Conclusions**. In the case of annual screening by 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 those patients with healthy cognition and mild symptoms of MS might benefit the most from early detection of cognitive decline.

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

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. [**2020 Clarivate IF: 4.339**]

Study 2 investigated the predictive value of sNfL and CSF-NfL levels in newly diagnosed MS patients for the development of cognitive decline after long-term follow-up.

**Methods.** The 58 patients from SET study included in this study underwent a cognitive evaluation at timepoints baseline, year 1, year 9 and had available analysis of neurofilament light chain levels in serum (sNfL) at year 1. We analyzed the association of cognition with average levels of sNfL or CSF-NfL within the first 2 years. 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.

**Results.** We did not observe associations between early sNfL levels and cross-sectional or longitudinal cognitive measures, except for a trend for association between higher sNfL levels at screening and lower California Verbal Learning Test-II (CVLT-II) scores at year 1 (rho = -0.31, unadjusted p = 0.028). A higher level of sNfL was not associated with an increased risk of cognitive decline, except for a trend for an increased risk of CVLT-II decrease in patients with higher sNfL levels at 1 year (OR = 15.8; 95% CI = 1.7–147.0; unadjusted p = 0.015). Similar trends were observed for CSF-NfL.

**Discussion.** These results are consistent with other longitudinal studies investigating the relationship between sNfL levels and cognitive outcomes (Chitnis et al., 2018; Jakimovski et al., 2020). This nonexistence of the relationship between early sNfL levels and cognitive performance could be explained accordingly with the theory of cognitive clinico-radiological paradox (Schoonheim et al., 2015; Uher et al., 2018).

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 (Uher et al., 2018) is related to cortical gray matter atrophy (Eijlers et al., 2018). 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 a concurrent relationship between sNfL levels and cognitive outcomes (Kalatha et al., 2019; Mattioli et al., 2020). Furthermore, the predictive value of sNfL levels in a short-term perspective of disease progression was well described, contrary to long-term prognosis, where the results were inconclusive and controversial (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. It could be that the

relationship would be stronger if the burden of the disease in our sample was higher. Or maybe if we were to use different cognitive assessment methods, 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).

**Conclusions. A**lthough 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 for this relationship.

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

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. [**2020 Clarivate IF: 1.961**]

This study described the relationship between articulation rate characteristics and information processing speed and investigated the potential role of objective speech analysis for the detection of cognitive decline in MS.

**Methods.** 122 patients with MS completed EDSS, speech, and neuropsychological examination. Acoustic speech assessment consisted of the following outcomes: 1) diadochokinetic rate (DDK rate); 2) articulation rate in

reading passage (ARR); and 3) articulation rate in spontaneous speech (ARS). The relationship between cognitive and speech characteristics was tested. Additionally, linear regression analyzes were used to investigate the association between articulation and cognitive measures. The ROC curve was constructed and the AUC was computed to assess the predictive accuracy of the articulation measures to detect abnormal information processing speed.

**Results.** We observed an association between articulation rate and cognitive measures (rho = 0.45–0.58; $p < 0.001$). Faster reading speed by one word per second was associated with an 18.7-point (95% confidence interval [CI] 14.9–22.5) increase in the SDMT score and 14.7 (95% CI 8.9–20.4) point increase in PASAT score (both $p < 0.001$). AUC values of articulation rate characteristics for the identification of processing speed impairment ranged between 0.67 and 0.79. Using a cutoff of 3.10 in reading speed, we were able to identify impairment in both the SDMT and PASAT with 91% sensitivity and 54% specificity.

**Discussion.** The strongest relationship between speech outcome and cognitive performance was observed in articulation rate in reading (ARR) and the SDMT and PASAT cognitive tests. 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. 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. It may 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 the prefrontal, frontal, and subcortical regions that mediate motor control and cognitive processing (Ralph H.B. Benedict et al., 2011).

Our study found that the 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 that they can't be measured otherwise than by the objective acoustic 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 a 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.

**Conclusions.** We showed a strong relationship between slowed articulation rates and a decrease 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.

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

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. [**2020 Clarivate IF: 3.181**]

Cognitive performance decline is known to be related to a worsening employment status due to MS, but reliable predictors of employment status change are lacking. This study identified early clinical and MRI markers of worsening employment status in MS patients at 12-year follow-up.

**Methods.** A total of 145 MS patients had all the necessary longitudinal follow-up data and did not show any signs of comorbidity or worsening employment status due to other reasons than MS. The employment status and hours worked were monitored during regular clinical examinations for 12 years. For the current analysis the employment status of patients was divided into 4 groups that characterize their employment status. 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.

**Results.** In univariate analysis, brain parenchymal fraction, T1 and T2 lesion volume were the best MRI predictors of worsening employment status over the 12-year follow-up period. Duration of MS at baseline (hazard ratio (HR) = 1.10, 95% confidence interval (CI) 1.03–1.18; p = 0.040) was the only significant clinical predictor. Having one extra milliliter of T1 lesion volume was associated with a 53% greater risk of worsening employment status (HR = 1.53, 95% CI 1.16–2.02; p = 0.018). A decrease in the parenchymal fraction of the brain

(BPF) of 1% increased the risk of worsening employment status by 22% (HR = 0.78, 95% CI 0.65–0.95; p = 0.034).

**Discussion.** Loss of employment is one of the severe socioeconomic and psychological consequences of MS. Not only for the individual but also for the society as a whole (Havrdova et al., 2017; Hilt Pfleger, Meulengracht Flachs, & Koch-Henriksen, 2010). The worsening in employability and possible downgrade in career aspirations are also closely related to cognitive performance (Morrow et al., 2010; Rao, Leo, Ellington, et al., 1991; L. Strober, Chiaravalloti, Moore, & DeLuca, 2014).

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).

Interestingly, when we compare the current results with our previous study on predictors of cognitive impairment (Uher 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 (Uher et al., 2017). In our current study we see, already at the baseline, that patients with a worsening employment status due to MS after 12 years had a lower BPF (M = 85.91, ±1.79) and a higher T2 lesion load (M = 2.20, ±5.20) at the beginning of the study. 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.

**Conclusions.** Our study suggested integrated clinical and MRI markers that could suggest a higher 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 factors.

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

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**]

This study provided data on the feasibility of a new computer-based cognitive rehabilitation training intended for MS patients.

**Methods.** A cognitive rehabilitation program intended for restorative training, called Kote, was used. 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 cognitive rehabilitation program 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 questionnaires and a survey to report their experiences with the computer-based program and cognitive training. The training experience and the neuropsychological results were analyzed to provide the first data on the feasibility of the new cognitive training program.

**Results.** The pilot feasibility study included 4 patients with MS. The four patients had a higher neurological deficit with an EDSS range between 5.0 and 6.5 and a 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 Match-ing, 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.

**Discussion.** 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 consistent with other subjective experiences with cognitive training (Klein, Drummond, Mhizha-Murira, Mansford, & Das Nair, 2019).

In this regard, it is questionable whether 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 (Sumowski et al., 2014). We see that people who are physically and intellectually active are more resistant to cognitive deterioration due to MS. The results of cognitive training are promising (Ralph H. B. Benedict et al., 2020; Lampit et al., 2019), but, on the other hand, it has been shown that the training results wane without further continuation, and 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 (Martínez-González & Piqueras, 2015).

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

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

**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)]

This study investigated sex differences in cognitive performance of MS patients, in the context of brain pathology and disease burden.

**Methods.** 1,052 individuals from the GQ study 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.

**Results.** Females had higher scores on the SDMT and the CVLT, but not the BVMT-R or PASAT. Paradoxically, women evaluated their cognitive

performance as worse than males (on MSNQ). 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. Females had a trend for a weaker negative correlation between T2-LL and SDMT, the duration of the disease and CVLT and between EDSS and BVMT-R. On the other hand, women had a trend for a stronger correlation between BPF and BVMT-R, depression and BVMT-R, age and PASAT and EDSS and PASAT. All these trends were not significant after correction for the false discovery rate.

**Discussion.** 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). 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). 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).

Our findings 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.

**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. Sex differences in cognitive performance were not explained by brain pathology or neurological disability.

# 4. 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.

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. More than 81% of patients with MS experiencing isolated cognitive decline showed concurrent radiological activity.

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. 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.

# 5. Conclusions

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

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# 7. List of Publications

## 7.1 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**]

## 7.2 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**]

Hejtmánek, L., Oravcová, I., **Motýl, J.**, Horáček, J., & Fajnerová, I. (2018). Spatial knowledge impairment after GPS guided navigation: Eye-tracking study in a virtual town. *International Journal of Human-Computer Studies, 116*, 15-24. [**2020 Clarivate IF: 3.632**]

Zaytseva, Y., Fajnerová, I., Dvořáček, B., Bourama, E., Stamou, I., Šulcová, K., **Motyl, J.**, ... & Španiel, F. (2018). Theoretical modeling of cognitive dysfunction in schizophrenia by means of errors and corresponding brain networks. *Frontiers in psychology*, *9*, 1027. [**2020 Clarivate IF: 2.988**]

**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**]

## 7.3 Oral Presentations

**Motyl, J.**, Kadrnozkova, L., Dusankova, B. J., Havrdova, E., Horakova, D., & Uher, T. (2017, July). Clinical utility of individual BICAMS tests for cognitive screening. In *Multiple Sclerosis Journal* (Vol. 23, No. 8, pp.

NP9-NP10). ). London: Sage Publications. [**IMSCOGS 2017 Düsseldorf**].

**Motyl, J.**, Kadrnozkova, L., Blahova Dusankova, J., Uher, T., Horakova, D., & Nikolai, T. (2018). Comparison of MS patients with noticeable cognitive abilities decline and improvement in BDI-II, MSNQ and BAI. [**INS 2018 Prague**].

Vozenilek, D., **Motyl, J**., Friedova, L., Uher, T., Lizorva Preiningerova, J., Tyblova, M., Vaneckova, M., Krasensky, J., Kubala Havrdova, E., & Horakova, D. (2021, October). Parameters explaining cognitive outcomes in a reevaluation of the original ASA and SET cohorts after 19 and 10 years of follow-up. In Multiple Sclerosis Journal (Vol 27, Issue 2_Suppl, pp. 30). ). London: Sage Publications. [**ECTRIMS 2021 Virtual Meeting**].

## 7.4 Posters – Presenting Author

**Motyl, J.**, Kadrnozkova, L., Uher, T., & Horakova, D. (2018, May). Influence of sleep duration on cognitive assessment. In *Multiple Sclerosis Journal* (Vol. 24, No. 6, pp. 878-878). ). London: Sage Publications. [**RIMS 2018 Amsterdam**].

**Motyl, J.**, Friedova, L., Uher, T., Preiningerova, J. L., Tyblova, M., Vaneckova, M., ... & Horakova, D. (2019, September). Complex clinical, imaging, cognitive and self-reported outcomes measures re-evaluation of the original ASA and SET cohorts after 19 and 10 years of follow-up. In *Multiple Sclerosis Journal* (Vol. 25, pp. 650-651). ). London: Sage Publications. [**ECTRIMS 2019 Stockholm**].

**Motyl, J.**, Kadrnozkova, L., Dusankova, J. B., Havrdova, E., Horakova, D., & Uher, T. (2019, July). Czech normative study: BICAMS tests for cognitive screening. In *Multiple Sclerosis Journal* (Vol. 25, No. 8, pp. NP14-NP14). ). London: Sage Publications. [**IMSCOGS 2019 Amsterdam**].

**Motyl, J.**, Kadrnozkova, L., Dusankova, J. B., Andelova, M., Uher, T., Vaneckova, M., & Horakova, D. (2019). Cognition as a Disability Progression Marker: Two-Years Follow-Up of People with Multiple Sclerosis (P5. 2-015). [**AAN 2019 Philadelphia**].