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ORIGINAL ARTICLE

Association between cognitive impairment and the disability in people with multiple sclerosis.

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Abstract

BACKGROUND: Cognitive impairment (CI) may be present in people with multiple sclerosis (PwMS) in different stages of the disease, as well as in PwMS with various degrees of disability. This study aimed to investigate cognitive decline over a period of 12 months and to examine an association between cognition and the disability in PwMS, also over a period of 12 months.
METHODS: The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery was used, containing the Symbol Digit Modalities Test (SDMT), the Categorical Verbal Learning Test (CVLT), and the Brief Visuospatial Memory Test-Revised (BVMT-R). The Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9-HPT) were used to assess the degree of disability. For the analysis of cognitive decline over the period of 12 months, Wilcoxon signed-rank test (paired sample t-test) was used. For the correlation between cognition and disability, Spearman's correlation test was used.
RESULTS: We observed statistically meaningful difference only in one measure of cognition (CVLT), not the other two (SDMT and BVMT-R). SDMT significantly correlated with methods assessing the degree of disability in both time points. In the second examination, we observed a correlation between BICAMS and 9-HPT. Similarly, SDMT and BVMT-R also correlated with EDSS.
CONCLUSION: To investigate the cognitive decline in PwMS, a longer period of time probably should have been chosen. EDSS is commonly used to monitor disease progression, but it does not include the evaluation of various parameters, such as cognition or upper limb function. Its use with the 9-HPT and cognitive tests may represent a more reliable and comprehensive assessment of a patient's clinical condition.

Abbreviations:

9-HPT	- 9-Hole Peg Test
BICAMS	- Brief International Cognitive Assessment for Multiple Sclerosis
BVMT-R	- Brief Visuospatial Memory Test-Revised
CI	- Cognitive Impairment
CNS	- Central Nervous System
CVLT	- Categorical Verbal Learning Test
DMT	- Disease Modifying Treatment
EDSS	- Expanded Disability Status Scale
MS	- Multiple sclerosis
MSFC	- Multiple Sclerosis Functional Composite
PASAT	- Paced Auditory Serial Addition Test
PwMS	- People with Multiple Sclerosis
SDMT	- Symbol Digit Modalities Test
T25FW	- Timed 25-Foot Walk

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) that typically affects young people at working age (Compston & Coles 2008; Trapp & Nave 2008). One of the MS symptoms is cognitive impairment (CI) (Benedict *et al.* 2020; Sumowski *et al.* 2018) and is probably directly linked to the etiopathogenesis of MS (Benedict *et al.* 2017).

CI is probably present in approximately 34-65% of people with MS (PwMS) at various stages of the disease (Benedict *et al.* 2020) and tends to worsen over time (Amato *et al.* 2010). The frequency of CI varies across studies. Some sources report a frequency of up to 75% (Trenova *et al.* 2016) other (Benedict *et al.* 2020) states that CI may be present in 34% to 65 % of PwMS. Results of various research studies (Banwell *et al.* 2005; Eijlers *et al.* 2018; Motyl *et al.* 2021) indicate that longer disease duration may be linked to a higher possibility of developing CI and also to gradually increasing disability. On the other hand, long-term use of disease-modifying treatment (DMT) may reverse this phenomenon (Harel *et al.* 2019). Nevertheless, more severe CI and a higher degree of disability may be associated (Ruano *et al.* 2017).

Disability and disease progression are usually assessed by the Expanded Disability Status Scale (EDSS) (Kurtzke 1983). However, this scale has its disadvantages (for the purpose of this article just some of them will be mentioned) – (1) EDSS does not evaluate the upper limb function and (2) it's impossible to determine the severity of acquired CI (Ozakbas *et al.* 2004). Methods overcoming some disadvantages of the EDSS have been proposed to use for disease progression monitoring (Inojosa *et al.* 2020). One of them is the Multiple Sclerosis Functional Composite (MSFC) (Fischer *et al.* 1999). Apart from assessing the walking ability in PwMS, MSFC is focused on the upper limb function and focuses on cognitive assessment. The limitation is that there's only one cognitive test in MSFC, which may not be sufficient for a detailed evaluation of cognition in PwMS, but it does suffice as a screening method for the presence of CI. Despite that, MSFC is probably a more sensitive screening tool than EDSS when evaluating disease progression (Polman & Rudick 2010).

This study aimed to investigate a cognitive decline after 12 months and closely examine the association between tests assessing cognition and methods evaluating disability in PwMS.

METHODS

Research design and participants

The research sample consisted of 139 PwMS, chosen by accidental sampling from larger long-term prospective observational studies conducted at the Centre of demyelinating diseases at the Department of Neurology and the Centre of clinical neurosciences of Charles University, the 1. Faculty of Medicine and General University Hospital in Prague (studies GA UK 154218 study, AZV grant NV18-04-00168). The studies were approved by the Ethical Committee of the General University Hospital in Prague. All of the participants signed the informed consent with participation in the research.

The original, long-term observational studies consisted of 638 PwMS selected by judgmental sampling to proportionally represent all major MS forms as seen in the Prague MS Centre population. The inclusion criteria for PwMS were as follows: clinically isolated syndrome or clinically definite MS confirmed by magnetic resonance imaging (MRI) and cerebrospinal fluid examination (Thompson *et al.* 2018), native Czech speaker, participation in a brain MRI volumetric assessment program, and aged ≥ 18 years. The exclusion criteria were signs and symptoms suggestive of a disease other than MS and a serious psychiatric disorder. The research and the data collection ran annually between May 2018 and November 2021.

For this study, the data were selected from participants who were examined twice between May 2018 and October 2020, 12 months apart. Both examinations had to be completed as follows: 1) complete neurological evaluation (EDSS); 2) administration of 9-HPT and T25FW; 3) neuropsychological examination, where SDMT, CVLT, and BVMT-R were administered. As previously mentioned, the final sample of this study consisted of 139 participants who fulfilled these criteria.

The initial interview has always been completed. After that, the administration of methods for evaluating disability and cognition followed.

Clinical assessment

As a measure of cognition, we used the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) screening battery in a version validated for the use in Czech language environment (Dušánková *et al.* 2012). The battery consists of 3 tests:

1. The Symbol Digit Modalities test (SDMT) (Smith 1973), assessing information processing speed (Van

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Tab. 1. Baseline demographic and clinical characteristics of the research sample

Number of participants	139 (F = 91, M = 48)
Age at the disease onset (mean, in years)	27 (SD: 7.90)
Disease duration (mean, in years)	11.3 (SD: 6.58)
Mean age at the baseline clinical assessment (in years)	38.3 (SD: 8.95)

Tab. 2. Median (range) of EDSS and Mean (SD) of disability scores at baseline and after 12 months

Median (range)	**Baseline**	**After 12 months**	***p*-value (effect size)**
EDSS	2.00 (0.0-5.5)	2.00 (0.0-5.5)	0.467 (0.123)
Mean (SD)	**Baseline**	**After 12 months**	***p*-value (effect size)**
T25FW	4.46 (1.21)	4.42 (1.17)	0.483 (0.071)
9-HPT dominant hand	19.2 (3.17)	18.8 (2.91)	0.061 (0.185)
9-HPT non-dominant hand	20.3 (3.74)	19.9 (3.59)	0.064 (0.183)

EDSS: Expanded Disability Status Scale, T25FW: Timed 25-Foot, 9-HPT: The 9-Hole Peg Test,
$^{**}p < 0.01$, $^{*}p < 0.05$

Schependom *et al.* 2014), but some sources (Leavitt 2021) state that in MS it's rather a general cognitive screener. In our study, we used an oral version of SDMT. A total test score is the sum of all correct answers.

2. The Categorical Verbal Learning Test (CVLT) (Bezdíček & Preiss 2009), assessing verbal learning and memory and resembling California Verbal Learning Test. The total score is the sum of correctly reproduced words in all trials.
3. The Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict 1997) focuses on assessing visuospatial memory (Benedict *et al.* 2012a). The total score is the sum of points the participant got in all 3 attempts.

To minimize the learning effect, after 12 months alternative versions of the tests mentioned above were administered.

To assess disability, we used:

1. The Expanded Disability Status Scale (EDSS), a method rating overall neurological impairment in PwMS (Kurtzke 1983).
2. 9-Hole Peg Test (9-HPT), assessing the upper limb function (Feys *et al.* 2017). There are 2 trials with the dominant and 2 with the non-dominant hand.

The Timed 25-Foot Walk (T25FW), assessing walking ability by tracking the walking speed (Kalinowski *et al.* 2022). The task is to walk 25-foot long distance (approximately 7.6 meters, 2 trials must be completed).

Data analysis

The raw test scores of the BICAMS battery tests were converted to the z-scores. The population-based norms were used for the SDMT (Strober *et al.* 2020), CVLT (Dušánková *et al.* 2012) and BVMT-R (Havlík *et al.* 2020). Cognitive impairment was defined as a z-score of 1.5 standard deviation or more below the average. Cognitive decline was defined as a decrease of a z-score by 1.5 standard deviation or more compared to the baseline neuropsychological examination.

In methods assessing disability, the scores were used as follows. In EDSS, the total score is given by the specialized neurologist as a part of the routine medical examination, which took place on the same day as the cognitive testing. In 9-HPT, the average time of 2 trials (in seconds) for the dominant hand and the average time of 2 trials (in seconds) for the non-dominant hand. In T25FW, the average time of 2 trials (in seconds).

For the statistical analysis, we used the JAMOVI program (version 1.2.27.0) Since our data were not normally distributed, which we discovered using the Shapiro-Wilk normality test, the non-parametric tests were used. Regarding cognitive tests, the first step was to investigate cognitive decline after a period of 12 months by analyzing z-scores. For that purpose, the Wilcoxon signed-rank test (paired sample t-test) was used. To investigate the association between cognitive tests and methods assessing the disability, Spearman's correlation test was used. The level of statistical significance was set at $\alpha = 0.05$.

RESULTS

The main demographic and clinical characteristics of the research sample at baseline are stated in Tab. 1. Median and its range of EDSS, mean raw scores and their standard deviations that participants obtained in cognitive tests and methods assessing the disability can be seen in Tab. 2.

At baseline, CI was present in 35 of 139 participants. After 12 months, CI was present in 37 of 139 participants (24 of them had CI also at the baseline neuropsychological examination).

Tab. 3. Mean (SD) of raw scores and their z-score (effect size) from both neuropsychological examinations (baseline and after 12 months)

Cognitive test	Baseline Mean (SD)	Baseline Z-score (effect size)	After 12 months Mean (SD)	After 12 months Z-score (effect size)	*p*-value (effect size)
SDMT	62.1 (10.7)	0.0791 (1.27)	62.1 (10.5)	0.122 (1.18)	0.434 (-0,098)
CVLT	59.4 (9.43)	0.0308 (1.15)	57.0 (10.7)	-0.270 (1.29)	**< 0.001** (0,407)**
BVMT-R	29.5 (4.58)	0.0586 (1.01)	29.7 (4.46)	0.115 (0.955)	0.420 (-0,080)

SDMT: Symbol Digit Modalities Test, CVLT: Categorical Verbal Learning Test, BVMT-R: Brief Visual Memory Test-Revised, **$p < 0.01$, *$p < 0.05$

Tab. 4. Correlation matrix showing the association between cognition and disability – first measure

		EDSS	T25FW	9-HPT dominant hand	9-HPT non-dominant hand
SDMT	Spearman's rho	-0.285	-0.181	-0.440	-0.417
	p-value	**< 0.001****	**0.033***	**<0.001****	**< 0.001****
CVLT	Spearman's rho	-0.119	-0.116	-0.285	-0.239
	p-value	0.162	0.175	**< 0.001****	**0.005 ****
BVMT-R	Spearman's rho	-0.080	-0.058	-0.112	-0.133
	p-value	0.349	0.494	0.189	0.118

Cognition: SDMT: Symbol Digit Modalities Test, CVLT: Categorical Verbal Learning Test, BVMT-R: Brief Visual Memory Test-Revised.
Disability: EDSS: Expanded Disability Status Scale, T25FW: Timed 25-Foot, 9-HPT: The 9-Hole Peg Test.
**$p < 0.01$, *$p < 0.05$

Results of disability measures, stated in Tab. 2, did not prove any statistically meaningful change after 12 months from baseline. When investigating cognitive decline, we observed statistically meaningful change after 12 months only in one test (CVLT), not the other two (SDMT, BVMT-R). For that reason, correlation analysis between cognition and disability was conducted for each measure separately and the effect of time was not analyzed any further. Results of both neuropsychological examinations (baseline and after 12 months) are stated in Tab. 3.

As we can see in Tab. 4 and Tab. 5, an association between disability and cognition was recorded especially between SDMT and the methods assessing the disability – in the first measure, this was observed between SDMT and all methods assessing the disability; as for the second measure, this was observed between SDMT with EDSS and 9-HPT. Also, an association between CVLT and 9-HPT was recorded in the first measure.

Apart from the results stated above, the second time point showed an association between cognitive tests and methods assessing the degree of disability, especially between cognitive tests and 9-HPT. The results for the second measure can be seen in Tab. 5.

DISCUSSION

In our study, we focused on the association between cognition and disability in PwMS. The first step was to investigate cognitive decline after 12 months. This phenomenon was observed only in one cognitive test (CVLT). The results of disability measures did not show any statistically meaningful change after 12 months. For that reason, the possible effect of time was not analyzed any further. In our results, this association was present between SDMT and the methods assessing the disability. In CVLT, this was present with 9-HPT at both time points. As for BVMT-R, we recorded a relationship with EDSS and 9-HPT dominant hand, but only in the second time point.

Regarding changes in cognition, results of some studies (Amato *et al.* 2010; Harel *et al.* 2019) indicate, that a follow-up examination after 12 months may not show a meaningful change in cognition in PwMS, which may be the reason why this phenomenon was not observed. EDSS is used for monitoring the disease progression and can also be associated with other parameters of MS, such as disease duration (Filippi *et al.* 2020). However, EDSS is probably not the most effective tool for complex assessment of the degree of disability in PwMS (Rommer *et al.* 2019). Results of neuropsychological assessment can provide us with information about the presence of CI. Regrettably, this assessment is not involved in EDSS. For that reason, even though it's a screening battery, BICAMS can provide us with information about cognition in PwMS that EDSS alone can't (Saccà *et al.* 2017). Therefore, their concurrent use in routine clinical practice is more than logical.

T25FW and 9-HPT are a part of the MSFC screening tool. Using this tool, it's possible to assess the degree of disability more accurately than via EDSS (Bin Sawad *et al.* 2016). MSFC is considered to be more sensitive when it comes to identifying subtle changes

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Tab. 5. Correlation matrix showing the association between cognition and disability – second measure

		EDSS	T25FW	9-HPT dominant hand	9-HPT non-dominant hand
SDMT	Spearman's rho	-0.261	-0.054	-0.304	-0.294
	p-value	**0.002****	0.527	**< 0.001****	**<0.001****
CVLT	Spearman's rho	-0.117	-0.096	-0.233	-0.194
	p-value	0.171	0.264	**0.006****	**0.022***
BVMT-R	Spearman's rho	-0.176	-0.081	-0.192	-0.161
	p-value	**0.039***	0.342	**0.025***	0.060

Cognition: SDMT: Symbol Digit Modalities Test, CVLT: Categorical Verbal Learning Test, BVMT-R: Brief Visual Memory Test-Revised.
Disability: EDSS: Expanded Disability Status Scale, T25FW: Timed 25-Foot, 9-HPT: The 9-Hole Peg Test.
**$p < 0.01$, *$p < 0.05$

in the clinical state of PwMS. Also, MSFC focuses on assessing more disease parameters than EDSS (Krysko & O'Connor, 2011) A part of MSFC is a different test measuring information processing speed – Paced Auditory Serial Addition Test (PASAT). For various reasons, PASAT may be substituted in MSFC for SDMT, such as an easier administration process and a much lower risk of practice effect in SDMT, without compromising the validity and reliability of MSFC (Drake *et al.* 2010). Our results also showed the correlation between SDMT and other methods involved in MSFC.

The BICAMS battery is suitable for use in routine clinical practice, which is a conclusion that can be drawn from the results of our study. It's easy to administer, the duration of its administration usually doesn't last more than 15-20 minutes, and examines cognitive domains most prone to be impaired in PwMS (Benedict *et al.* 2012a). In our study, to minimize the learning effect, alternative forms of cognitive tests were used. Alternative forms of SDMT have great test-retest validity (Benedict *et al.* 2012b) and it is recommended to include them in routine clinical practice. The development of alternative word lists for CVLT and their use is even more necessary for the even greater possibility of learning effect (Costers *et al.* 2017). For the same reason, the alternative forms of BVMT-R should be included not only in the clinical setting but also in future research studies (Cai *et al.* 2023).

Our results also point out the importance and relevance of involving MSFC as a part of the clinical examination of PwMS. MSFC contains methods assessing upper limb function and cognition, which is not involved in EDSS. CI is most likely present in the majority of PwMS (Amato *et al.* 2010), but in some of them, it can be more subtle and not very obvious (Potagas *et al.* 2008). Regarding upper limb function in PwMS, some studies (Çelik 2018) indicate its association with cognition. Therefore, the administration of a method assessing upper limb function can provide relevant information about the clinical state of PwMS.

The short follow-up period is one of the limitations of this study. Results stated above pointed out the fact that a period of 12 months is probably not long enough to observe a meaningful change in cognition in PwMS. The emergence of various disease-modifying treatments available for PwMS probably means not only a lower degree of disability but also more preserved cognition and a milder form of CI. Future studies should probably be focused on a more detailed investigation of this phenomenon. BICAMS is a screening battery assessing cognitive domains more prone to be impaired in PwMS. The reason that led to the development of BICAMS was to provide clinicians with a battery sensitive enough to detect CI in PwMS and its time of administration is not too long (Langdon *et al.* 2012). However, to thoroughly investigate an association between cognition and disability, using a more comprehensive battery of cognitive tests would be more suitable. For the same reason, our study should have consisted of a higher proportion of more disabled participants. Also, to complete our analysis, disease duration should have been included as another variable.

In conclusion, a period of 12 months is probably not long enough to observe a notable change in cognition in PwMS. Regarding cognition and disability in PwMS, an association between these variables was present in our research sample. The strongest relationship was recorded between SDMT and all methods assessing disability. In future research studies, a battery containing more cognitive tests is probably more suitable to use. As stated in other sources (Sandry *et al.* 2021), SDMT is very sensitive for the detection of CI, but a poor score in this test only indicates the presence of CI, but it does not specify its character, which may be crucial when investigating the relationship between cognition and other disease characteristics.

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Neuroscience, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interest

All authors declare that they have no conflict of interest.

Ethical approval

This research was realized as a part of larger long-term prospective observational studies conducted at the Centre of demyelinating diseases at the Department of Neurology and the Centre of clinical neurosciences of Charles University, the 1. Faculty of Medicine and General University Hospital in Prague (studies GA UK 154218 study, AZV grant NV18-04-00168). The studies were approved by the Ethical Committee of the General University Hospital in Prague.

Informed consent

Informed consent was obtained from all individual participants included in the study.

The institution where work was performed

Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic.

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