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# Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study

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ABSTRACT

*Background:* The definition of benign multiple sclerosis (BMS) is still debated. It is mainly based on physical status, however, there is an attempt to involve cognitive functioning or paraclinical factors in order to avoid unnecessary long-term treatment with disease-modifying therapies and to identify these subjects in the early stages of the disease. Therefore the aim of our two-year follow-up study was to investigate the pattern of cognitive functioning and depression in patients with BMS compared to treated relapsing-remitting MS (RRMS) patients and healthy controls.

*Methods:* A group of 22 BMS patients was tested against matched RRMS patients and healthy controls. All individuals underwent neuropsychological evaluation exploring mood and the cognitive domains most frequently impaired in MS. MS patients were retested at two-year follow-up.

*Results:* In terms of cognitive functions there were no differences between BMS and RRMS patients either at baseline or at two-year follow-up. Compared to healthy controls BMS patients showed poorer performance in long-term visuo-spatial memory and information processing speed, whereas, complex attention, working memory, long-term verbal memory – despite slower verbal learning – and executive function were found to be intact. RRMS patients showed significant difference in complex attention, long-term visual memory and information processing speed. Cognitive impairment differed in the patient groups in terms of severity. Both patient groups were depressed compared to controls, but significant differences were found only between BMS and healthy individuals.

*Conclusion:* The results of our study confirm that cognitive functions and mood can be affected in MS independent of disease course and disease modifying treatment. The "benign" label should be treated as only a reference to physical status and non-motor symptoms should be routinely monitored. Without receiving therapy it is an existing entity with longstanding minimal disability.

## 1. Introduction

Benign multiple sclerosis (BMS) has been receiving growing attention because of the uncertainty of precise definition (Amato and Portaccio, 2012; Correale et al., 2012b; Gajofatto et al., 2016; Hawkins, 2012). It is a subgroup of patients who show little or no disease progression and minimal disability minimum a decade after the clinical onset. Recent studies are focusing on the role of paraclinical factors in diagnosing and predicting benign cases (Amato et al., 2008; Benedict and Fazekas, 2009; Correale et al., 2012a; Glad et al., 2010).

The definition of different MS courses does not account sufficiently for other disease-related changes such as cognitive deficits, depression, fatigue or pain (Correale et al., 2012a) which may be as disabling as motor impairment resulting in an adverse effect on quality of life (Gajofatto et al., 2016). Despite preservation of motor functioning, the prevalence of significant cognitive impairment, depression and fatigue in BMS is comparable to those reported in MS patients at large (Correale et al., 2012a). These results confirmed that a simple definition of benign MS on the basis of EDSS score may be misleading and the proportion of benign subjects may be overestimated (Amato et al., 2006).

In MS most frequently affected cognitive domains are attention (complex, selective and divided), memory (mainly retrieval from long-term verbal as well as visuo-spatial storage), processing speed and executive function (concept formation, feedback utilization, and set shifting) (Chiaravalloti and DeLuca, 2008). Several studies have shown that the disease course, unlike the brain tissue damage (Vinciguerra et al., 2019), does not predict the degree of cognitive

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involvement, neither physical disability status nor disease duration is associated with the impairment (Engel et al., 2007; Rogers and Panegyres, 2007).

In a longitudinally followed cohort of benign MS patients, around one in five patients had moderate to severe depression (Sayao et al., 2011) that is comparable with the yearly proportion of 20% in the whole MS population (Sa, 2008). Depression in MS is reported to be associated with the level of neurological disability and with poor cognition, especially, working memory, executive function and information processing speed (Feinstein et al., 2014).

Therefore current studies aim at a more comprehensive understanding of BMS, a more accurate assessment of physical status, cognitive impairment, fatigue, pain and social functioning. It would result in a consensus on BMS criteria in order to avoid unnecessary long-term treatment with disease-modifying therapies (DMT) (Amato and Portaccio, 2012; Leray et al., 2013) and to solve the practical problem of how to accurately identify these subjects in the early stages of the disease.

The aim of our two-year follow-up study was to investigate the pattern of cognitive functioning and depression in patients with BMS compared to a comparison group of treated relapsing-remitting MS (RRMS) patients and healthy controls. We were hoping to provide further insight into the different aspects of truly remained benign cases. We were interested in the difference between the cognitive status of patients with benign course without any disease modifying treatment (DMT) and the profile of RRMS patients treated from the beginning of the disease onset.

We hypothesized that cognitive functions of BMS patients would differ from those of healthy controls, whereas, RRMS patients would present the same cognitive performance. The level of depression would be higher in both MS groups than in the healthy group and it would not differ in the two patient groups. As for the two-year follow-up, we hypothesized that there would not be any change in cognitive performance of treated patients, that is, therapeutic efficacy of DMT on somatic symptoms would not be confirmed in relation to cognitive functions. In BMS group the cognitive performance would remain stable. Without treatment, the level of depression would not change.

## 2. Method

### 2.1. Participants and study design

A study was conducted based on the analysis of clinical data acquired from a registry of 400 MS outpatients from the year of 2014 at the Department of Neurology of Semmelweis University. Patients were included in the BMS group based on a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria) and a benign course defined as an EDSS score $\leq 3.0$ after at least 10 years from the clinical onset of the disease (Polman et al., 2011). These patients have never been treated with immunomodulatory drugs. They follow the natural course of the disease. Of 30 eligible patients (7.5%), 22 gave consent for neuropsychological assessment.

A comparison group of 22 MS patients was recruited. Inclusion criteria were: (1) a definite diagnosis of MS (according to 2010 McDonald diagnostic criteria); (2) relapsing remitting course (Polman et al., 2011); (3) receiving of disease modifying treatment. In the beginning of disease course, the disease activity was higher in this group compared to BMS group. Therefore drugs were started in each patient after their first relapse in the setting of everyday clinical practice (based on the legislation of National Health Insurance Fund of Hungary).Controlling for demographic and clinical characteristics, cases in the patient groups were matched in terms of age, gender, education and disease duration.

Exclusion criteria for both MS groups included: (1) an acute MS relapse; (2) corticosteroid treatment within 90 days before the cognitive assessment; (3) other significant neurologic or psychiatric illnesses; (4) treatment with psychoactive drugs for depression or fatigue and (5) alcohol or drug abuse.

After a 2-year period patients were clinically reevaluated. In both groups patients had the same disease course remaining in the same MS group. RRMS patients continued to receive the DMT. None of them were treated especially for cognitive impairment or depression. They were reassessed through the use of the same neuropsychological testing battery that had been initially administered.

Healthy volunteers matched with the sample for gender, age and education were also studied at baseline. None of them referred to any previous neurological or systemic diseases potentially affecting the central nervous system function, and the neurological exam was normal in all cases.

All participants gave an informed consent. The study was approved by the Regional Ethical Committee.

### 2.2. Neuropsychological assessment

Participants underwent a neuropsychological evaluation exploring the cognitive domains most frequently impaired in MS: complex attention [Paced Auditorial Serial Attention Test 3 seconds (PASAT-3)] (Rao et al., 1989); visuo-spatial memory [Rey-Osterrieth Complex Figure Test (CFT)]; learning, verbal memory [Auditory-Verbal Learning Test (AVLT)]; working memory [Digit Span (DS)]; information processing speed [Wechsler's Digit Symbol Test (WDST)]; and executive function [Tower of Hanoi (TH)] (Muriel Deutsch Lezak, 2012). The neuropsychological battery was administered in 45 min by a trained psychologist in a preordered sequence.

Our evaluation incorporated the recommendations of the latest battery for cognitive assessment to be applied in clinical routine, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Benedict et al., 2012; Langdon et al., 2012). It detects cognitive changes in the domains of information processing speed, verbal and visual memory including Symbol Digit Modalities Test, California Verbal Learning Test and Brief Visuospatial Memory Test. It was completed with testing complex attention, working memory and executive function.

Test failure was defined as a performance of $<1.5$ standard deviations below healthy control subjects (Borghi et al., 2013; Jonsson et al., 2006). Patients failing at least two tests or subtests were considered cognitively impaired (CI), failing 0–1 test meant cognitively preserved (CP) status (Amato et al., 2010; Lopez-Gongora et al., 2015). The neuropsychological performance was classified as worsened at 2-year follow-up if the patient failed at least two more tests compared to baseline assessment (Sayao et al., 2011).

### 2.3. Depression assessment

Depression was assessed using the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). It is a 20-item questionnaire that has been shown to have good construct validity for measuring depression in medically ill populations and has been used for patients with MS (Skokou et al., 2012).

### 2.4. Statistical analysis

Demographic and clinical characteristics of the participants were summarized as mean $\pm$ standard deviation (SD). Data were tested for normal distribution using the Shapiro–Wilk test. Group differences in EDSS score were determined using non-parametric Mann–Whitney $U$ test. Differences in cognitive parameters and depression between groups were determined using the multivariate analysis of variance tests. At baseline, Kruskal–Wallis $H$ test was applied in case the assumption of normal distribution failed. The Bonferroni correction adjusted multiple comparisons between groups. Analyzing follow-up data, between group comparisons were assessed using the 2-tailed $t$-test for

**Table 1**
Demographic and clinical characteristics of the study sample, baseline.

| | BMS 1 $n = 22$ | RRMS 2 $n = 22$ | Control 3 $n = 22$ | $p$-value 1–2 | 1–3 | 2–3 |
|---|---|---|---|---|---|---|
| Gender, $n$ (men/women) | 5/17 | 5/17 | 5/17 | n.s. | n.s. | n.s. |
| Age, $y$, mean (SD) | 44.9 (9.5) | 45.1 (9.2) | 44.9 (9.6) | n.s. | n.s. | n.s. |
| Education, $y$, mean (SD) | 13.6 (2.1) | 14.1 (2.2) | 13.9 (2.5) | n.s. | n.s. | n.s. |
| Disease duration, $y$, mean (SD) | 14.9 (6.1) | 13.7 (6) | n.r. | n.s. | – | – |
| EDSS score, mean (SD) | 1.2 (0.9) | 1.7 (1.5) | n.r. | n.s. | – | – |
| DMT, $n$ | | | | | | |
| Interferon beta 1b | 0 | 5 | n.r. | n.r. | – | – |
| Glatiramer acetate | 0 | 6 | n.r. | n.r. | – | – |
| Natalizumab | 0 | 2 | n.r. | n.r. | – | – |
| Fingolimod | 0 | 1 | n.r. | n.r. | – | – |
| Teriflunomide | 0 | 3 | n.r. | n.r. | – | – |
| Dimethyl fumarate | 0 | 5 | n.r. | n.r. | – | – |
| Depression score, mean (SD) | 43.4 (10.1) | 39.4 (7.5) | 35.9 (5.7) | n.s. | 0.008 | n.s. |

*Note.* $y$: years, SD: standard deviation, EDSS: expanded disability status scale, DMT: disease modifying treatment, n.s.: not significant, n.r. not relevant.

unpaired samples or the non-parametric Mann–Whitney $U$ test. The Wilcoxon test or 2-tailed $t$-test for paired samples was used for within group comparisons. Pearson's correlation was performed to evaluate the association between depression and the different cognitive domains. All analyses were carried out using the SPSS software (version 25.0 for Windows; SPSS Inc., Chicago, Illinois, USA). In all cases $p$ values $<0.05$ were taken as significant.

## 3. Results

Demographic and main clinical data of the subjects included in the study at baseline and at 2-year follow-up are shown in Tables 1 and 2. The mean level of EDSS was 1.2 (SD = 0.9) in BMS group and 1.7 (SD = 1.5) in RRMS group. There was no significant difference between them. Clinical characteristics including EDSS scores of MS patients did not change after two years (1.2, SD = 0.9; 1.8, SD = 1.7), they were considered still benign or relapsing-remitting.

The mean level of depression was more elevated in the BMS group compared to the RRMS group, however, significant differences were found only between BMS and healthy groups (43.4 (SD = 10.1) vs. 35.9 (SD = 5.7), $p = 0.008$). At two-year follow-up, mean level of depression did not change significantly in the MS groups.

Cognitive scores at baseline are presented in Table 3. Non-significant differences between MS groups were noted in the measured cognitive domains. In comparison with the healthy control group, there were significant differences in the BMS group in the following mean scores and domains: CFT (18.34 (SD = 5.3) vs. 24.43 (SD = 7.5), $p = 0.005$) – visuo-spatial memory; AVLT-L (51.82 (SD = 8.8) vs. 58.23 (SD = 8.4), $p = 0.04$) – auditory–verbal learning; and WDST (42.05 (SD = 10.5) vs. 52.00 (SD = 10.8), $p = 0.017$) – information processing speed. Scores of complex attention, verbal memory, working memory and executive function did not differ significantly between the two groups. In RRMS group significant differences were found compared to healthy group in terms of PASAT-3 (35.55 (SD = 12.5) vs. 45.82 (SD = 11.5), $p = 0.032$) – complex attention; CFT (19.72 (SD = 5.7) vs. 24.43 (SD = 7.5), $p = 0.044$) – visuo-spatial memory; and WDST (38.23 (SD = 13.2) vs. 52.00 (SD = 10.8), $p = 0.001$) – information processing speed. Scores of verbal learning, verbal memory, working memory and executive function did not differ significantly between the two groups.

**Table 2**
Demographic and clinical characteristics of the study sample, 2-year follow-up.

| | BMS 1 $n = 22$ | RRMS 2 $n = 22$ | $p$-value 1–2 |
|---|---|---|---|
| Gender, $n$ (men/women) | 5/17 | 5/17 | n.s. |
| Age, $y$, mean (SD) | 46.9 (9.5) | 47.1 (9.2) | n.s. |
| Education, $y$, mean (SD) | 13.6 (2.1) | 14.1 (2.2) | n.s. |
| Disease duration, y, mean (SD) | 16.9 (6.1) | 15.7 (6) | n.s. |
| EDSS score, mean (SD) | 1.2 (0.9) | 1.8 (1.7) | n.s. |
| DMT, $n$ | | | |
| Interferon beta 1b | 0 | 5 | n.r. |
| Glatiramer acetate | 0 | 6 | n.r. |
| Natalizumab | 0 | 2 | n.r. |
| Fingolimod | 0 | 1 | n.r. |
| Teriflunomide | 0 | 3 | n.r. |
| Dimethyl fumarate | 0 | 5 | n.r. |
| Depression score, mean (SD) | 44.6 (9.0) | 40.9 (7.9) | n.s. |

*Note.* $y$: years, SD: standard deviation, EDSS: expanded disability status scale,. DMT: disease modifying treatment, n.s.: not significant, n.r. not relevant.

**Table 3**
Neuropsychological scores at baseline, comparison between groups .

| Domain and test | BMS 1 $n = 22$ | RRMS 2 $n = 22$ | Control 3 $n = 22$ | $p$-value 1–2 | 1–3 | 2–3 |
|---|---|---|---|---|---|---|
| Complex attention | | | | | | |
| PASAT-3 | 40.09 (11.1) | 35.55 (12.5) | 45.82 (11.5) | n.s. | n.s. | 0.015 |
| Memory | | | | | | |
| CFT | 18.34 (5.3) | 19.72 (5.7) | 24.43 (7.5) | n.s. | 0.005 | 0.044 |
| AVLT-L | 51.82 (8.8) | 55.14 (8.8) | 58.23 (8.4) | n.s. | 0.04 | n.s. |
| AVLT | 10.73 (3.3) | 11.41 (3.2) | 12.36 (2.6) | n.s. | n.s. | n.s. |
| DS | 12.05 (2.1) | 12.27 (2.2) | 12.18 (2.3) | n.s. | n.s. | n.s. |
| Information processing speed | | | | | | |
| WDST | 42.05 (10.5) | 38.23 (13.2) | 52.00 (10.8) | n.s. | 0.017 | 0.001 |
| Executive function | | | | | | |
| TH* | 26.86 (4.1) | 29.23 (4.5) | 28.00 (5.4) | n.s. | n.s. | n.s. |

*Note.* Scores are mean (SD).
PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi.
n.s.: not significant.
* Lower value means better performance.

Cognitive scores at two-year follow-up compared to baseline are shown in Table 4. The cognitive evaluation showed no significant differences between BMS patients and RRMS patients. In BMS group, significantly higher mean scores were found on AVLT-L subtest (51.82 (SD = 8.8) vs. 55.77 (SD = 10.1), $p = 0.024$) and on WDST test (42.05 (SD = 10.5) vs. 45.43 (SD = 12.0), $p = 0.022$) at two-year follow-up cognitive evaluation compared to baseline performance. Auditory–verbal learning and information processing speed improved. The cognitive performance of RRMS patients remained stable.

Cognitive scores of different domains were not correlated to depression scores either at baseline or at two-year follow-up.

Cognitive impairment related data by domains are summarized in Table 5. In BMS group at baseline assessment, the most frequently involved tests were those assessing information processing speed (WDST,

**Table 4**
Neuropsychological scores, 2-year follow-up, comparison within groups and between groups.

| Domain and test | BMS 1($t_1$), $n$ = 22 | BMS 1($t_2$) | $p$ | RRMS 2($t_1$), $n$ = 22 | RRMS 2($t_2$), $n$ = 22 | $p$ | $p$-value, 1($t_2$) − 2($t_2$) |
|---|---|---|---|---|---|---|---|
| Complex attention | | | | | | | |
| PASAT-3 | 40.09 (11.1) | 41.68 (10.8) | n.s. | 35.55 (12.5) | 39.23 (12.7) | n.s. | n.s. |
| Memory | | | | | | | |
| CFT | 18.34 (5.3) | 19.27 (6.5) | n.s. | 19.72 (5.7) | 19.43 (6.0) | n.s. | n.s. |
| AVLT-L | 51.82 (8.8) | 55.77 (10.1) | 0.024 | 55.14 (8.8) | 56.45 (9.4) | n.s. | n.s. |
| AVLT | 10.73 (3.3) | 11.23 (3.8) | n.s. | 11.41 (3.2) | 11.36 (3.3) | n.s. | n.s. |
| DS | 12.05 (2.1) | 11.45 (2.3) | n.s. | 12.27 (2.2) | 11.86 (2.4) | n.s. | n.s. |
| Information processing speed | | | | | | | |
| WDST | 42.05 (10.5) | 45.43 (12.0) | 0.022 | 38.23 (13.2) | 39.57 (14.5) | n.s. | n.s. |
| Executive function | | | | | | | |
| TH* | 26.86 (4.1) | 28.59 (5.1) | n.s. | 29.23 (4.5) | 29.73 (7.9) | n.s. | n.s. |

*Note.* Scores are mean (SD).
PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi.
$t_1$: baseline; $t_2$: 2-year follow-up.
n.s.: not significant.
* Lower value means better performance.

**Table 5**
Neuropsychological test results in BMS and in RRMS patients at baseline and at 2-year follow-up.

| Number of failed cognitive tests in study groups, $n$ (%) | | | | |
|---|---|---|---|---|
| | Baseline | | 2-year follow-up | |
| Domain and test | BMS $n$ = 22 | RRMS $n$ = 22 | BMS $n$ = 22 | RRMS $n$ = 22 |
| Complex attention | | | | |
| PASAT-3 | 4 (18%) | 7 (32%) | 4 (18%) | 6 (27%) |
| Memory | | | | |
| CFT | 5 (23%) | 5 (23%) | 4 (18%) | 3 (14%) |
| AVLT-L | 6 (27%) | 3 (14%) | 5 (23%) | 2 (9%) |
| AVLT | 6 (27%) | 4 (18%) | 4 (18%) | 4 (18%) |
| DS | 1 (5%) | 2 (9%) | 2 (9%) | 1 (5%) |
| Information processing speed | | | | |
| WDST | 7 (32%) | 10 (45%) | 6 (27%) | 7 (32%) |
| Executive function | | | | |
| TH | 1 (5%) | 2 (9%) | 1 (5%) | 3 (14%) |

*Note.* PASAT-3: Paced Auditorial Serial Attention Test 3 seconds; CFT: Rey-Osterrieth Complex Figure Test; AVLT-L: Auditory-Verbal Learning Test, learning; AVLT: Auditory-Verbal Learning Test, verbal memory; DS: Digit Span; WDST: Wechsler's Digit Symbol Test; TH: Tower of Hanoi.

32%), verbal learning and memory (AVLT-L, 27%; AVLT, 27%), visual memory (CFT, 23%) and complex attention (PASAT-3, 18%). Working memory and executive function was found to be less affected. At two-year follow-up slight improvement were observed in information processing speed (WDST, 27%), verbal learning and memory (AVLT-L, 23%; AVLT, 18%) and visual memory (CFT, 18%). In RRMS group the most frequently involved domains were information processing speed (WDST, 45%), complex attention (PASAT-3, 32%), visual memory (CFT, 23%) and verbal memory (AVLT, 18%). At two-year follow-up the number of failed tests decreased in the field of information processing speed (WDST, 32%), complex attention (PASAT-3, 27%) and visual memory (CFT, 14%).

Table 6 shows the individual cognitive status and severity of impairment. The neuropsychological assessment allowed for the identification (failed at least two cognitive tests or subtests) of ten cognitively impaired BMS patients (45%), eight cognitively impaired RRMS patients (36%) at baseline and seven cognitively impaired BMS patients (32%), six cognitively impaired RRMS patients (27%) at two-year follow-up. In BMS group one case, in RRMS group no case was found for worsening. Improvement was detected in three cases in both groups.

**Table 6**
Number of failed cognitive tests per individual in patient groups at baseline and at 2-year follow-up.

| Number of failed cognitive tests | Baseline, $n$ (%) | | 2-year follow-up, $n$ (%) | |
|---|---|---|---|---|
| | BMS $n$ = 22 | RRMS $n$ = 22 | BMS $n$ = 22 | RRMS $n$ = 22 |
| 0 | 10 (45%) | 10 (45%) | 11 (50%) | 11 (50%) |
| 1 | 2 (9%) | 4 (18%) | 4 (18%) | 5 (23%) |
| 2 | 5 (23%) | 4 (18%) | 2 (9%) | 3 (14%) |
| 3 | 2 (9%) | 1 (5%) | 2 (9%) | 0 |
| 4 | 3 (14%) | 0 | 3 (14%) | 1 (5%) |
| 5 | 0 | 1 (5%) | 0 | 1 (5%) |
| 6 | 0 | 1 (5%) | 0 | 1 (5%) |
| 7 | 0 | 1 (5%) | 0 | 0 |
| CI, $n$ (%) | 10 (45%) | 8 (36%) | 7 (32%) | 6 (27%) |

*Note.* CI: cognitively impaired.

## 4. Discussion

This study represents to our knowledge the first attempt of evaluating cognitive functions of BMS patients never treated compared to RRMS patients treated with disease modifying therapy. We report a cohort of benign MS patients followed longitudinally for two years, with repeated disability measures and a battery of neuropsychological assessments, compared to healthy controls and RRMS patients. In our clinic the prevalence of BMS patients is in line with the occurrence rate revealed in other studies (Correale et al., 2012b). We tested the hypothesis that cognitive performance of BMS patients is similar to the capabilities of RRMS patients and both of them differ from the cognitive profile of people without MS. Furthermore, the level of depression is more elevated in both patient groups compared to healthy individuals.

Cognitive impairment is common in MS including deficits in complex attention, information processing speed, executive function and long-term memory (Chiaravalloti and DeLuca, 2008). Similar cognitive profile in BMS patients was found as in the whole MS population (Correale et al., 2012a). We found that both BMS and RRMS patients differed from healthy controls in terms of cognitive functioning. BMS patients showed worse performance in long-term visuo-spatial memory and information processing speed, whereas, complex attention, working memory, long-term verbal memory – despite slower verbal learning – and executive function were found to be intact. RRMS patients showed significant difference in complex attention, long-term visual memory and information processing speed compared to people without MS. While working memory, long-term verbal memory – even verbal learning – and executive function were not affected. This may support

the finding that executive function is a less frequently involved domain than memory and information processing speed. The most frequently affected complex attention and speed of information processing can significantly influence the performance in other domains, meaning these functions could be targeted with cognitive rehabilitation.

As previously reported (Chiaravalloti and DeLuca, 2008), we did not find differences in cognitive functioning between BMS and RRMS patients. This result did not change after two years despite the improvement of the BMS group in verbal learning and information processing speed. Here we may consider practice effect, however, it was ferreted out by the study design, reevaluating two patient groups. The verbal learning may improve due to intact executive function and less involved complex attention compared to RRMS group, thus, patients can generate reconstituted learning strategy in the repeated test situation. In case of information processing speed, individual cases may bias the result (two BMS subjects had a performance of 1.55 standard deviations above mean BMS value). Our findings are in line with those studies suggesting that immunomodulatory treatment may not result in significant reductions in cognitive symptoms (Haase et al., 2004; Sundgren et al., 2016) and cognitive deficits can occur independent of physical disability.

Cognitive impairment in the patient groups was in the range previously reported (BMS: 45%; RRMS: 36% at baseline) (Borghi et al., 2013; Rao et al., 1991). The difference between BMS and RRMS patients is the severity in case we analyze the number of failed tests per individual. This aspect of cognitive performance supports the findings that information processing speed is the most involved in both MS groups, complex attention is more involved in RRMS patients than in BMS patients, working memory and executive function is less involved in both MS groups.

A high prevalence rate of depression (31%) in MS was demonstrated (Boeschoten et al., 2017). A twelve-month prevalence rate of about 20% and a lifetime prevalence rate of 50% were reported (Sa, 2008). Untreated depression is associated with suicidal ideation, impaired cognitive function and poor adherence to immunomodulatory treatment (Ziemssen, 2009). The presence of depressive disorder does not correlate well with the level of neurological disability (Goldman, 2005). However, we observed an elevated level of depression in the BMS group compared to people without MS. Herein we may consider that this patient group does not receive DMT and they do not attend regular check-up resulting in the lack of external control of the disease. It would underline the importance of involving them in the clinical routine in order to strengthen their feeling of security (Vattakatuchery et al., 2011).

Previous studies have demonstrated that the association between depression and cognitive impairment affects specific cognitive domains, such as working memory, processing speed, attention and executive functions (Arnett et al., 2008; Morrow et al., 2016; Sundgren et al., 2013). Herein, we did not find correlation between depression and the different cognitive domains in any patient groups. However further investigation could give deeper insights into the relationship.

Our study presents some strengths. The study design allowed a detailed neuropsychological assessment of matched cohorts followed longitudinally. The inclusion criteria of BMS group involved the natural course of the disease enabling the examination of the effect of disease modifying therapy on cognitive functioning. The presented cognitive profile provided implication for cognitive rehabilitation apart from DMT. It outlined the higher level of depression in BMS patients.

We need to mention some limitations that may have an impact on the findings of present study. Our design was clinic-based instead of population-based with relatively low sample size. However, all registered patients were involved, including those not necessarily returning to the clinic for regular check-ups. Two-year follow-up and the low number of patients involved allowed us to present preliminary data and tendency. Paraclinical factors, such as fatigue, were not investigated which could have an impact on cognition itself. Further limitation of our study could be the absence of MRI data, however, our aim included the focus on clinical – more precisely – on neuropsychological status. Further study should include the MRI parameters of the patient groups in order to have a better understanding of cognitive functioning.

## 5. Conclusions

The results of our study confirm that cognitive functions and mood can be affected in MS independent of disease course. Therefore “benign” label should be treated as only a reference to physical status. Cognitive and psychological status should be assessed and managed irrespectively to MS subtype, meaning the need for routine monitoring of non-motor symptoms in BMS. Although the clinical relevance of BMS is said to be limited (Reynders et al., 2017) we consider this patient group with longstanding minimal disability without DMT as an existing entity. As cognitive functioning in treated RRMS patients has not changed in a two-year period, it may implicate that disease modifying treatment might not have influence on cognitive functions. Prognostic factors of BMS status still need to be identified. The ability to predict clinical course would be important in order to optimize patient management and to select the most appropriate therapeutic interventions.

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## Declaration of Competing Interest

The authors confirms that there are no known conflicts of interest regarding the work described in the manuscript.

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