Cognitive impairment in multiple sclerosis phenotypes: Neuropsychological assessment in a portuguese sample

Cláudia Sousa, Teresa Jacques, Maria José Sá & Rui A. Alves

To cite this article: Cláudia Sousa, Teresa Jacques, Maria José Sá & Rui A. Alves (2022): Cognitive impairment in multiple sclerosis phenotypes: Neuropsychological assessment in a portuguese sample, Applied Neuropsychology: Adult, DOI: 10.1080/23279095.2022.2112681

To link to this article: https://doi.org/10.1080/23279095.2022.2112681

Published online: 17 Aug 2022.

Submit your article to this journal

Article views: 117

View related articles

View Crossmark data
Cognitive impairment in multiple sclerosis phenotypes: Neuropsychological assessment in a portuguese sample

Cláudia Sousa, Teresa Jacques, Maria José Sá, and Rui A. Alves

Objective: This study aims to assess the cognitive function in a hospital-based cohort of Portuguese MS patients, to allow estimating the prevalence of cognitive impairment in different phenotypes.

Methods: Three hundred and thirteen patients with Multiple Sclerosis (MS) underwent neuropsychological assessment with the brief repeatable battery of neuropsychological tests (BRBN-T) and the brief international cognitive assessment for multiple sclerosis (BICAMS).

Results: Differences were observed in the cognitive impairment profile of different disease phenotypes and of the different disease severity stages. RRMS patients performed better in the cognitive test of the BRBN-T and BICAMS than those with progressive disease phenotypes. Relationships between cognitive impairment and disability and professional status were relevant. Although similarities could be observed in the cognitive profile of the MS phenotypes, with predominant involvement of verbal memory, verbal fluency, and information processing speed, the latter was found to be more frequent as the disease progressed.

Conclusion: This study contributes to improve knowledge about the cognitive profile of the different MS phenotypes and understand the cognitive characteristics of Portuguese patients.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that can be clinically categorized into different phenotypes: clinically isolated syndrome (CIS), relapsing/remitting (RRMS), primary progressive and secondary progressive MS (PPMS and SPMS), and can be sub-classified according to its clinical and radiological activity (Lublin et al., 2014). In most patients, MS starts as a remitting-remission and in about 15–30% it progresses to secondary progressive (Thompson et al., 2018). Only a few patients have a primary progressive course at onset (Miller & Leary, 2007).

Cognitive impairment (CI) often occurs in MS and affects patients’ performance in everyday activities, behavior, and quality of life, and it influences role fulfillment in work and social life, independently of physical disability (Amato et al., 2001). Neuropsychological studies have shown that 40–65% of patients are cognitively affected (Benedict et al., 2020; Meca-Lallana et al., 2021; Rao et al., 1991), encompassing all disease stages and types of clinical course (Huijbregts et al., 2006). Relapsing-remitting (RR) patients perform better than primary progressive (PP) or secondary progressive patients (SP) on specific neuropsychological batteries (Huijbregts et al., 2006; Rao et al., 1991) and on several other cognitive tasks (Zakzanis, 2000).

The cognitive functions most frequently involved are attention, information processing speed (IPS), executive, memory, and visuo-spatial functions (Langdon et al., 2012; Rao et al., 1991). However, significant differences in specific cognitive domains exist in all three subtypes (RR, PP, SP) suggesting heterogeneity and different cognitive profiles, depending on the course of the disease (Brochet & Ruet, 2019; Huijbregts et al., 2006). Some similarities can be seen in the cognitive profiles of the different phenotypes, with predominant involvement of IPS and episodic memory, but other differences can be observed, too. Memory and executive function (EF) deficits appear to be more frequent as the disease progresses, although IPS appears to occur earlier and progress slowly (Gouveia et al., 2017). Although clinical phenotypes may differ in the prevalence or severity of cognitive impairment (CI), the main determinants are physical disability as measured by EDSS, and patients’ age (Ruano et al., 2017).
Two batteries of neuropsychological tests are widely used to obtain a general assessment of the cognitive functioning in patients with MS: the Brief Repeatable Battery Neuropsychological-Test (BRBN-T; Rao et al., 1991) and the Minimum Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS; Benedict et al., 2006). A brief battery of cognitive assessment for MS was also recently developed, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012). BICAMS can be used by any health professional, which is an added advantage.

BRBN-T and BICAMS were recently validated in the Portuguese population (Sousa et al., 2018, 2021), thus we were able to evaluate the cognitive profile of MS patients applying these two batteries in the present study.

The aim of our research was to investigate and describe the prevalence and the profile of CI in a sample of Portuguese MS patients, with a specific focus on prevalence and neuropsychological profiles across different disease subtypes. We expect to find similarities in the frequency of cognitive impairment in the different phenotypes, but taking into account clinical experience, we also expect to find different prevalence in some cognitive domains. Additionally, we assess the association between CI and main demographic and clinical features.

This study was designed to validate the knowledge already acquired on the cognitive deficit in the phenotypes of the disease, as well as, it should verify and understand the cognitive characteristics of Portuguese patients.

### Methods

#### Study design and participants

This cross-sectional study was designed to evaluate the cognitive impairment in different MS subtypes. Three hundred and thirteen MS patients recruited from the MS Clinic Department of Neurology of the Centro Hospitalar Universitário S. João, Oporto (CHUSJ), from 2019 to May 2021, participated in the study. Data collection followed a non-probabilistic approach since participants consisted of every patient diagnosed with MS that agreed to participate. Estimates of sample size were deemed appropriate using G*Power 3.1 (Faul et al., 2009), as a sample size of 305 participants was estimated to achieve .95 power ($f = .25$).

The Ethics Committee of the CHUSJ approved the study protocol (CE-390-19) and informed consent was obtained from all participants before inclusion in the study.

Two neuropsychological batteries of validated measures were administered. Inclusion criteria were: 20 years old or above; Portuguese as a native language; a neurologist-confirmed diagnosis of definite MS according to the last revision of the McDonald criteria (Thompson et al., 2018). Exclusion criteria were: history of neurological disorder, history of serious head injury, the presence of a major psychiatric illness, history of alcohol or drug abuse, history of a learning disability, and regular use of antidepressants or anxiolytics. Each candidate had the necessary visual, auditory, and motor skills to complete the neuropsychological assessment. To ensure that all inclusion and exclusion criteria were fulfilled, a researcher-created questionnaire was used to collect information about participants’ medical history, socio-demographic, and health status. A well-trained clinical psychologist performed the neuropsychological assessment, in a standardized and systematic manner.

#### Cognitive assessment

All study participants underwent a neuropsychological evaluation with the BRBN-T (Rao et al., 1991) and BICAMS (Langdon et al., 2012) batteries, both adapted and validated in the Portuguese language (Sousa et al., 2018, 2021). The BRBN-T evaluates the most frequently impaired cognitive domains in MS, including tests of verbal learning and memory (Selective Reminding Test [SRT]), Long-term Storage [LTS], Consistent Long-term Retrieval [CLTR], and delayed recall; visual or spatial learning and memory (10/36 Spatial Recall Test [SPART]) and its delayed recall; complex attention and information processing speed (Paced Auditory Serial Addition Test [PASAT]) and Symbol Digit Modalities Test [SDMT]); and verbal fluency on semantic and phonemic stimulus (Controlled Oral Word Assessment Test [COWAT]).

The Bushke Verbal Selective Reminding Test (SRT; 6-trial version) is a measure of verbal learning/memory of a 12-word list. The Long-Term Storage (LTS) score represents the sum of words recalled on two consecutive trials without reminding. The Consistent Long-Term Retrieval (CLTR) score is the sum of words recalled on all subsequent trials without reminding. The Delayed Recall (SRTD) score is the number of words recalled after a delay of 15 min.

The 10/36 Spatial Recall Test measures visuospatial learning and memory. It requires participants to recall the placement of 10 checkers that are randomly placed on a 6 × 6 checkerboard. Two scores are recorded; one is the sum of correct responses in the three immediate recall trials (SPARTi), and the second is the delayed recall after 15 min (SPARTd).

The Symbol Digit Modalities Test (SDMT: oral version) examines the speed of visual information processing, complex visual scanning, and sustained attention. Participants have to verbally substitute meaningless symbols with the corresponding number. The score is the number of correct substitutions in 90 s.

The PASAT 3-s version is a widely used cognitive screening test in MS tapping into processing speed, divided attention, and working memory. Participants are asked to add numbers in a 1-back-like fashion during a continuous auditory presentation (one number presented every 3 s) and verbally state the correct sums continuously. Outcome measure is the number of correct calculations during a fixed time period. The administration was carried out in accordance with the manual including a preceding training trial.

The Controlled Oral Word Assessment Test (COWAT) is a phonemic verbal fluency test that evaluates the spontaneous production of words and mental flexibility when given a letter from the alphabet (PFS, Portuguese version) and within a limited amount of time (1 min). The scoring procedures consist of totaling the correct responses. We used also a semantic verbal fluency test that evaluates the spontaneous production of names of a given category (animals) within 60 s. The score is the number of correct words.
Fatigue, anxiety, and depression assessment

Fatigue was assessed using the Modified Fatigue Impact Scale MFIS (score range: 0–84 for each item, with the highest score indicating greater fatigue severity; Gomes, 2011; Larson, 2013). Anxiety and depression were assessed with the Hospital Anxiety Depression Scale (HADS), a validated self-report screening scale used to investigate the prevalence of emotional distress among patients in general medical clinics (Crawford et al., 2001). The scale has seven items, rating two components—anxiety and depression. Each question is scored in a simple Likert fashion (0–3) yielding a range of scores from 0 to 21 for each item (Honarmand & Feinstein, 2009). The patient reports how they have been feeling in the past week. The questionnaire includes three cutoff scores indicating different levels of clinically relevant distress: a score between 0–7 = normal status, 8–10 = borderline, and 11–21 = an abnormal depression or anxiety rate (Zigmond & Snaith, 1983). The HADS is widely used in clinical practice and has been validated in the MS population (Honarmand & Feinstein, 2009; Silva et al., 2011). In the present study, we used a cutoff point of ≥11 to differentiate between MS subjects with and without anxiety/depression (Pais Ribeiro et al., 2018).

Statistical analysis

Statistical analysis was conducted using SPSS statistics 26.0. Descriptive results are expressed as either frequency (percentages) or mean ± SD. Multiple Quade’s tests (a non-parametric alternative to ANCOVA) were conducted for the BRBN-T subscales: [long term storage (LTS), consistent long term retrieval (CLTR), 10/36 spatial recall test (SPART), Paced Auditory Serial Addition Test (PASAT), symbol digit modalities test (SDMT), controlled oral word association test (COWAT)], and BICAMS subscales [California Verbal Learning Test (CVLT-II), brief visuospatial memory test (BVMT-R) and SDMT] and category verbal fluency (animals) as the dependent variable. The measures of MS phenotypes (CIS, RRMS, SPMS, PPMS) were used as a factor since one of the goals was to check if these cognitive measures could differ depending on the phenotype. Age, duration of disease, depression, and anxiety scores, were used as covariates. The same was done with EDSS as a factor. Since we have differences in size between groups, that are characteristic of the dispersion of MS phenotypes in the Portuguese populations, we took into account the possibility of the analysis not meeting assumptions. In those cases, we conducted a Quade’s test. To understand the data in more detail, additional ANCOVA’s/Quade’s tests were conducted comparing only RRMS and SPMS and also comparing these two groups only in participants with a diagnosis of 15 years or more. Scheffe or Bonferroni corrections were checked for any type 1 errors. Correlations between all measures were calculated for each phenotype, to see what factors affected each subtest and how each subtest was related to each other. Pearson correlation was reported for all measures unless they did not meet the assumption of normality in that case Spearman’s rho is reported. Finally, various multiple linear regression analyses were conducted using phenotype, professional status (categorical), and EDSS (raw values from 0 to 10; continuous) as predictor variables for both the BRBN-T and the BICAMS subscales (continuous variables; each sub-scale was added to the analysis as the dependent variable), to observe what factors predicted cognitive deficit. Statistical analyses were conducted with an α threshold of .05. Outliers were identified through box plot analysis based on the interquartile range (1.5 × IQR) and removed from the database by assigning missing values to the outlier variables (1% of the data).

Results

Demographics and clinical characteristics of the sample

The study sample included all four MS phenotypes totaling 313 patients (see Table 1). SPMS patients presented
Table 1. Clinical and demographic characteristics, psychological symptomatology, prevalence, and profile of cognitive impairment of the study patients.

<table>
<thead>
<tr>
<th>Total sample</th>
<th>CIS (n = 19)</th>
<th>RRMS (n = 243)</th>
<th>SPMS (n = 44)</th>
<th>PPMs (n = 7)</th>
<th>Progressive (SPMS + PPMs; n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) (years)</td>
<td>44.40 (12.4)</td>
<td>40.53 (13.95)</td>
<td>42.42 (11.41)</td>
<td>54.93 (10.90)</td>
<td>57 (9.66)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>213 (68.1%)</td>
<td>14 (73.7%)</td>
<td>165 (67.9%)</td>
<td>30 (68.2%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>100 (31.9%)</td>
<td>5 (26.3%)</td>
<td>78 (32.1%)</td>
<td>14 (31.8%)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>Education, mean (SD) (years)</td>
<td>12.57 (4.50)</td>
<td>13.68 (3.40)</td>
<td>12.90 (4.36)</td>
<td>10.86 (5.02)</td>
<td>8.71 (4.82)</td>
</tr>
<tr>
<td>Duration of disease, mean (SD) (years)</td>
<td>44.40 (12.4)</td>
<td>40.53 (13.95)</td>
<td>42.42 (11.41)</td>
<td>54.93 (10.90)</td>
<td>57 (9.66)</td>
</tr>
<tr>
<td>Professional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>197 (62.9%)</td>
<td>16 (84.2%)</td>
<td>166 (68.3%)</td>
<td>10 (22.7%)</td>
<td>5 (71.4%)</td>
</tr>
<tr>
<td>Inactive</td>
<td>116 (37.1%)</td>
<td>3 (15.8%)</td>
<td>77 (31.7%)</td>
<td>34 (77.3%)</td>
<td>34 (66.7%)</td>
</tr>
<tr>
<td>EDSS, median (IQR)</td>
<td>2 (4.55)</td>
<td>8.00 (8.57)</td>
<td>8.33 (4.45)</td>
<td>6.89 (4.67)</td>
<td>4.00 (6.75)</td>
</tr>
<tr>
<td>Treatment with DMDs, n (%)</td>
<td>266 (85%)</td>
<td>13 (68.4%)</td>
<td>212 (87.2%)</td>
<td>37 (84.1%)</td>
<td>37 (80.4%)</td>
</tr>
<tr>
<td>Cognitive impairment for BRBN-T, n (%)</td>
<td>131 (41.9%)</td>
<td>7 (36.8%)</td>
<td>84 (34.6%)</td>
<td>37 (84.1%)</td>
<td>40 (78.4%)</td>
</tr>
<tr>
<td>Verbal learning (CLTR), n (%)</td>
<td>136 (43.5%)</td>
<td>8 (42.1%)</td>
<td>96 (39.5%)</td>
<td>30 (68.2%)</td>
<td>32 (62.7%)</td>
</tr>
<tr>
<td>Visuo-spatial learning (SPART), n (%)</td>
<td>82 (26.2%)</td>
<td>6 (31.6%)</td>
<td>54 (22.2%)</td>
<td>19 (43.2%)</td>
<td>22 (43.1%)</td>
</tr>
<tr>
<td>Information processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASAT, n (%)</td>
<td>74 (23.6%)</td>
<td>3 (15.8%)</td>
<td>37 (15.2%)</td>
<td>4 (57.1%)</td>
<td>34 (66.7%)</td>
</tr>
<tr>
<td>SDMT, n (%)</td>
<td>88 (28.1%)</td>
<td>4 (21.1%)</td>
<td>54 (22.2%)</td>
<td>29 (65.9%)</td>
<td>30 (58.8%)</td>
</tr>
<tr>
<td>Cognitive impairment for BICAMS, n (%)</td>
<td>131 (41.9%)</td>
<td>7 (36.8%)</td>
<td>84 (34.6%)</td>
<td>37 (84.1%)</td>
<td>40 (78.4%)</td>
</tr>
<tr>
<td>Verbal learning (CLVT-II), n (%)</td>
<td>84 (34.6%)</td>
<td>4 (21.1%)</td>
<td>47 (19.3%)</td>
<td>12 (27.3%)</td>
<td>13 (25.5%)</td>
</tr>
<tr>
<td>Information processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDMT, n (%)</td>
<td>88 (28.1%)</td>
<td>4 (21.1%)</td>
<td>54 (22.2%)</td>
<td>29 (65.9%)</td>
<td>30 (58.8%)</td>
</tr>
</tbody>
</table>

RIS: radiologic isolated syndrome; CIS: clinically isolated syndrome; RR: relapsing-remitting; SP: secondary progressive; PP: primary progressive; SD: standard deviation; EDSS: expanded disability status scale; IQR: interquartile range; DMDs: disease-modifying drugs; MFIS: modified fatigue impact scale; HADS: Hospital Anxiety and depression scale; BRBN-T: brief repeatable battery of neuropsychological tests; LTS: long term storage; CLTR: consistent long term retrieval; SPART: 10/36 spatial recall test; PASAT: paced auditory serial addition test (PASAT); SDMT: symbol digit modalities test; COWAT: controlled oral word association test; BICAMS: Brief International Cognitive Assessment for MS; CVLT-II: California verbal learning test; BVMT-R: brief visuospatial memory test; Cognitive impairment for BRBN-T: >2 domains; Cognitive impairment for BICAMS: >1 domains; H denotes values for the Kruskal-Wallis H test; * denotes F values in between-group comparisons; p denotes statistical significance.
significantly longer disease duration and were more professionally inactive when compared to the other groups. As expected, CIS and RRMS patients had lower EDSS scores than SPMS and PPMS patients.

Across all phenotypes, 79 patients had anxious symptoms and 36 depressive symptoms. Eighty-eight patients revealed fatigue according to the MFIS. Most patients treated with disease-modifying drugs (DMDs) had an RRMS phenotype (212 out of 243; 87.2%). Neither mood, anxiety nor fatigue differed among the groups (see Table 1).

The prevalence of cognitive impairment (CI) in the sample was 42% when measured by BRBN-T and 42% when measured by BICAMS (see Figures 1 and 2). In addition, there was neither significant difference in gender between cognitively preserved and impaired patients when assessed by BRBN-T and when assessed by the BICAMS (Table 2).

**Differences in cognitive impairment by phenotype, duration of disease, and EDSS**

Overall, there were significant differences between phenotypes on all BRBN-T subtests, with the Progressive group showing lower scores in comparison to RR: LTS, *p* = .002, CLTR, *p* = .033, SPART and SDMT, *p* < .001, PASAT, *p* < .001, and phonemic verbal fluency, *p* = .001. For SDMT, CIS also had higher scores than the Progressive group SDMT (*p* = .001). In addition, there were significant differences between EDSS scores in LTS, *p* = .005, PASAT, *p* = .048, and SDMT, *p* < .001.

There were also significant differences between RR and the Progressive phenotype for all three BICAMS subtests: SDMT, *p* < .001, BVMT, *p* = .002, and CVLT, *p* = .002. In addition, there were significant differences between EDSS scores for all subtests: SDMT, *p* < .001, BVMT, *p* = .010, and CVLT, *p* = .002.

To better understand the differences between the two most common phenotypes, additional analyses comparing only RR and SP were conducted on all measures with RR scoring significantly higher on every subtest (see Table 3).

To understand the magnitude of the differences found we calculate the effect sizes (see Table 4). For EDSS, those with lower EDSS tended to be significantly higher in LTS, CLTR, PASAT, SDMT, CVLT, and BVMT, *p* < .001, CVLT, *p* = .036. Since the differences between RR (*n* = 86) and SP (*n* = 29) could be affected by the duration of disease (≥15 and <15 years), patients that had been diagnosed for 15 years or longer were compared on all measures. Still, RR showed significantly higher scores on all subtests (see Table 3 for results). For EDSS, those with lower EDSS tended to score significantly higher in SPART, *p* = .041.

**Factors affecting cognitive deficit**

For the CIS, the duration of the disease is negatively correlated with SPART, *r*(17) = -.528, *p* = .024, and EDSS is negatively correlated with phonemic verbal fluency, *r*(17) = -.511, *p* = .025. LTS is positively correlated with CLTR, *r*(17) = .866, *p* < .001, and phonemic verbal fluency, *r*(17) = -.577, *p* = .015, and SDMT positively correlated with PASAT, *r*(17) = .563, *p* = .019. Also, phonemic verbal fluency is positively correlated with CLTR, *r*(17) = .613, *p* = .009. Finally, the BVMT positively correlated with SDMT, *r*(17) = .635, *p* = .006. For RR and the Progressive Group almost all measures are correlated with each other. For the full list of correlations in the two phenotypes, see Table 5.

**Relationship between the BRBN-T and the BICAMS**

For the CIS phenotype, the CVLT-II is positively correlated with the CLTR, *r*(17) = .643, *p* = .005, and the BVMT is positively correlated with PASAT, *r*(17) = .489, *p* = .046. For RR and the Progressive group, all BICAMS subtests were correlated with the BRBN-T subtests. For a full list of correlations, see Table 5.

**Phenotype, disease duration, professional status, and severity of disease**

Professional status and EDSS were both significant predictors for all measures in both cognitive test batteries, and phenotype was not a significant predictor for any of the measures for both tests (see Table 6).
In this study, we evaluated the cognitive performance of patients with MS using two neuropsychological batteries developed specifically for the disease (BRBN-T and BICAMS). As far as we know, this is the first study to compare the cognitive performance profile of Portuguese MS patients in different types and disease severity involving one of the main national MS departments, thus providing a reasonable representation of the MS patient population from the north of Portugal. The prevalence of CI found in our study was 41.8% (assessed by BRBN-T) and 40.9% (assessed by BICAMS), these values are in line with typical values found in some previous studies (Chiaravalloti & DeLuca, 2008), particularly in verbal fluency (31.9%), which was the second particularly in verbal fluency (31.9%), which was the second

Discussion

In this study, we evaluated the cognitive performance of patients with MS using two neuropsychological batteries developed specifically for the disease (BRBN-T and BICAMS). As far as we know, this is the first study to compare the cognitive performance profile of Portuguese MS patients in different types and disease severity involving one of the main national MS departments, thus providing a reasonable representation of the MS patient population from the north of Portugal. The prevalence of CI found in our study was 41.8% (assessed by BRBN-T) and 40.9% (assessed by BICAMS), these values are in line with typical values reported in the literature (Amato et al., 2006; Chiaravalloti & DeLuca, 2008; Maubeue et al., 2021; Potagas et al., 2008; Skorve et al., 2019; Walker et al., 2016). Both batteries detected approximately the same prevalence of cognitive impairment, thus demonstrating good accuracy.

Just like all symptoms of MS, cognitive impairment is characterized by high variability between patients. When the results were analyzed in a group of MS patients, IPS and memory were most often involved. Deficits in executive function and visuospatial processing are also reported, but less frequently (Benedict et al., 2020; Rao et al., 1991). In our study, the profile of the total CI sample agrees well with what has already been described. We found that decreases in information processing speed (28.1%) and selective verbal memory (43.5%) were the most prevalent. Nonetheless, we found in our cohort that the prevalence of a deficit in executive function was higher than what has been reported in some previous studies (Chiaravalloti & DeLuca, 2008), particularly in verbal fluency (31.9%) which was the second
Disease duration measures have been shown to have contradictory results due to the use of different neuropsychological assessments in different normative populations. Cognitive impairment in MS has been widely studied and progresses, although IPS appears to occur earlier and function (EF) deficits appear to be more frequent as the disease population, and study samples are small (Benedict, et al., 2020). Overall, we think our findings reinforce the importance of assessing executive function in MS patients and advocate for an inclusion and further evaluation of tools, such as the COWAT or WLG test when for example only BICAMS tests are administered.

Cognitive impairment in MS has been widely studied and has been analyzed in different courses of the disease (Johnen et al., 2017; Ruano et al., 2017), but sometimes can reveal contradictory results due to the use of different neuropsychological assessment instruments and different normative population data. However, in most studies, patients with a progressive course of the disease have been shown to have more prominent cognitive impairment than those with RRMS (Gaudino et al., 2001; Huijbregts et al., 2004; Lynch et al., 2005; Potagas et al., 2008; Ruet et al., 2013; Sepulcre et al., 2006). Significant differences were also found between disease phenotypes in our study. For example, CI was more frequent in patients with SPMS than RRMS (84.1 vs. 34.6%).

Patients with RRMS performed better than patients with a progressive disease course (SPMS, PPMS) on virtually all RRBN-T and BICAMS tests, with the sole exception of CVLT-II.

When the RRMS, SPMS, and PPMS groups were compared in our study, the SPMS group showed more prominent cognitive impairment than the RRMS and PPMS groups. This cognitive result in PPMS may be due to the fact that the prevalence of the primary progressive disease varies greatly, as this phenotype comprises <10% of the overall disease population, and study samples are small (Benedict et al., 2020).

Analyzing the cognitive profile among the disease phenotypes, our study reveals that the cognitive performance profile in the RRBN-T was relatively similar between the RRMS and the progressive group. In both groups of patients, the most impaired cognitive domain was verbal memory followed by the phonemic verbal fluency and IPS domain. These findings are in line with previous studies (Portaccio et al., 2009; Ruano et al., 2017) as memory and executive function (EF) deficits appear to be more frequent as the disease progresses, although IPS appears to occur earlier and progress slowly (Gouveia et al., 2017). Interestingly, when we observed our results of cognitive profile in CIS and RRMS patients we found impaired verbal and visual-spatial
memory and verbal fluency, thus calling into attention that memory tests seem more adequate and accurate to assess cognitive impairment in those patients. These results corroborate previous studies that found similar cognitive alterations in CIS and RRMS phenotypes (Reuter et al., 2011; Ruano et al., 2017; Viterbo et al., 2013). Thus highlighting the presence of cognitive deficits even in patients with small lesion burden and short duration of illness.

Focusing on progressive phenotypes, we found similar results with previous investigation evidence showing a greater deficit in both cognitive processing speed and acquisition of new verbal material in PPMS than in RRMS (Bergendal et al., 2007; Gaudino et al., 2001; Jonkman et al., 2015). Some previous studies indicate that impairments in word list learning are closely linked to reduced processing speed in patients with MS (Archibald & Fisk, 2000; Gaudino et al., 2001). Taken together, our findings suggest that neuropsychological assessment of MS patients should incorporate in-depth examinations of processing speed, verbal learning, and verbal memory to best discriminate among disease subtypes.

Although, the relationship between CI and both disability and the duration of the disease is still controversial (Haase et al., 2007; Lynch et al., 2005; Ruano et al., 2017; Sepulcre et al., 2006), we observed a strong association between CI and disability. In each and every test of the BRBN-T and BICAMS, patients with low disability performed better than those with high disability. However, we cannot exclude the possible impact of other variables that were not evaluated in this study like biological changes associated with aging, increased lesion burden on the brain, and atrophy (Rocca et al., 2015).

Another strong association in our study was the relationship between CI and professional status. In a review of the literature on the relationships between cognition and employment outcomes in MS patients, Clemens and Langdon (2018) found that those who were unemployed or with reduced working hours had a higher cognitive impairment than those who remained employed or maintained their working hours. Processing speed, immediate and delayed recall, and executive functions were the domains that often differentiated employed from unemployed patients (Campbell et al., 2016; Goverover et al., 2015; Vanotti et al., 2017). In this study, we divided the sample into professionally active or inactive patients, and we found significant differences, revealing that active patients had lower scores on the cognitive tests. In this study, professional status was a predictor of cognitive impairment. This finding should encourage future research to study if patients who are cognitively intact are more likely to remain professionally active or if the patients that remain professionally active do so because they are cognitively intact. It seems to us that, professional status should be better defined to distinguish the professionally inactive, between those who have daily activities that stimulate cognition and how much time they spend on those tasks. Moreover, the association between phenotype and disease duration was weak.

There are limitations to this study. Firstly, disease severity within phenotypes was also different. Second, this study did not include healthy control subjects. Finally, although all patients were naive to the versions of the cognitive tests performed (the validated version), we could not control if participants were naive to any version of the tests. Future studies might circumvent these inherent clinical limitations.

Conclusions

In conclusion, the results obtained in this clinical series imply that the presence of CI is more related to disease severity and professional activity than to the duration or subtype of the disease itself. Furthermore, this study documents and corroborates that, Portuguese MS patients show a significant presence of CI from the early stages of MS, which increases in frequency and severity as the disease progresses. Our study confirms also that BICAMS is a good screening tool for CI, being quick and easy to use in clinical practice, but it is also important to add verbal fluency tools to the assessment protocol. Thus, these findings reinforce the idea that early neuropsychological assessment and monitoring throughout the course of the disease seems essential for better therapeutic optimization, better patient adaptation, and the early initiation of cognitive strategies that minimize the impact of cognitive impairment. In addition, we consider that the evaluation of a larger cohort of MS patients to determine cognitive phenotypes is a very important next step.

Acknowledgments

We would like to thank all the people with MS followed as out-patients at the MS Clinic Department of Neurology by Centro Hospitalar Universitário S. João, Oporto (CHUSJ) for their participation in this research. Also, we thank all the neurologists in the consultation: Joana Guimarães, Pedro Abreu, Teresa Mendonça, and Ricardo Reis.

Author contributions

Claudia Sousa: contributed to study concept and design, drafting and revising the manuscript, and in the acquisition and interpretation of data. Teresa Jacques: drafting and revising the manuscript, and in the acquisition and interpretation of data. Maria José Sá: contributed to study concept and design, drafting and revising the manuscript, and in the analysis and interpretation of data and study supervision. Rui Alves: contributed to study concept and design, drafting and revising the manuscript, and in the analysis and interpretation of data and study supervision. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.
ORCID
Rui A. Alves https://orcid.org/0000-0002-1657-8945

References


