Neurological Sciences (2018) 39:1237–1244
https://doi.org/10.1007/s10072-018-3417-z

ORIGINAL ARTICLE

The Italian validation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) and the application of the Cognitive Impairment Index scoring procedure in MS patients

Ornella Argento[1] · Chiara C. Incerti[1] · Maria E. Quartuccio[3] · Giuseppe Magistrale[1] · Ada Francia[3] · Carlo Caltagirone[1,2] · Valerio Pisani[1] · Ugo Nocentini[1,2]

Received: 15 December 2017 / Accepted: 20 April 2018 / Published online: 27 April 2018

Abstract
Cognitive dysfunction occurs in almost 50–60% of patients with multiple sclerosis (MS) even in early stages of the disease and affects different aspects of patient's life. Aims of the present study were (1) to introduce and validate an Italian version of the minimal assessment of cognitive functions in MS (MACFIMS) battery and (2) to propose the use of the Cognitive Impairment Index (CII) as a scoring procedure to define the degree of impairment in relapsing-remitting (RRMS) and secondary-progressive (SPMS) patients. A total of 240 HC and 123 MS patients performed the Italian version of the MACFIMS composed by the same tests as the original except for the Paced Auditory Serial Addition Test. The CII was derived for each score of the 11 scales for participants of both groups. The results of the study show that cognitive impairment affects around 50% of our sample of MS patients. In RRMS group, only the 15.7% of patients reported a severe impairment, while in the group of SPMS, the 51.4% of patients felt in the "severely impaired" group. Results are in line with previously reported percentages of impairment in MS patients, showing that the calculation of the CII applied to the Italian version of the MACFIMS is sensitive and reliable in detecting different degrees of impairment in MS patients.

Keywords MACFIMS · Cognitive Impairment Index · Multiple sclerosis · Italian validation

Introduction

Cognitive impairment (CI) affecting different domains is frequent in patients with multiple sclerosis (MS). It occurs in almost 50–60% of patients [1] and has a great impact on their quality of life [2, 3], rate of employment and vocational status [2, 4–6], instrumental activities of daily living [7], and adherence to and benefits from rehabilitation programs [8]. CI varies greatly among individuals. It can occur in early stages and throughout the disease. Given the frequency and impact of CI, a great effort is being made to develop neuropsychological assessment batteries that are able to detect it in MS patients.

Various neuropsychological batteries have been proposed over the years. They range from brief to comprehensive and vary for the tests selection and the cognitive domains assessed. Some batteries were developed for an easy non-time-consuming administration in clinical practice, whereas others were developed to thoroughly investigate all cognitive domains affected by MS. Both approaches have limitations: The former may result in loss of important information about the cognitive functioning of a single patient, and the latter may be too time-consuming to be administered in clinical practice.

The Brief Repeatable Battery of Neuropsychological Tests-BRB-N is the most used brief battery [9]. The five tests that comprise this battery were chosen by means of statistical calculations of a pool of 23 tests selected on the basis of the guidelines for Neuropsychological Research in MS: Selective Reminding Test-SRT [10], 7/24 Spatial Recall Test-SPART-7/24 [11], Symbol Digit Modality Test-SDMT [12], Controlled

✉ Ornella Argento
o.argento@hsantalucia.it

[1] Neurology and Neurorehabilitation Unit, I.R.C.C.S. "Santa Lucia" Foundation, Via Ardeatina, 306, 00179 Rome, Italy

[2] Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy

[3] Department of Neurological Sciences, University of Rome "Sapienza", Rome, Italy

Oral Word Association Test-COWAT [13], and Paced Auditory Serial Addition Test-PASAT [14]. Subsequently, in the newest version, SPART-7/24 was replaced by SPART-10/36 and a Word List Generation-WLG [15] test was added; total administration time is 25–30 min [16].

It has been proposed that a short but complete neuropsychological assessment can be carried out with the minimal assessment of cognitive functions in MS (MACFIMS). For this purpose, seven tests have been recommended: the PASAT, SDMT, California Verbal Learning Test-II-CVLT-II [17], Brief Visuo-Spatial Memory Test-Revised-BVMT-R [18], Delis–Kaplan Executive Function System Sorting Test-DKEFS [19], Judgment of line orientation test-BJLO [20], and COWAT. The MACFIMS provides a complete assessment of the cognitive domains most affected in MS patients; it takes about 90 min to administer [21].

To surpass the limits of more extended batteries, a screening battery (Brief International Cognitive Assessment for MS-BICAMS) has been proposed; it consists of three sub-tests derived from the MACFIMS [22], the short forms of both the CVLT-II and BVMT-R and the SDMT; total administration is about 15 min [23].

A recent study also introduced the MS-COG. This is a new battery that is easy to administer and is aimed at determining the effects of disease and modifying therapies for cognitive functioning in MS patients [24]. This battery consists of the SRT, BVMT-R, PASAT, and SDMT; administration time is about 20 min.

Different studies have also compared tests assessing the same cognitive domain to determine those most useful for that domain. A recent study comparing PASAT and SDMT found that SDMT is more reliable and valid than PASAT for the assessment of information processing speed in MS [25].

In any case, an extended test battery that does not require excessive administration time is very useful. Therefore, the primary aim of this study was to propose an Italian version of the MACFIMS battery to a sample of healthy controls (HC) representative of the Italian population and to obtain a Cognitive Impairment Index (CII) for each single test score and a total CII representative of performance on the whole test battery. The second aim was to assess the validity of this scoring procedure for discriminating between HC and patients with MS in terms of degree of impairment and between the two main phenotypes of MS (relapsing-remitting-RRMS; secondary-progressive-SPMS).

Method

Participants

A total of 240 HC (127 females) from the community volunteered to participate in this study. An attempt was made to recruit them from different regions of Italy and from urban and rural areas based on the distribution of the Italian population (ISTAT, 2010). Inclusion criteria were as follows: being Caucasian and Italian native speakers, age from 20 to 80 years, and formal education from 5 to 18 years. Following the procedure of a previous study [26], we followed a specific procedure to obtain homogeneous groups for demographics in which a minimum of five subjects were collected for each group. Table 1 shows participants' characteristics.

Participants were designated as "healthy" after a clinical interview in which inclusion and exclusion criteria were verified; those above 65 years of age were also assessed with the Mini-Mental State Examination (MMSE) to verify their suitability [27]. Exclusion criteria for HC were a score < 23 on the MMSE, adjusted following the Italian norms of [28], a history of central nervous system diseases, protracted treatment or hospitalization for psychiatric illness or substance abuse, and other medical pathologies (such as hypertension and diabetes).

By using the same inclusion and exclusion criteria as for HC (except for the MMSE), a total of 130 patients with a definite diagnosis of MS (McDonald's criteria, 2005) [29] with the RRMS or SPMS phenotype were also recruited.

Three trained neuropsychologists administered the battery to the subjects in a quiet room with adequate light. Their auditory acuity had to be adequate to complete the test in a 1-day session of around 60 min. All participants gave their written informed consent, as required by the Local Ethics Committee.

Neuropsychological assessment

After having ascertained their eligibility, all participants performed the entire test battery in the same fixed order: CVLT-II, BVMT-R, SDMT, JLO, COWAT, and D-KEFS.

- *CVLT-II* [17]: verbal learning and memory test consisting of a 16-item word list from four semantic categories. As in previous studies [23, 30, 31] the CVLT-II word list used was forward translated from English into Italian by a professional native-speaking Italian translator. Outcome measures derived from this task were total learning over five trials (*CVLT2-IR*) and the number of correct recalls following the delay (*CVLT2*-DR).
- *BVMT-R* [18]: visuo-spatial learning and memory test consisting of six geometric figures on a sheet of paper presented in three, 10-s trials. The instructions of the BVMT-R were applied as in a previous study [26], and the outcome measures were Immediate Recall (BVMTR-IR) and Delayed Recall (BVMTR-DR).
- *SDMT:* sustained attention and processing speed test consisting of a grid with nine meaningless symbols, each one associated with a number from 1 to 9. Test procedures were the same as those described in [32].

Table 1 Comparisons of demographic variables and raw scores of MACFIMS scales between MS and HC

	HC ($n = 217$)				MS ($n = 123$)				
	Mean	SD	Range		Mean	SD	Range		Sig
			Min	Max			Min	Max	
Education	13.08	4.13	5	24	13.59	3.59	5	21	.253
Age	51.28	16.81	20	82	43.77	10.18	22	71	.000
CVLT2-IR	46.76	10.93	21	75	48.75	12.53	8	76	.127
CVLT2-DR	11.21	3.09	4	16	10.07	3.92	0	16	.003
SDMT	46.71	14.05	18	83	47.10	17.10	9	85	.820
BJLO	24.28	3.93	10	33	24.36	4.52	7	32	.864
COWAT	39.65	12.23	16	73	34.74	10.96	11	62	.000
DKEFS-CS1	5.1	1.5	1	8	4.6	1.8	0	8	.009
DKEFS-DS1	19.6	6.3	2	32	15.6	8.1	0	32	.000
DKEFS-CS2	5.1	1.3	1	8	4.3	1.6	1	8	.000
DKEFS-DS2	19.9	5.6	2	32	14.6	7.3	2	32	.000
BVMTR-IR	23.75	7.01	4	36	20.46	8.34	3	36	.000
BVMTR-DR	8.96	2.60	0	16	7.86	3.22	0	12	.001

HC healthy controls, *MS* patients with Multiple Sclerosis, *CVLT2-IR* California Verbal Learning Test 2-Immediate Recall, *CVLT2-DR* California Verbal Learning Test 2-Delayed Recall, *SDMT* Symbol Digit Modalities Test, *BJLO* Benton Judgment of Line Orientation, *COWAT* Controlled Oral Word Association Test, *DKEFS-CS1* Delis–Kaplan Executive Function System-Card Sorting 1, *DKEFS-DS1* Delis–Kaplan Executive Function System-Description Score 1, *DKEFS-CS2* Delis–Kaplan Executive Function System-Card Sorting 2, *DKEFS-DS2* Delis–Kaplan Executive Function System-Description Score 2, *BVMTR-IR* Brief Visuo-Spatial Memory Test Revised-Immediate Recall, *BVMTR-DR* Brief Visuo-Spatial Memory Test-Revised-Delayed Recall

- *BJLO* [23]: test measuring the accuracy of orientation-based judgments about a pair of angled lines that visually match with an identical pair hidden within an 11-line semicircular array. The outcome measure is the total score of all pairs of lines correctly indicated.
- *COWAT* [13]: phonemic fluency test in which the subject is given 60 s to name as many words as possible beginning with one specific letter (F-A-S). The outcome measure obtained is the total number of the correct word named the total number of words named correctly in the three trials.
- *DKEFS* [19]: test measuring concept-formation skills, modality-specific problem-solving skills (verbal/nonverbal), and the ability to explain sorting concepts abstractly. The Italian version of the test used in this study was the one reported in [33]. Outcomes for each card set were the number of corrected free card sorting concepts (DKEFS-CS) and the verbal description score (DKEFS-DS).

Data analysis

Behavioral and clinical data were analyzed using SPSS (SPSS Inc., Chicago, Illinois). Demographic data of MS and HC were compared using an independent sample *t* test for age and education and a *chi-squared* test for gender group difference.

The normality, linearity, and homoscedasticity of the distribution of data were statistically ascertained. In the HC group, all 11 scores of the battery were correlated (using Pearson's correlation coefficient) with demographic/gender characteristics. Multiple linear regression analyses (MRA) were performed for each score that reached significance ($p < .05$) in the previous analysis using sex, age, and education as independent variables. Consequently, a regression model was developed that made it possible to calculate (for each index) the scores corrected for significant variables (Table 3). With this model, the adjusted scores were calculated for the performance of both MS and HC by adding or subtracting the contribution of each demographic variable.

After all performances of each participant in both groups were adjusted, the corrected scores obtained were converted into *z-scores* by using the mean and standard deviation (M ± SD) of HC performances for all scores of the battery.

Then, a procedure was applied for each variable to define degrees of impairment by using the number of SDs below the mean normative value, as proposed by [34]. With this procedure, a grade of zero was attributed when the participant scored at or above the mean of HC; a grade of 1 was assigned when the score was below the controls' mean, but above 1 SD of the same mean; then a grade of 2 was given to scores < 1 SD and ≤ 2 SD from controls' mean; and finally, a grade of 3 was given for scores < 2 SD from controls' mean [35]. These grades were then summed across all variables to obtain an

overall measure of cognitive dysfunction (t-CII). A non-parametric mean group comparison was obtained for all scores as well as for t-CII between MS and HC and within SPMS (EDSS 4.87 ± 1.10; disease duration 18.10 ± 9.48) and RRMS (EDSS 2.40 ± 1.03; disease duration 9.21 ± 7.51) by means of a Mann-Whitney analysis test. Finally, the mean and SD of t-CII of HC were used to define three degrees of global performance: *Cognitively Preserved* (up to 1 SD > mean), *Mildly Impaired* (from 1 to 2 SD above the controls' mean), and *Severely Impaired* (more than 2 SD above controls' mean). The percentage of SPMS and RRMS in these three groups was computed, and a chi-square analysis was performed in order to assess the statistical difference between groups.

Results

Following the ISTAT data and in order to obtain homogeneous data for demographics, the final sample of HC consisted of 44% of participants from high-density areas, 39% from areas with middle density, and 16% from low-density areas; finally, a total of 38 groups of participants were obtained according to different gender and demographic characteristics.

Multiple regression analysis

In the HC group, before correlating the scores of each of the 11 scales of the battery with age, sex, and years of education, the normality of the distribution of each variable was ascertained by calculating linearity and homoscedasticity. As reported in Table 2, all scales were significantly correlated with age and education. The BJLO score was also correlated with sex, with males performing better than females. The significantly correlated demographic variables were then used to build the regression model to transform the raw scores into corrected scores.

The regression equation was as follows:

$$y = -B\ \text{age} \times (\text{age}-51.28) - B\ \text{education} - (\text{education}-13.08) + (B\ \text{sex}/2)\ \text{if female or} - (B\ \text{sex}/2)\ \text{if male.}$$

The *B*-scores corresponded to the unstandardized *B*-coefficients of the influence of, respectively, age, education, and sex, on the performance on each given variable, all of which were derived from the previous multiple regression analysis (Table 3).

Both MS and HC participants' scores were corrected using this formula and then transformed into *z*-scores by using the mean and SD of the corrected scores of the HC group.

Table 2 Correlations between MACFIMS scales and demographic variables

	Pearson's correlation		Chi-squared
	Age	Education	Sex
CVLT2-IR	*.000*	*.000*	.079
CVLT2-DR	*.000*	*.000*	.164
SDMT	*.000*	*.000*	.261
BJLO	*.000*	*.000*	*.000*
COWAT	*.000*	*.000*	.812
DKEFS-CS1	*.000*	*.000*	.298
DKEFS-DS1	*.000*	*.000*	.273
DKEFS-CS2	*.000*	*.000*	.137
DKEFS-DS2	*.000*	*.000*	.161
BVMTR-IR	*.000*	*.000*	.654
BVMTR-DR	*.000*	*.000*	.992

CVLT2-IR California Verbal Learning Test 2-Immediate Recall, *CVLT2-DR* California Verbal Learning Test 2-Delayed Recall, *SDMT* Symbol Digit Modalities Test, *BJLO* Benton Judgment of Line Orientation, *COWAT* Controlled Oral Word Association Test, *DKEFS-CS1* Delis–Kaplan Executive Function System-Card Sorting 1, *DKEFS-DS1* Delis–Kaplan Executive Function System-Description Score 1, *DKEFS-CS2* Delis–Kaplan Executive Function System-Card Sorting 2, *DKEFS-DS2* Delis–Kaplan Executive Function System-Description Score 2, *BVMTR-IR* Brief Visuo-Spatial Memory Test Revised-Immediate Recall, *BVMTR-DR* Brief Visuo-Spatial Memory Test-Revised-Delayed Recall

Each box in the table reports the *p* value of each combination

Group comparisons

The final sample was composed of 217 HC (114 women) and 123 MS (77 women; the *chi-squared* significance for sex was .088) (Table 1). The between-group demographic comparison showed no significance for education but a significant difference for age ($p = .000$).

Cognitive Impairment Index estimation

The CII was derived for each score on the 11 scales for both groups of participants. Table 4 reports the results of the between-group comparison showing a significant difference for CII scores between MS and HC on all scales except for the CVLT2-IR and COWAT. Furthermore, for the MS (RRMS and SPMS), a significant difference was found in all CII scores except for the BJLO and the second card set of the DKEFS for both sorting and description scores (Table 4).

Finally, the t-CII performance of HC was used to define three degrees of global performance: "Cognitively preserved" performance included subjects who obtained 0–11 points on the t-CII (from the mean of HC up to 1 SD > mean); "mildly impaired" included subjects who obtained 12–16 points (from 1 to 2 SD above the mean of HC); "severely impaired"

Table 3 MRA equation variables

	Constant	Age	Education	Sex	R^2	SD of residuals
CVLT2-IR	55.486	− .302	.517	n.s.	.316	9.076
CVLT2-DR	13.685	− .077	.112	n.s.	.239	2.711
SDMT	64.765	− .498	.573	n.s.	.452	10.477
BJLO	29.288	− .057	.142	− 2.575	.221	3.493
COWAT	37.532	− .155	.767	n.s.	.150	11.323
DKEFS-CS1	4.533	− .191	.109	n.s.	.163	1.380
DKEFS-DS1	16.719	− .061	.453	n.s.	.145	5.840
DKEFS-CS2	5.665	− .023	.045	n.s.	.133	1.236
DKEFS-DS2	21.520	− .092	.233	n.s.	.135	5.263
BVMTR-IR	31.117	− .191	.186	n.s.	.255	6.077
BVMTR-DR	10.262	− .050	.097	n.s.	.160	2.395

CVLT2-IR California Verbal Learning Test 2-Immediate Recall, *CVLT2-DR* California Verbal Learning Test 2-Delayed Recall, *SDMT* Symbol Digit Modalities Test, *BJLO* Benton Judgment of Line Orientation, *COWAT* Controlled Oral Word Association Test, *DKEFS-CS1* Delis–Kaplan Executive Function System-Card Sorting 1, *DKEFS-DS1* Delis–Kaplan Executive Function System-Description Score 1, *DKEFS-CS2* Delis–Kaplan Executive Function System-Card Sorting 2, *DKEFS-DS2* Delis–Kaplan Executive Function System-Description Score 2, *BVMTR-IR* Brief Visuo-Spatial Memory Test Revised-Immediate Recall, *BVMTR-DR* Brief Visuo-Spatial Memory Test-Revised-Delayed Recall

included subjects who obtained a t-CII of 17 or more points (2 SD above HC mean). Table 5 reports the percentages of RRMS and SPMS in the three degrees of impairment. As reported, about 46% of our MS patients showed from moderate to severe CI, whereas the percentage of HC with CI was around 15%. In the MS group, the RRMS included 63% of preserved patients and 37% who showed some degree of impairment. Conversely, the SPMS group consisted of 32% preserved patients and 68% mildly to severely impaired patients. The difference in the distribution of patients in the three conditions was statistically different in the two groups of patients (Table 5).

Discussion

MACFIMS is one of the most widely used batteries for assessing all potential cognitive domains that may be involved in MS [21]. Until now, some of the tests chosen by an expert panel of psychologists and neuropsychologists to construct the MACFIMS have been separately validated for Italian. For example, the BVMT-R [26], DKEFS [33], and SDMT [32] have been validated in samples with different characteristics and using different statistical methods (e.g., regression-based versus discrete norms analysis). Thus, for the purpose of the present study, we decided that it was preferable to use data derived from the administration of the battery to a unique group of HC than to use norms derived from separate test validations.

Furthermore, in both clinical and research practice, it is important to have statistical thresholds to define different degrees of CI. In fact, it is not only necessary to detect the presence and degree of CI in MS patients but also to longitudinally compare the progression of the pathology among patients, and to compare degrees of impairment in different samples. Cognitive assessment is also important in clinical practice to facilitate decisions about pharmacological (disease modifying drugs or symptomatic treatments) and non-pharmacological (cognitive rehabilitation) interventions and to longitudinally monitor progress [36, 37].

All of this requires the availability of an easy and reliable procedure to transform the scores obtained on different tests into comparable scores. A first attempt was proposed in a previous study that introduced the "Cognitive Impairment Index" [34], in which higher scores were attributed to greater degrees of impairment. Therefore, we proposed to apply a scoring procedure, i.e., the CII, that can provide clinicians with comparable scores that indicate a graduated levels of cognitive efficiency in MS patients.

When we collected the available Italian validated versions of all tests in the battery, we decided to include the word list of the CVLT-II (which is included in the Italian version of the BICAMS [23]) but added a free delayed recall in order to have further information about long-term verbal memory efficiency. We also decided not to include the PASAT because a recent study showed the higher validity of the SDMT compared to the PASAT-3 s, resulting in a further reduction of about 10 min of administration time [25].

Table 1 shows that HC and MS patients were statistically different only for age. However, this was acceptable because the sample of HC had to be representative of the whole population, whereas MS had to represent the MS characteristics. Furthermore, all test scores had to be corrected for significant demographic variables before any other analysis could be carried out.

Table 4 Comparison of the CII scores between MS and HC and within MS

Cognitive Impairment Index				
	Mann-Whitney		Mann-Whitney	
CVLT2-IR	MS HC	.622	RRMS SPMS	.000
CVLT2-DR	MS HC	.000	RRMS SPMS	.005
SDMT	MS HC	.001	RRMS SPMS	.000
BJLO	MS HC	.000	RRMS SPMS	.451
COWAT	MS HC	.215	RRMS SPMS	.000
DKEFS-CS1	MS HC	.000	RRMS SPMS	.007
DKEFS-DS1	MS HC	.000	RRMS SPMS	.020
DKEFS-CS2	MS HC	.000	RRMS SPMS	.471
DKEFS-DS2	MS HC	.000	RRMS SPMS	.860
BVMTR-TR	MS HC	.001	RRMS SPMS	.001
BVMTR-DR	MS HC	.012	RRMS SPMS	.001
t-CII	MS HC	.000	RRMS SPMS	.000

HC healthy controls, *MS* patients with multiple sclerosis, *RRMS* patients with relapsing-remitting MS, *SPMS* patients with secondary progressive MS, *CVLT-IR* California Verbal Learning Test 2-Immediate Recall, *CVLT-DR* California Verbal Learning Test 2-Delayed Recall, *SDMT* Symbol Digit Modalities Test, *BJLO* Benton Judgment of Line Orientation, *COWAT* Controlled Oral Word Association Test, *DKEFS-CS1* Delis–Kaplan Executive Function System-Card Sorting 1, *DKEFS-DS1* Delis–Kaplan Executive Function System-Description Score 1, *DKEFS-CS2* Delis–Kaplan Executive Function System-Card Sorting 2, *DKEFS-DS2* Delis–Kaplan Executive Function System-Description Score 2, *BVMTR-IR* Brief Visuo-Spatial Memory Test Revised-Immediate Recall, *BVMTR-DR* Brief Visuo-Spatial Memory Test-Revised-Delayed Recall, *t-CII* Total Cognitive Impairment Index

Table 5 Distribution of degrees of impairment in HC, MS, RRMS, and SPMS

	MS	HC	RRMS	SPMS	Sig.*
Cognitively preserved	53.7%	83.9%	62.7%	32.4%	*.000*
Mildly impaired	20.3%	10.6%	21.6%	16.2%	*.000*
Severely impaired	26%	5.5%	15.7%	51.4%	*.000*

HC healthy controls, *MS* patients with Multiple Sclerosis, *RRMS* patients with relapsing-remitting MS, *SPMS* patients with secondary progressive MS

*Chi-square significance between RRMS and SPMS

Each box in the table reports the *p* value of each combination

Results of the correlation analysis in the HC sample showed that all test scores were significantly correlated with age and education, as expected; by contrast, BJLO performances were also influenced by sex, with men outperforming women, as expected for visuo-spatial tasks [38, 39].

Several observations can be made from the different CII derived from our statistical analysis. Interestingly, in MS, the presence of CI is estimated to be present in about 50% of all cases, as expected, and assumes a specific pattern in two forms: In the RRMS group, 62.7% of the patients were classified as cognitively preserved and only 37.3% showed mild to severe impairment. This percentage is in line with that of a previous study in an Italian sample of RRMS [32]. In this study, the percentage of impaired patients reached 39.3%. Conversely, in the SPMS group, the pattern was in the opposite direction: Only 32.4% of SPMS was classified as cognitively preserved, whereas 67.6% ranged from mild to severe cognitive impairment with 51.4% of SPMS in the severely impaired group. This percentage is also in line with a previous study of a sample of Italian MS patients (including a cohort of SPMS) in which the percentage of patients with CI in the secondary progressive course was 53% [40].

These results confirm that the CII procedure applied to the MACFIMS battery has a certain reliability in detecting cognitive impairment in both relapsing-remitting and secondary- progressive MS patients and that it can also detect specific degrees of impairment between the two types of MS courses. This may help clinicians in their longitudinal work with patients and in adequately directing cognitive rehabilitation programs that can benefit patients most. Furthermore, it is important to have a clear definition of the cognitive profile of patients so that adequate pharmacological and non-pharmacological therapies can be proposed and so that their efficiency can be monitored longitudinally.

Despite the importance of providing an Italian version of the MACFIMS battery as a specific and widely recognized tool for assessing cognitive impairment in MS and proposing the CII as a procedure to define different degrees of impairment, this study has the limitation of having removed some scores from each test. However, this choice was made to provide clinicians with a complete battery that can be administered in a clinical setting with a reliable scoring procedure that can be applied in everyday clinical practice.

Compliance with ethical standards

Conflict of interest The authors report no conflicting financial interests.

Ethical approval All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local ethical committee on

May 28, 2014 (Prot. CE/PROG.444-09). Informed consent was obtained from all individual participants included in the study. We thank the patients for their willing participation in the study.

References

1. Chiaravalloti ND, DeLuca J (2008) Cognitive impairment in multiple sclerosis. Lancet Neurol 7(12):1139–1151. https://doi.org/10.1016/S1474-4422(08)70259-X
2. Campbell J, Rashid W, Cercignani M, Langdon D (2016) Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life. Postgrad Med J. https://doi.org/10.1136/postgradmedj-2016-134071
3. Magistrale G, Pisani V, Argento O, Incerti CC, Bozzali M, Cadavid D, Caltagirone C, Medori R, DeLuca J, Nocentini U (2015) Validation of the World Health Organization disability assessment schedule II (WHODAS-II) in patients with multiple sclerosis. Mult Scler 21(4):448–456. https://doi.org/10.1177/1352458514543732
4. Langdon DW (2011) Cognition in multiple sclerosis. Curr Opin Neurol 24:244–249. https://doi.org/10.1097/WCO.0b013e328346a43b
5. Morrow SA, Drake A, Zivadinov R, Munschauer F, Weinstock-Guttman B, Benedict RH (2010) Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline. Clin Neuropsychol 24(7):1131–1145. https://doi.org/10.1080/13854046.2010.511272
6. Incerti CC, Magistrale G, Argento O, Pisani V, Di Battista G, Ferraro E, Caltagirone C, Benedict RH, Nocentini U (2015) Occupational stress and personality traits in multiple sclerosis: a preliminary study. Mult Scler Relat Disord 4(4):315–319. https://doi.org/10.1016/j.msard.2015.06.001
7. Amato MP, Ponziani G, Pracucci G, Bracco L, Siracusa G, Amaducci L (1995) Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch Neurol 52(2):168–172
8. Bruce JM, Hancock LM, Arnett P, Lynch S (2010) Treatment adherence in multiple sclerosis: association with emotional status, personality, and cognition. J Behav Med 33(3):219–227. https://doi.org/10.1007/s10865-010-9247-y
9. Rao SM, and the Cognitive Function Study Group of the National Multiple Sclerosis Society (1990) A manual for the brief repeatable battery of neuropsychologic tests in multiple sclerosis. Medical College of Wisconsin, Milwaukee
10. Buschke H (1984) Cued recall in amnesia. J Clin Exp Neuropsychol 6(4):433–440
11. Rao SM, Hammeke TA, McQuillen MP, Khatri BO, Lloyd D (1984) Memory disturbance in chronic progressive multiple sclerosis. Arch Neurol 41(6):625–631
12. Smith A (1982) Symbol digit modalities test (SDMT) manual (revised) western psychological services. Los Angeles
13. Spreen O, Strauss E (1991) Controlled oral word association (word fluency). A compendium of neuropsychological tests. Oxford Univ Pr, Oxford, pp 219–227
14. Gronwall DMA (1977) Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 44(2):367–373
15. Goodglass H, Kaplan E, Barresi B (2001) The assessment of aphasia and related disorders. Lippincott Williams & Wilkins
16. Boringa JB, Lazeron RH, Reuling IE, Ader HJ, Pfennings LE, Lindeboom J, de Sonneville LM, Kalkers NF, Polman CH (2001) The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. Mult Scler 7(4):263–267. https://doi.org/10.1177/135245850100700409
17. Delis DC, Kramer JH, Kaplan E, Ober BA (2000) CVLT-II: California verbal learning test: adult version. Psychological Corporation, San Antonio
18. Benedict RH, Schretlen D, Groninger L, Dobraski M, Shpritz B (1996) Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity. Psychol Assess 8(2):145–153
19. Delis DC, Kaplan E, Kramer JH (2001) Delis-Kaplan executive function system (D-KEFS). Harcourt Assessment Company, Psychological Corporation, San Antonio
20. Benton AL, Hamsher KDES, Varney NR, Spreen O (1983) Contributions to Neuropsychological Assessment: A Clinical Manual. Oxford University Press, New York
21. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J et al (2002) Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol 16(3):381–397. https://doi.org/10.1017/S1355617709990750
22. Benedict RH, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S et al (2012) Brief international cognitive assessment for MS (BICAMS): international standards for validation. BMC Neurol 12(1):55–898. https://doi.org/10.1177/1352458511431076
23. Goretti B, Niccolai C, Hakiki B, Sturchio A, Falautano M, Minacapelli E, Martinelli V, Incerti C, Nocentini U, Murgia M, Fenu G, Cocco E, Marrosu MG, Garofalo E, Ambra FI, Maddestra M, Consalvo M, Viterbo RG, Trojano M, Losignore NA, Zimatore GB, Pietrolongo E, Lugaresi A, Langdon D, Portaccio E, Amato MP (2014) The brief international cognitive assessment for multiple sclerosis (BICAMS): normative values with gender, age and education corrections in the Italian population. BMC Neurol 14(1):171. https://doi.org/10.1186/s12883-014-0171-6
24. Erlanger DM, Kaushik T, Caruso LS, Benedict RH, Foley FW, Wilken J, Cadavid D, DeLuca J (2014) Reliability of a cognitive endpoint for use in a multiple sclerosis pharmaceutical trial. J Neurol Sci 340(1):123–129. https://doi.org/10.1016/j.jns.2014.03.009
25. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM (2014) Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Mult Scler 20(4):481–488. https://doi.org/10.1177/1352458513501570
26. Argento O, Smerbeck A, Pisani V, Magistrale G, Incerti CC, Caltagirone C, Benedict RH, Nocentini U (2016) Regression-based norms for the brief visuospatial memory test-revised in Italian population and application in MS patients. Clin Neuropsychol 30(1):1469–1478. https://doi.org/10.1080/13854046.2016.1183713
27. Folstein MF, Folstein SE, McHugh PR, Fanjiang G (2000) Mini-Mental State Examination: MMSE user's guide. Psychology Assessment Resources, Odessa
28. Measso G, Cavarzeran F, Zappalà G, Lebowitz BD, Crook TH, Pirozzolo FJ, Amaducci LA, Massari D, Grigoletto F (1993) The mini-mental state examination: normative study of an Italian random sample. Dev Neuropsychol 9(2):77–85. https://doi.org/10.1080/87565649109540545
29. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". Ann Neurol 58(6):840–846. https://doi.org/10.1002/ana.20703
30. Dusankova JB, Kalincik T, Havrdova E, Benedict RH (2012) Cross cultural validation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) and the brief international cognitive assessment for multiple sclerosis (BICAMS). Clin Neuropsychol 26(7):1186–1200. https://doi.org/10.1080/13854046.2012.725101

31. Migliore S, Ghazaryan A, Simonelli I, Pasqualetti P, Landi D, Palmieri MG, Moffa F, Rinaldi P, Vernieri F, Filippi MM (2016) Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) in the Italian population. Neurol Sci 37(8): 1261–1270. https://doi.org/10.1007/s10072-016-2578-x
32. Nocentini U, Giordano A, Di Vincenzo S, Panella M, Pasqualetti P (2006) The symbol digit modalities test-oral version: Italian normative data. Funct Neurol 21(2):93–96
33. Mattioli F, Stampatori C, Bellomi F, Scarpazza C, Galli P, Guarneri C, Corso B, Montomoli C, Niccolai C, Goretti B, Amato MP, Riboni E, Tomasina CD, Falautano M, Capra R (2014) Assessing executive function with the D-KEFS sorting test: normative data for a sample of the Italian adult population. Neurol Sci 35(12):1895–1902. https://doi.org/10.1007/s10072-014-1857-7
34. Camp SJ, Stevenson VL, Thompson AJ, Miller DH, Borras C, Auriacombe S, Brochet B, Falautano M, Filippi M, Herisse-Dulo L, Montalban X, Parrcira E, Polman CH, de Sa J, Langdon DW (1999) Cognitive function in primary progressive and transitional progressive multiple sclerosis. Brain 122(7):1341–1348
35. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, Atzori M, Bernardi V, Barachino L, Rinaldi L, Perini P, Gallo P, Filippi M (2009) Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 66(9):1144–1150. https://doi.org/10.1001/archneurol.2009.174
36. Amato MP, Langdon D, Montalban X, Benedict RH, DeLuca J, Krupp LB et al (2013) Treatment of cognitive impairment in multiple sclerosis: position paper. J Neurol 260(6):1452–1468. https://doi.org/10.1007/s00415-012-6678-0
37. Miller E, Morel A, Redlicka J, Miller I, Saluk J (2017) Pharmacological and non-pharmacological therapies of cognitive impairment in multiple sclerosis. Curr Neuropharmacol. https://doi.org/10.2174/1570159X15666171109132650
38. Desmond DW, Glenwick DS, Stern Y, Tatemichi TK (1994) Sex differences in the representation of visuospatial functions in the human brain. Rehabil Psychol 39:3–14
39. Goyette SR, McCoy JG, Kennedy A, Sullivan M (2012) Sex differences on the judgment of line orientation task: a function of landmark presence and hormonal status. Physiol Behav 105(4): 1045–1051
40. Comi G, Filippi M, Martinelli V, Campi A, Rodegher M, Alberoni M et al (1995) Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. J Neurol Sci 132(2):22–227