



Validation of a Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) and comparison with reference batteries

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| Keywords: | Multiple sclerosis, Cognition, BICAMS, MACFIMS |
| Abstract: | <p>Background: The Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) is a short neuropsychological battery for persons with multiple sclerosis (PwMS).</p> <p>Objectives: The main objective of the study is to validate the BCCAMS.</p> <p>Methods: PwMS and healthy subjects (HS) were evaluated using the BCCAMS which include two computerized tests, the Computerized Speed Cognitive Test and the Computerized Episodic Visual Memory Test (CEVMT), a newly developed visuospatial memory test, and the French learning test. The MACFIMS including the BICAMS tests, was also administered. Regression-based norms of the BCCAMS were calculated in 276 HS. BCCAMS was compared to BICAMS and MACFIMS for detection of cognitive impairment (CI).</p> <p>Results: Out of 120 PwMS, CI was detected using the BCCAMS, BICAMS (one impaired test), and MACFIMS (two impaired tests) in 59.1%, 50%, and 37.9%, respectively. The BCCAMS produced the same predictive value as that of the BICAMS battery for detecting CI in the MACFIMS.</p> <p>Conclusion: This study validated the BCCAMS as a validated computerized short assessment for information processing speed and</p> |

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| | learning in MS. |
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Manuscripts

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3 **Validation of a Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) and**
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5 **comparison with reference batteries**
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3 ABSTRACT:
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5 Background: The Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) is a short
6 neuropsychological battery for persons with multiple sclerosis (PwMS).
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8 Objectives: The main objective of the study is to validate the BCCAMS.
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11 Methods: PwMS and healthy subjects (HS) were evaluated using the BCCAMS which include two
12 computerized tests, the Computerized Speed Cognitive Test and the Computerized Episodic Visual
13 Memory Test (CEVMT), a newly developed visuospatial memory test, and the French learning test. ,
14 The MACFIMS including the BICAMS tests, was also administered. Regression-based norms of the
15 BCCAMS were calculated in 276 HS. BCCAMS was compared to BICAMS and MACFIMS for detection
16 of cognitive impairment (CI).
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22 Results: Out of 120 PwMS, CI was detected using the BCCAMS, BICAMS (one impaired test), and
23 MACFIMS (two impaired tests) in 59.1%, 50%, and 37.9%, respectively. The BCCAMS produced the
24 same predictive value as that of the BICAMS battery for detecting CI in the MACFIMS.
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28 Conclusion: This study validated the BCCAMS as a validated computerized short assessment for
29 information processing speed and learning in MS.
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3 Assessment of cognitive impairment (CI) is important for the clinical care of persons with multiple
4 sclerosis (PwMS).¹ However, a comprehensive clinical cognitive assessment using large batteries,
5 such as the Minimal Assessment of Cognitive Function in MS (MACFIMS),² is not routinely available in
6 many centers because of the absence of the required expert staff. The Brief International Cognitive
7 Assessment for Multiple Sclerosis (BICAMS) battery, a short assessment that combines three
8 neuropsychological (NP) tests has been proposed.³ It includes a test of information processing speed
9 (IPS), the Symbol Digit Modalities Test (SDMT),⁴ and the first learning trials of two measures of
10 episodic memory, the California Verbal Learning Test-II (CVLT-II)⁵ and the Brief Visuospatial Memory
11 Test Revised (BVMT-R).⁶ This short battery is validated in many languages, including French,⁷ and is
12 found to be very useful for centers without access to neuropsychologists. However, the manner of
13 performing the tests is essential for the good reliability of results. To increase the reproducibility of
14 the testing procedure, one option is using computerized tests with a standardized presentation. Our
15 group validated a computerized test of IPS, namely, the computerized speed cognitive test (CSCT),
16 which can detect disorders of IPS in MS.⁸ The computerized presentation provides a better
17 standardization of the test and decreases the practice effect compared with typical test, such as the
18 SDMT, even when using alternate forms, because the key provided for the test changes for every
19 testing.^{8,9} On the same principle, we propose a short battery, which is inspired by the BICAMS
20 (assessment of IPS and episodic memory). It is called the Brief Computerized Cognitive Assessment
21 for MS (BCCAMS), which combines the CSCT and a new computerized test of visual episodic memory,
22 namely, the Computerized Episodic Visual Memory Test (CEVMT). The third test, the French learning
23 test [FLT], consists of the learning trials of a verbal episodic memory test included in the French
24 adaptation of the BICAMS and was not presented on a computer.^{7,10}

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52 The main objective of the study was to validate the BCCAMS. The regression-based norms of the
53 CEVMT and the three-test battery (BCCAMS) were established using a sample of healthy subjects
54 (HS). The validity of the tests was examined in a sample of PwMS with different phenotypes. Finally,
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3 the three-test battery (BCCAMS) was compared to the BICAMS and a two-test version of the BCCAMS
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5 (BCCAMS2T) to detect CI, using the MACFIMS as a reference.
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10 **SUBJECTS AND METHODS**

11 This study was approved by the institutional review board of Bordeaux (CPP SOOM No. 2014/95) and
12
13 was registered at Clinical Trial.gov (NCT02391064). All participants signed a written consent form.
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16 ***SUBJECTS***

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18 All participants were native speakers of French. Individuals aged 18 to 64 years were eligible.
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20 *Healthy subjects*

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22 The study recruited a sample of HS without cognitive complaints through advertisements. They were
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24 excluded if they had a history of a neurological, psychiatric, or severe chronic disease. Subjects
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26 undergoing psychoactive medication or substance abuse, pregnant women, and HS who participated
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28 in a cognitive study in the previous year were excluded. The HS were given monetary compensation
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30 for participating in the study.
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34 *Patients*

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36 PwMS fulfilling the 2017 McDonald diagnostic criteria¹¹ for relapsing–remitting (RR), primary
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38 progressive (PPMS), or secondary progressive MS (SPMS)¹¹ were recruited from 15 expert MS centers
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40 in France between February 2015 and June 2017. The exclusion criteria were as follows: history of a
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42 neurological or psychiatric disease, history of a severe chronic disease, use of psychotropic drugs in
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44 the previous two months (start, stop, or dosage change), change in disease-modifying therapy (DMT)
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46 in the previous month (start, stop, or dosage change), steroid treatment in the previous month, and
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48 motor, visual, or sensory impairment precluding the ability to complete cognitive tests. PwMS
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50 fulfilling inclusion criteria were invited to participate by neurologists of the participating centers
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52 during routine clinical visits.
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59 ***METHODS***

Neuropsychological assessment

Qualified senior neuropsychologists administered all NP tests. At baseline, the assessment included the BCCAMS and MACFIMS tests (test 1), which includes the BICAMS tests. The BCCAMS assessment was repeated after one and six months for all PwMS and half of the HS group (tests 2 and 3). BCCAMS (CSCT and CEVMT) testing was conducted using a personal computer. The CSCT was described in detail and previously validated.⁸ Briefly, it is based on the principle of code/number substitution tests, such as the digit code test of the Wechsler Adult Intelligence Test, SDMT, and other related tests. The particularity of the CSCT is that it is computerized, which enables the code and number pairs to be reassigned during each test to reduce the test–retest learning effect. The test is freely available online (<https://csct-cogms-bordeaux.fr/>).

The CEVMT is a new computerized test of episodic visual memory. A chessboard (16 squares, 4 × 4) is presented on a monitor screen. A complex figure formed by the assembly of contiguous squares and gray triangles is presented on the board for 25 s (Figure 1). Immediately after, an empty grid appears. The subject should attempt to reproduce the figure by dragging the elements (squares and gray triangles) displayed at the bottom of the screen toward the grid using a mouse. Afterward, the subject validates the answer. Three trials are conducted, whereas four shapes (alternate forms) can be used. Different forms were used for this study at the different visits. As a part of the BCCAMS, only the three initial learning trials of the CEVMT are administered. The score is the total number of correct answers recorded across the three trials. In the full version of the test, a delayed recall is performed after 15 min, and a recognition test is finally conducted.

The FLT is an assessment of episodic verbal memory, which was adapted from the CVLT.^{7,10} For the BCCAMS, the test included five trials for learning a 16-word list (list A) corresponding to four semantic categories. For each trial, the subject is instructed to make a free reminder after the psychologist recalls the complete list. The list was used at months 1 and 6 (test 1). At month 3 (test 2), the five learning trials of the French version of the CVLT were used (list A).¹² The BCCAMS2T includes only the CSCT and learning trials of the CEVMT.

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3 The MACFIMS were described in detail previously.² The adapted MACFIMS battery, which was
4 recently validated in France,¹⁰ included the Paced Auditory Serial Addition Test with a 3.0-s
5 interstimulus interval¹⁴ (working memory and IPS), the SDMT⁴ (IPS), the FLT (total learning and
6 delayed recall),^{7,10} the Brief Visuospatial Memory Test-Revised (BVMTR; visual episodic memory, i.e.,
7 total learning and delayed recall),⁶ the French adaptation of the Delis–Kaplan Executive Function
8 System Sorting Test,¹⁵ the “épreuve de classement de cartes de Champagne” (ECCC) developed by
9 one of the researchers (NE) (total correct sorts and description score; previously described),⁹ the
10 Judgment of Line Orientation Test¹⁶ (spatial orientation), and the Controlled Oral Word Association
11 Test (COWAT).¹⁶

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23 The BICAMS is composed of the SDMT, the five learning trials of the FLT, and the first three learning
24 trials of the BVMTR.³

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27 All tests were administered in a single testing session in the following order: CSCT, CEVMT, CVLT,
28 JLOT, CEVMT-DR, SDMT, CVLT DR, BVMTR, PASAT 3 s, ECCC, BVMTR-DR and COWAT.

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32 The study flow-chart is presented in Figure 2.

33 34 *Neurological evaluation*

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37 The French adaptation of the Expanded Disability Status Scale (EDSS)¹⁶ was used to measure
38 neurological disability.

39 40 *Patient-related outcomes*

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43 All subjects completed the questionnaires for patient-related outcomes in terms of depressive
44 symptoms (fast Beck Depression Inventory [FAST-BDI]),¹⁸ anxiety (State Trait Anxiety Inventory
45 [STAI]),¹⁹ mood (Echelle d’Humeur Dépressive [EHD-PRO]),²⁰ and subjective fatigue (the French
46 version of the Fatigue Impact Scale [EMIF-SEP]).²¹

47 48 49 *Statistical analyses*

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54 SPSS version 23 was used for statistical analysis. Significance was set to $\alpha < 0.05$. Student’s t-test and
55 χ^2 test were employed to analyze between-group differences for continuous variables and to test for
56 categorical variables, respectively. Effect size was calculated using Cohen’s d.

Psychometric properties of the CEVMT

1. Reliability was assessed using Pearson's correlations between scores for (a) trial 1 versus trial 2 and (b) trial 2 versus trial 3 in HS and PwMS at baseline.
2. The *internal consistency* of the test trials was measured using Cronbach's alpha.
3. *The equivalence of the four forms of the CEVMT*, namely, A, B, C, and D, was tested using ANOVA between four groups of HS.
4. *The effects of age, sex, and educational level* were assessed using regression analysis as explained in subsequent text.
5. *Validity*: Pearson's correlation analysis was performed between the z-scores for the CEVMT and BVMT-R to assess the ability of the CEVMT to detect deficits in visual episodic memory.
6. The *practice effect* was evaluated using a paired sample t-test between tests 1, 2, and 3 using alternate forms.

Regression-based norms

The paper presents the norms only for the CEVMT and BCCAMS. Norms of the other individual tests have been previously published (FLT, ECCC, CSCT).^{7,8,10}

The methodology for regression-based norms is described previously.^{7,10,22,23} The detailed method is presented as a supplementary material.

Definition of impairment and comparison with reference batteries

On the basis of the MACFIMS, impairment was defined as the presence of at least two abnormal tests (<1.5 SD), whereas on the basis of the BICAMS and BCCAMS, it was defined by the presence of at least one abnormal test.

The study analyzed the BCCAMS2T and BCCAMS screening value against the BICAMS to detect CI at the MACFIMS by performing Bayesian analysis (i.e., specificity, sensitivity, and accuracy). The area under the curve (AUC) was calculated through receiver operating characteristic (ROC) analyses to compare the respective value of the short batteries to predict CI at the MACFIMS.

RESULTS

CHARACTERISTICS OF SUBJECTS

The study recruited 276 HS and 120 PwMS (39, 40, and 41 with RRMS, SPMS, and PPMS, respectively). Table 1 presents the clinical and demographic characteristics of the participants.

Psychometric properties of the CEVMT

Table 1 presents the mean CEVMT scores.

Reliability and retest

The test-retest reliability between baseline and month 1 evaluated in 147 HS was 0.70 ($p < 0.001$) in HS and 0.60 ($p < 0.001$) in PwMS.

Internal consistency of different computerized test trials

The Cronbach's alpha coefficient between the three trials was 0.86 in HS and 0.84 in PwMS

Equivalence of the four forms of the CEVMT

Forms A, B, C, and D of the CEVMT were tested between four groups of HS at baseline. The groups corresponding to each test, which were formed with approximately equal numbers of participants (group sizes ranged from 65 to 72), did not differ significantly with respect to age, gender, or educational level (examined by ANOVA and the chi-square test). Moreover, no significant difference was observed between the mean scores for the groups for the CEVMT ($p = 0.302$).

Validity and construct validity

All scores for the CEVMT were significantly different between PwMS and HS.

The Pearson's correlation coefficients between z-scores for immediate and delay recall in the CEVMT and BVMT-R were $r = 0.52$ ($p < 0.001$) and $r = 0.51$ ($p < 0.001$), respectively.

Practice effect

The CEVMT practice effect was tested in PwMS. The mean score at baseline was 18.01 (± 6.42), which improved significantly at month 1 (mean score = 20.38 (± 7.41); $p < 0.001$). No significant difference was observed between months 1 and 6 ($p = 0.57$).

Effect of phenotypes of MS

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3 According to the phenotype of MS, the difference observed for the CEVMT was non significant (mean
4 score = 19.49 (± 6.75) vs. 17.1 (± 6.07); $p = 0.054$).

7 *Effect of confounding factors*

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10 No significant correlations were observed between the CEVMT scores and the FAST-BDI, STAI A and
11 B, MFIS, and EHD in the MS patient group.

14 *Vocational status*

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16 No significant difference was found in CEVMT scores between unemployed and employed MS
17 patients for immediate recall (17.61 (± 6.24) vs. 18.20 (± 6.58); $p = 0.61$).

21 *Regression-based norms*

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23 Table 2 features the scale conversion and Table 3 presents the regression model for the CEVMT,
24 CSCT, and FLT, which were used to derive demographically adjusted z-scores for MS patients,
25 including agec (age – 43.83), agec², gender, and education as predictor variables. The method for
26 using of the regression-based norms is explained in supplementary material.
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30 Table 4 summarizes the proportion of MS patients with CI for each test that applies these norms. A
31 significant difference was observed between groups on the four tests of the BCCAMS.

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34 The study classified 13.3% of PwMS as impaired for the CEVMT-IR, 36.7% for the CSCT, and 36.6% for
35 the FLT (immediate recall; five trials).

41 *Comparison with reference batteries*

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43 The proportions of PwMS with CI detected by the BCCAMS, BCCAMS2T, and BICAMS were 59.1%,
44 38.4%, and 50%, respectively.

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47 The number of patients considered impaired on the BCCAMS battery differs according to the
48 phenotype of the disease with 30.8%, 60%, and 39% of patients with RRMS, SPMS, and PPMS,
49 respectively, considered impaired ($p = 0.025$).

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52 Sensitivity analysis indicated that 95.0% [86.1–99.0] of subjects with CI in the BICAMS were with CI in
53 the BCCAMS. Specificity analysis revealed that 76.7% [64.–86.6] of subjects not impaired in the
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3 BICAMS were not deficient in the BCCAMS. Accuracy between the BCCAMS and BICAMS was
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5 evaluated at 85.8% [78.3–91.5].
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7 *Comparison to the MACFIMS*

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9 Ninety-nine PwMS were able to pass the entire MACFIMS battery test.

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11 The MACFIMS detected 32.3% of patients with CI. Table 5 presents the comparative data from the
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13 BCCAMS and BICAMS.
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16 On the basis of the ROC analysis, the BCCAMS battery was associated with a similar AUC value
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18 (0.836) as that of the BICAMS battery (0.841) for detecting CI in MACFIMS.
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20 21 22 23 **DISCUSSION**

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26 The BCCAMS battery was a short cognitive battery that enables the rapid assessment of IPS and
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28 episodic memory in PwMS. The battery was inspired by the BICAMS battery, which includes one test
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30 from IPS, the SDMT, and the first learning trials of two learning tests, namely, the CVLT-II and BVMT-
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32 R. In the BCCAMS, the test of IPS is the CSCT, which is previously validated in MS and HS with good
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34 psychometric properties. It has been shown to be similar in sensitivity to the SDMT but with less
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36 practice effect. For visual episodic memory, the study developed a new test, the CEVMT, and
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38 demonstrated that the test exhibits correct psychometric properties (i.e., reliability, consistency, and
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40 equivalence for the four forms). Test retest reliability between baseline and month 1 for PwMS and
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42 HS are poor (0.70 and 0.60 respectively) as they are for the BVMT-R in the same sample previously
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44 published (0.52 and 0.66 respectively).¹⁰ A significant practice effect was observed at one month but
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46 not after six months. Further improvement of the tests (new alternate forms) should be done to
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48 improve test-retest correlation coefficient. However, it satisfactorily discriminated PwMS from HS.
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51 The relatively low correlation between the CEVMT and BVMT-R suggests that the two tests do not
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53 measure exactly the same function. The strategy used by participants during the CEVMT (reproducing
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55 a complex figure by placing the different parts) probably include different executive skills than the
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57 BVMT-R based on the reproduction of drawing. Further studies are needed to analyze these
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3 differences. However, the CEVMT shows good qualities to detect impairment in PwMS. The
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5 confounding factors, which were investigated using self-report questionnaires on mood, depressive
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7 symptoms, anxiety, and fatigue, did not influence the results of the test, although the scores for
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9 these scales were significantly different between MS patients and HS.

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11 For the verbal memory the study employed, we used the first learning trials of the FLT, which was
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13 adapted from the CVLT and recently validated.¹⁰ A computerized version of the test is in
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15 development, and it will be incorporated to the computerized battery.
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19 The study used a regression-based procedure for establishing the norms of the BCCAMS battery.

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21 Using these norms, the study demonstrated that the battery was able to identify CI in 59.1% of
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23 PwMS. Using the BICAMS, 50% were classified as impaired. This proportion is close to that reported
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25 in another study using the BICAMS, which is consistent with the proportion of CI in MS reported in
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27 the literature. The performances of the two batteries are relatively similar, whereas impairment at
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29 the BCCAMS predicts impairment at the BICAMS with a very high accuracy (85.8%). The
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31 performances of the two batteries for predicting CI at the MACFIMS are relatively similar with
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33 excellent accuracy and sensibility. The BCCAMS easily and quickly detected 100% of the patients,
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35 which were discriminated as cognitively affected by the MACFIMS battery.
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39 Recently, the literature showed that the use of only two tests of the BICAMS (SDMT and BVMT-R)
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41 could be an alternative to the entire BICAMS when time is restricted.²⁴ The study illustrated that the
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43 BCCAMS2T has lower sensitivity and accuracy but a higher specificity than the three-test battery.
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46 This study has several limitations. First, the FLT was not presented on the computer and the battery
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48 is not fully computerized. A computerized version of the FLT is currently under validation. Second,
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50 HCs and PwMS differ significantly in age and education. However, the norms were not established by
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52 direct comparisons of these groups but by using the methodology of based-regression norms taking
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54 into account these differences. Third, we did not randomize the order of the tests because patients
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56 take only one time each test and the results of FLT and BVMT were used for both the MACFIMS and
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3 the BICAMS. Finally, the test-retest reliability is quite low probably due to too many differences
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5 between the alternate forms and further improvement should be done.
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7 Several proposition of computerized cognitive tests for MS have been made recently.²⁵ However,
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9 there is still a need for tests validated in MS with comparable sensitivity to the MACFIMS and the
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11 BICAMS. Moreover, one interest of this battery is that it is the first one validated for French-speaking
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13 subjects.
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16 In conclusion, the use of the proposed BCCAMS battery facilitates a short and valid evaluation of
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18 verbal and visuospatial episodic memory and IPS in PwMS in clinical practice.
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7 Other authors did not disclose conflict of interest.

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12 **FIGURE LEGEND:**

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14 Figure 1: Example of figure of the CEVMT.

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16 Figure 2: Study flow-chart

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ABSTRACT:

Background: The Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) is a short neuropsychological battery for persons with multiple sclerosis (PwMS).

Objectives: The main objective of the study aims is to establish regression-based norms for validate the BCCAMS and to compare it to the Brief International Cognitive Assessment for MS (BICAMS) and the Minimal Assessment of Cognitive Function in MS (MACFIMS).

Methods: PwMS and healthy subjects (HS) were evaluated using the BCCAMS which include two computerized tests, the Computerized Speed Cognitive Test and the Computerized Episodic Visual Memory Test (CEVMT), a newly developed visuospatial memory test, and the French learning test. , The MACFIMS including the BICAMS tests, was also administered. Regression-based norms of the BCCAMS were calculated in 276 HS. BCCAMS was compared to BICAMS and MACFIMS for detection of cognitive impairment (CI).

Results: Out of 120 PwMS, CI was detected using the BCCAMS, BICAMS (one impaired test), and MACFIMS (two impaired tests) in 59.1%, 50%, and 37.9%, respectively. The BCCAMS produced the same predictive value as that of the BICAMS battery for detecting CI in the MACFIMS.

Conclusion: This study validated the BCCAMS as a validated computerized short assessment for information processing speed and learning in MS.

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3 Assessment of cognitive impairment (CI) is important for the clinical care of persons with multiple
4 sclerosis (PwMS).¹ However, a comprehensive clinical cognitive assessment using large batteries,
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6 such as the Minimal Assessment of Cognitive Function in MS (MACFIMS),² is not routinely available in
7
8 many centers because of the absence of the required expert staff. The Brief International Cognitive
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10 Assessment for Multiple Sclerosis (BICAMS) battery, a short assessment that combines three
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12 neuropsychological (NP) tests has been proposed.³ It includes a test of information processing speed
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14 (IPS), the Symbol Digit Modalities Test (SDMT),⁴ and the first learning trials of two measures of
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16 episodic memory, the California Verbal Learning Test-II (CVLT-II)⁵ and the Brief Visuospatial Memory
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18 Test Revised (BVMT-R).⁶ This short battery is validated in many languages, including French,⁷ and is
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20 found to be very useful for centers without access to neuropsychologists. However, the manner of
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22 performing the tests is essential for the good reliability of results. To increase the reproducibility of
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24 the testing procedure, one option is using computerized tests with a standardized presentation. Our
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26 group validated a computerized test of IPS, namely, the computerized speed cognitive test (CSCT),
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28 which can detect disorders of IPS in MS.⁸ The computerized presentation provides a better
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30 standardization of the test and decreases the practice effect compared with typical test, such as the
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32 SDMT, even when using alternate forms, because the key provided for the test changes for every
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34 testing.^{8,9} On the same principle, we propose a short battery, which is inspired by the BICAMS
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36 (assessment of IPS and episodic memory). It is called the Brief Computerized Cognitive Assessment
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38 for MS (BCCAMS), which combines the CSCT and a new computerized test of visual episodic memory,
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40 namely, the Computerized Episodic Visual Memory Test (CEVMT). The third test, the French learning
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42 test [FLT], consists of the learning trials of a verbal episodic memory test included in the French
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44 adaptation of the BICAMS and was not presented on a computer.^{7,10}
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52 The main objective of the study was to validate the BCCAMS. The regression-based norms of the
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54 CEVMT and the three-test battery (BCCAMS) were established using a sample of healthy subjects
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56 (HS). The validity of the tests was examined in a sample of PwMS with different phenotypes. Finally,
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3 the three-test battery (BCCAMS) was compared to the BICAMS and a two-test version of the BCCAMS
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5 (BCCAMS2T) to detect CI, using the MACFIMS as a reference.
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10 **SUBJECTS AND METHODS**

11 This study was approved by the institutional review board of Bordeaux (CPP SOOM No. 2014/95) and
12
13 was registered at Clinical Trial.gov (NCT02391064). All participants signed a written consent form.
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15

16 ***SUBJECTS***

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18 All participants were native speakers of French. Individuals aged 18 to 64 years were eligible.
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20 *Healthy subjects*

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22 The study recruited a sample of HS without cognitive complaints through advertisements. They were
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24 excluded if they had a history of a neurological, psychiatric, or severe chronic disease. Subjects
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26 undergoing psychoactive medication or substance abuse, pregnant women, and HS who participated
27
28 in a cognitive study in the previous year were excluded. The HS were given monetary compensation
29
30 for participating in the study.
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34 *Patients*

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36 PwMS fulfilling the 2017 McDonald diagnostic criteria¹¹ for relapsing–remitting (RR), primary
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38 progressive (PPMS), or secondary progressive MS (SPMS)¹¹ were recruited from 15 expert MS centers
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40 in France between February 2015 and June 2017. The exclusion criteria were as follows: history of a
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42 neurological or psychiatric disease, history of a severe chronic disease, use of psychotropic drugs in
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44 the previous two months (start, stop, or dosage change), change in disease-modifying therapy (DMT)
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46 in the previous month (start, stop, or dosage change), steroid treatment in the previous month, and
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48 motor, visual, or sensory impairment precluding the ability to complete cognitive tests. PwMS
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50 fulfilling inclusion criteria were invited to participate by neurologists of the participating centers
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52 during routine clinical visits.
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59 ***METHODS***

Neuropsychological assessment

Qualified senior neuropsychologists administered all NP tests. At baseline, the assessment included the BCCAMS and MACFIMS tests (test 1), which includes the BICAMS tests. The BCCAMS assessment was repeated after one and six months for all PwMS and half of the HS group (tests 2 and 3). BCCAMS (CSCT and CEVMT) testing was conducted using a personal computer. The CSCT was described in detail and previously validated.⁸ Briefly, it is based on the principle of code/number substitution tests, such as the digit code test of the Wechsler Adult Intelligence Test, SDMT, and other related tests. The particularity of the CSCT is that it is computerized, which enables the code and number pairs to be reassigned during each test to reduce the test–retest learning effect. The test is freely available online (<https://csct-cogms-bordeaux.fr/>).

The CEVMT is a new computerized test of episodic visual memory. A chessboard (16 squares, 4 × 4) is presented on a monitor screen. A complex figure formed by the assembly of contiguous squares and gray triangles is presented on the board for 25 s (Figure 1). Immediately after, an empty grid appears. The subject should attempt to reproduce the figure by dragging the elements (squares and gray triangles) displayed at the bottom of the screen toward the grid using a mouse. Afterward, the subject validates the answer. Three trials are conducted, whereas four shapes (alternate forms) can be used. Different forms were used for this study at the different visits. As a part of the BCCAMS, only the three initial learning trials of the CEVMT are administered. The score is the total number of correct answers recorded across the three trials. In the full version of the test, a delayed recall is performed after 15 min, and a recognition test is finally conducted.

The FLT is an assessment of episodic verbal memory, which was adapted from the CVLT.^{7,10} For the BCCAMS, the test included five trials for learning a 16-word list (list A) corresponding to four semantic categories. For each trial, the subject is instructed to make a free reminder after the psychologist recalls the complete list. The list was used at months 1 and 6 (test 1). At month 3 (test 2), the five learning trials of the French version of the CVLT were used (list A).¹² The BCCAMS2T includes only the CSCT and learning trials of the CEVMT.

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3 The MACFIMS were described in detail previously.² The adapted MACFIMS battery, which was
4 recently validated in France,¹⁰ included the Paced Auditory Serial Addition Test with a 3.0-s
5 interstimulus interval¹⁴ (working memory and IPS), the SDMT⁴ (IPS), the FLT (total learning and
6 delayed recall),^{7,10} the Brief Visuospatial Memory Test-Revised (BVRT-R; visual episodic memory, i.e.,
7 total learning and delayed recall),⁶ the French adaptation of the Delis–Kaplan Executive Function
8 System Sorting Test,¹⁵ the “épreuve de classement de cartes de Champagne” (ECCC) developed by
9 one of the researchers (NE) (total correct sorts and description score; previously described),⁹ the
10 Judgment of Line Orientation Test¹⁶ (spatial orientation), and the Controlled Oral Word Association
11 Test (COWAT).¹⁶

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23 The BICAMS is composed of the SDMT, the five learning trials of the FLT, and the first three learning
24 trials of the BVRT-R.³

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27 All tests were administered in a single testing session in the following order: CSCT, CEVMT, CVLT,
28 JLOT, CEVMT-DR, SDMT, CVLT DR, BVRT, PASAT 3 s, ECCC, BVRT-DR and COWAT.

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32 The study flow-chart is presented in Figure 2.

33 34 *Neurological evaluation*

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37 The French adaptation of the Expanded Disability Status Scale (EDSS)¹⁶ was used to measure
38 neurological disability.

39 40 41 *Patient-related outcomes*

42
43 All subjects completed the questionnaires for patient-related outcomes in terms of depressive
44 symptoms (fast Beck Depression Inventory [FAST-BDI]),¹⁸ anxiety (State Trait Anxiety Inventory
45 [STAI]),¹⁹ mood (Echelle d’Humeur Dépressive [EHD-PRO]),²⁰ and subjective fatigue (the French
46 version of the Fatigue Impact Scale [EMIF-SEP]).²¹

47 48 49 50 51 *Statistical analyses*

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54 SPSS version 23 was used for statistical analysis. Significance was set to $\alpha < 0.05$. Student’s t-test and
55 χ^2 test were employed to analyze between-group differences for continuous variables and to test for
56 categorical variables, respectively. Effect size was calculated using Cohen’s d.

Psychometric properties of the CEVMT

1. Reliability was assessed using Pearson's correlations between scores for (a) trial 1 versus trial 2 and (b) trial 2 versus trial 3 in HS and PwMS at baseline.
2. The *internal consistency* of the test trials was measured using Cronbach's alpha.
3. *The equivalence of the four forms of the CEVMT*, namely, A, B, C, and D, was tested using ANOVA between four groups of HS.
4. *The effects of age, sex, and educational level* were assessed using regression analysis as explained in subsequent text.
5. *Validity*: Pearson's correlation analysis was performed between the z-scores for the CEVMT and BVM-T-R to assess the ability of the CEVMT to detect deficits in visual episodic memory.
6. The *practice effect* was evaluated using a paired sample t-test between tests 1, 2, and 3 using alternate forms.

Regression-based norms

The paper presents the norms only for the CEVMT and BCCAMS. Norms of the other individual tests have been previously published (FLT, ECCC, CSCT).^{7,8,10}

The methodology for regression-based norms is described previously.^{7,10,22,23} The detailed method is presented as a supplementary material.

Definition of impairment and comparison with reference batteries

On the basis of the MACFIMS, impairment was defined as the presence of at least two abnormal tests (<1.5 SD), whereas on the basis of the BICAMS and BCCAMS, it was defined by the presence of at least one abnormal test.

The study analyzed the BCCAMS2T and BCCAMS screening value against the BICAMS to detect CI at the MACFIMS by performing Bayesian analysis (i.e., specificity, sensitivity, and accuracy). The area under the curve (AUC) was calculated through receiver operating characteristic (ROC) analyses to compare the respective value of the short batteries to predict CI at the MACFIMS.

RESULTS

CHARACTERISTICS OF SUBJECTS

The study recruited 276 HS and 120 PwMS (39, 40, and 41 with RRMS, SPMS, and PPMS, respectively). Table 1 presents the clinical and demographic characteristics of the participants.

Psychometric properties of the CEVMT

Table 1 presents the mean CEVMT scores. ~~Psychometric properties of CEVMT are presented in the supplementary material.~~

Reliability and retest

~~The test-retest reliability between baseline and month 1 evaluated in 147 HS was 0.70 ($p < 0.001$) in HS and 0.60 ($p < 0.001$) in PwMS.~~

Internal consistency of different computerized test trials

~~The Cronbach's alpha coefficient between the three trials was 0.86 in HS and 0.84 in PwMS~~

Equivalence of the four forms of the CEVMT

~~Forms A, B, C, and D of the CEVMT were tested between four groups of HS at baseline. The groups corresponding to each test, which were formed with approximately equal numbers of participants (group sizes ranged from 65 to 72), did not differ significantly with respect to age, gender, or educational level (examined by ANOVA and the chi-square test). Moreover, no significant difference was observed between the mean scores for the groups for the CEVMT ($p = 0.302$).~~

Validity and construct validity

~~All scores for the CEVMT were significantly different between PwMS and HS.~~

~~The Pearson's correlation coefficients between z-scores for immediate and delay recall in the CEVMT and BVMT-R were $r = 0.52$ ($p < 0.001$) and $r = 0.51$ ($p < 0.001$), respectively.~~

Practice effect

~~The CEVMT practice effect was tested in PwMS. The mean score at baseline was 18.01 (± 6.42), which improved significantly at month 1 (mean score = 20.38 (± 7.41); $p < 0.001$). No significant difference was observed between months 1 and 6 ($p = 0.57$).~~

Effect of phenotypes of MS

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2
3 According to the phenotype of MS, the difference observed for the CEVMT was non significant (mean
4 score = 19.49 (± 6.75) vs. 17.1 (± 6.07); $p = 0.054$).

7 *Effect of confounding factors*

9 No significant correlations were observed between the CEVMT scores and the FAST-BDI, STAI A and
11 B, MFIS, and EHD in the MS patient group.

14 *Vocational status*

16 No significant difference was found in CEVMT scores between unemployed and employed MS
18 patients for immediate recall (17.61 (± 6.24) vs. 18.20 (± 6.58); $p = 0.61$).

21 *Regression-based norms*

23 Table 2 features the scale conversion and Table 3 presents the regression model for the CEVMT,
24 CSCT, and FLT, which were used to derive demographically adjusted z-scores for MS patients,
25 including agec (age – 43.83), agec², gender, and education as predictor variables. The method for
27 using of the regression-based norms is explained in supplementary material.

29 Using this formula and the coefficients in Table 3, the study can, for example, calculate the predicted
31 CSCT score of a 42-year old female MS patient (male: gender = 1; female: gender = 2) with a High
33 School Diploma (1):

$$9.511 - 0.100 \times (42 - 43.83) - 0.002 \times (42 - 43.83) + 0.051 \times 2 + 0.584 \times 1 = 10.727.$$

37 The patient's actual score on the CSCT (e.g., 46) can then be converted to a scaled score (i.e., 9) using
39 Table 2, which enables the calculation of the difference between predicted and actual scores. A z-
41 score can be calculated by dividing the difference between the actual scaled score and predicted
43 scaled score by the standard error of the residual of the regression model (Table 3) as follows:

$$z\text{-score} = (9 - 10.727) / 2.432 = -0.94.$$

45 Regression analyses revealed that agec and educational level were significant predictors ($p < 0.001$)
47 of CSCT performance in HS and agec, educational level and gender for CEVMT-IR, CEVMT-DR, and FLT
49 performances in HS ($p < 0.01$).

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3 Table 4 summarizes the proportion of MS patients with CI for each test that applies these norms. A
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5 significant difference was observed between groups on the four tests of the BCCAMS.

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8 The study classified 13.3% of PwMS as impaired for the CEVMT-IR, ~~17.5% of PwMS for the CEVMT-~~
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10 ~~DR~~, 36.7% for the CSCT, and 36.6% for the FLT (immediate recall; five trials).

11 Comparison with reference batteries

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14 The proportions of PwMS with CI detected by the BCCAMS, BCCAMS2T, and BICAMS were 59.1%,
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16 38.4%, and 50%, respectively.

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19 The number of patients considered impaired on the BCCAMS battery differs according to the
20
21 phenotype of the disease with 30.8%, 60%, and 39% of patients with RRMS, SPMS, and PPMS,
22
23 respectively, considered impaired ($p = 0.025$).

24
25 Sensitivity analysis indicated that 95.0% [86.1–99.0] of subjects with CI in the BICAMS were with CI in
26
27 the BCCAMS. Specificity analysis revealed that 76.7% [64.–86.6] of subjects not impaired in the
28
29 BICAMS were not deficient in the BCCAMS. Accuracy between the BCCAMS and BICAMS was
30
31 evaluated at 85.8% [78.3–91.5].

32 Comparison to the MACFIMS

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34
35 Ninety-nine PwMS were able to pass the entire MACFIMS battery test.

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37
38 The MACFIMS detected 32.3% of patients with CI. Table 5 presents the comparative data from the
39
40 BCCAMS and BICAMS.

41
42
43 On the basis of the ROC analysis, the BCCAMS battery was associated with a similar AUC value
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45 (0.836) as that of the BICAMS battery (0.841) for detecting CI in MACFIMS.

46 **DISCUSSION**

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53 The BCCAMS battery was a short cognitive battery that enables the rapid assessment of IPS and
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55 episodic memory in PwMS. The battery was inspired by the BICAMS battery, which includes one test
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57 from IPS, the SDMT, and the first learning trials of two learning tests, namely, the CVLT-II and BVM-T-
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59 R. In the BCCAMS, the test of IPS is the CSCT, which is previously validated in MS and HS with good
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3 psychometric properties. It has been shown to be similar in sensitivity to the SDMT but with less
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5 practice effect. For visual episodic memory, the study developed a new test, the CEVMT, and
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7 demonstrated that the test exhibits correct psychometric properties (i.e., reliability, consistency, and
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9 equivalence for the four forms). [Test retest reliability between baseline and month 1 for PwMS and](#)
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11 [HS are poor \(0.70 and 0.60 respectively\) as they are for the BVMT-R in the same sample previously](#)
12
13 [published \(0.52 and 0.66 respectively\).](#)¹⁰ A significant practice effect was observed at one month but
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15 not after six months. Further improvement of the tests (new alternate forms) should be done to
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17 improve test-retest correlation coefficient. However, it satisfactorily discriminated PwMS from HS.
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19 The relatively low correlation between the CEVMT and BVMT-R suggests that the two tests do not
20
21 measure exactly the same function. The strategy used by participants during the CEVMT (reproducing
22
23 a complex figure by placing the different parts) probably include different executive skills than the
24
25 BVMT-R based on the reproduction of drawing. Further studies are needed to analyze these
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27 differences. However, the CEVMT shows good qualities to detect impairment in PwMS. The
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29 confounding factors, which were investigated using self-report questionnaires on mood, depressive
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31 symptoms, anxiety, and fatigue, did not influence the results of the test, although the scores for
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33 these scales were significantly different between MS patients and HS.
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35 For the verbal memory the study employed, we used the first learning trials of the FLT, which was
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37 adapted from the CVLT and recently validated.¹⁰ A computerized version of the test is in
38
39 development, and it will be incorporated to the computerized battery.
40
41 The study used a regression-based procedure for establishing the norms of the BCCAMS battery.
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43 Using these norms, the study demonstrated that the battery was able to identify CI in 59.1% of
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45 PwMS. Using the BICAMS, 50% were classified as impaired. This proportion is close to that reported
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47 in another study using the BICAMS, which is consistent with the proportion of CI in MS reported in
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49 the literature. The performances of the two batteries are relatively similar, whereas impairment at
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51 the BCCAMS predicts impairment at the BICAMS with a very high accuracy (85.8%). The
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53 performances of the two batteries for predicting CI at the MACFIMS are relatively similar with
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3 excellent accuracy and sensibility. The BCCAMS easily and quickly detected 100% of the patients,
4 which were discriminated as cognitively affected by the MACFIMS battery.

5
6
7 Recently, the literature showed that the use of only two tests of the BICAMS (SDMT and BVMT-R)
8 could be an alternative to the entire BICAMS when time is restricted.²⁴ The study illustrated that the
9 BCCAMS2T has lower sensitivity and accuracy but a higher specificity than the three-test battery.

10
11
12 This study has several limitations. First, the FLT was not presented on the computer and the battery
13 is not fully computerized. A computerized version of the FLT is currently under validation. Second,
14 HCs and PwMS differ significantly in age and education. However, the norms were not established by
15 direct comparisons of these groups but by using the methodology of based-regression norms taking
16 into account these differences. Third, we did not randomize the order of the tests because patients
17 take only one time each test and the results of FLT and BVMT were used for both the MACFIMS and
18 the BICAMS. Finally, the test-retest reliability is quite low probably due to too many differences
19 between the alternate forms and further improvement should be done.

20
21
22 Several proposition of computerized cognitive tests for MS have been made recently.²⁵ However,
23 there is still a need for tests validated in MS with comparable sensitivity to the MACFIMS and the
24 BICAMS. Moreover, one interest of this battery is that it is the first one validated for French-speaking
25 subjects.

26
27
28 In conclusion, the use of the proposed BCCAMS battery facilitates a short and valid evaluation of
29 verbal and visuospatial episodic memory and IPS in PwMS in clinical practice.

30
31
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33
34
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11
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13

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24

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28
29

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31
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35 Other authors did not disclose conflict of interest.
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39 FIGURE LEGEND:

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41 Figure 1: Example of figure of the CEVMT.
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44 Figure 2: Study flow-chart
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For Peer Review

Table 1. Clinical and demographic characteristics of patients with MS (n = 120)

| | Patients (n = 120) | HS (n = 276) | |
|---------------------------------|---------------------------|---------------------|-----------|
| Age | 49.61 (9.33) | 43.84 (12.42) | p < 0.001 |
| Sex | | | ns |
| Male (%) | 45 (37.5%) | 118 (42.7%) | |
| Female (%) | 75 (62.5%) | 158 (57.3%) | |
| Education | | | p = 0.003 |
| LEL (%) | 55 (45.8%) | 114 (41.3%) | |
| HEL-BAC (%) | 22 (17.0%) | 22 (8.0%) | |
| HEL-BAC+2–4 (%) | 36 (30%) | 105 (38.0%) | |
| HEL-BAC+5 (%) | 7 (5.8%) | 35 (12.7%) | |
| Disease Duration (years) | 14.4 (9.1) | | |
| EDSS (median) | 4.0 [0–8] | | |
| Disease subtype | | | |
| RR (%) | 39 (32.5%) | | |
| SP (%) | 40 (33.3%) | | |
| PP (%) | 41 (34.2%) | | |
| FAST-BDI | 3.46 (3.04) | 1.47 (2.1) | p < 0.001 |
| EHD | 19.62 (5.44) | 16.03 (3.92) | p < 0.001 |
| STAI A | 35.04 (12.40) | 29.07 (8.13) | p < 0.001 |
| STAI B | 40.12 (11.04) | 34.53 (9.56) | p < 0.001 |
| MFIS-physical | 23.34 (8.95) | 9.09 (8.42) | p < 0.001 |
| MFIS-cognitive | 15.24 (9.59) | 9.28 (8.43) | p < 0.001 |
| MFIS-social | 3.80 (2.60) | 2 (2.18) | p < 0.001 |
| Employment | | | p < 0.001 |
| Unemployed (%) | 67 (55.8%) | 57 (20.7%) | |

| | | | |
|-------------------|---------------|--------------|-----------|
| Part-time job (%) | 21 (17.5%) | | |
| Full-time job (%) | 32 (26.7%) | 219 (79.3%) | |
| CEVMT | 17.88 (6.37) | 22.22 (6.21) | p < 0.001 |
| CSCT | 41.40 (10.01) | 50.71 (9.32) | p < 0.001 |
| FLT | 49.89 (12.77) | 57.78 (8.67) | p < 0.001 |

HS = healthy subjects; SD = standard deviation; ns = not significant; LEL = low educational level;
 HEL = high educational level; HEL-BAC = baccalauréat degree; HEL-BAC+2–4 = 2 to 4 years of
 secondary education; HEL-BAC +5 = more than four years of secondary education; EDSS =
 Expanded Disability Status Scale; RR = relapsing remitting; SP = secondary progressive; PP =
 primary progressive; FAST-BDI = Beck Depression Index-Fast Screen; STAI = State-Trait Anxiety
 Inventory (A = trait; B = state); EMIF-SEP = French adaptation of the Fatigue Impact Scale; CEVMT
 = Computerized Episodic Visual memory Test; CSCT = Computerized Speed Cognitive Test; FLT =
 French Learning Test

Table 2. Raw score to scaled score conversions

| Scaled Score | Raw score | | | |
|--------------|-----------|----------|-------|-------|
| | CEVMT-IR | CEVMT-DR | CSCT | FLT |
| 2 | <5 | <2 | <25 | <35 |
| 3 | 5–7 | 2 | 25–28 | 35–37 |
| 4 | 8 | 3 | 29–30 | 37–40 |
| 5 | 10–11 | | 31–35 | 41–43 |
| 6 | 12–14 | 4 | 36–39 | 44–45 |
| 7 | 15–16 | 5 | 40–42 | 46–48 |
| 8 | 17–18 | 6 | 43–45 | 49–52 |
| 9 | 19–20 | 7 | 46–48 | 53–55 |
| 10 | 21–24 | 8–9 | 49–53 | 56–61 |
| 11 | 25–26 | 10 | 54–56 | 62–63 |
| 12 | 27–28 | | 57–58 | 64–65 |
| 13 | 29 | 11 | 59–61 | 66–68 |
| 14 | 30–31 | | 62–65 | 69–70 |
| 15 | 32 | | 66–70 | 71 |
| 16 | | | 71–72 | 72 |

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| 17 | | | 73- 75 | 73 |
| 18 | >32 | >11 | >75 | >73 |

For Peer Review

Table 3. Final regression models for BCCAMS measures and for CEVMT delayed recall.

| Measure | Predictor | B | Standard error B | T | Standardized B | p | Total R square | RMSE |
|-----------|------------|--------|------------------|--------|----------------|--------|----------------|-------|
| CEVMT | (constant) | 10.798 | 0.557 | 19.387 | | <0.001 | 0.279 | 2.361 |
| | Agec | -0.096 | 0.012 | -8.241 | -0.429 | <0.001 | | |
| | Agec2 | 0.001 | 0.001 | 1.115 | 0.058 | 0.266 | | |
| | Gender | -1.016 | 0.292 | -3.479 | -0.181 | 0.001 | | |
| | Education | 0.518 | 0.129 | 4.003 | 0.209 | <0.001 | | |
| CSCT | (constant) | 9.511 | 0.574 | 16.580 | | <0.001 | 0.249 | 2.432 |
| | Agec | -0.100 | 0.012 | -8.349 | -0.444 | <0.001 | | |
| | Agec2 | -0.002 | 0.001 | -2.095 | -0.112 | 0.037 | | |
| | Gender | 0.051 | 0.301 | 0.170 | 0.009 | 0.865 | | |
| | Education | 0.584 | 0.133 | 4.382 | 0.233 | <0.001 | | |
| FLT TL | (constant) | 7.515 | 0.608 | 12.354 | | <0.001 | 0.173 | 2.579 |
| | Agec | -0.05 | 0.013 | -3.932 | -0.219 | <0.001 | | |
| | Agec2 | -0.003 | 0.001 | -2.348 | -0.132 | 0.02 | | |
| | Gender | 1.325 | 0.319 | 4.151 | 0.231 | <0.001 | | |
| | Education | 0.683 | 0.141 | 4.832 | 0.27 | <0.001 | | |

CEVMT = Computerized Episodic Visual memory Test; CSCT = Computerized Speed Cognitive Test; FLT = French Learning Test; TL = total learning; DR = delayed recall.

Table 4. Comparison between patient and HS participants on each metric using individual z-scores derived from the regression-based model.

| | Patients (n = 120) | | Controls (n = 276) | | p | Cohen's d |
|---------------|--------------------|-----------|--------------------|-----------|-----------|-----------|
| | z-score | Impaired* | z-score | Impaired* | | |
| CEVMT | -0.47 (1.09) | 13.3% | 0.01 (1.00) | 6.9% | p < 0.001 | 0.47 |
| CSCT | -1.14 (1.10) | 36.7% | -0.30 (1.00) | 9.1% | p < 0.001 | 0.82 |
| FLT-TL | -1.07 (1.40) | 36.6% | -0.33 (1.05) | 13.4% | p < 0.001 | 0.63 |

CEVMT = Computerized Episodic Visual memory Test; CSCT = Computerized Speed Cognitive

Test; FLT = French Learning Test; TL = total learning. *Defined as a z-score of ≤ -1.5 .

Table 5. Predictive value of the BCCAMS2T, BCCAMS, and BICAMS for MACFIMS impairment in 99 PwMS.

| | Sensitivity [95% CI] | Specificity [95% CI] | Accuracy [95% CI] |
|----------|-------------------------|-------------------------|----------------------|
| BCCAMS2T | 62.5 [43.7–78.9] | 73.1 [60.9–83.2] | 69.7 [59.7–78.5] |
| BCCAMS | 100 [89.1–100] | 67.1 [54.6–78.2] | 77.8 [68.3–85.5] |
| BICAMS | 90.6 [75.0–98.0] | 77.6 [65.8–86.9] | 81.8 [72.8–88.9] |

BCCAMS = Brief Computerized Cognitive Assessment for Multiple Sclerosis; BCCAMS2T = 2-tests version of the BCCAMS; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; MACFIMS = Minimal Assessment of Cognitive Function in Multiple Sclerosis. CI = Confidence interval; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve

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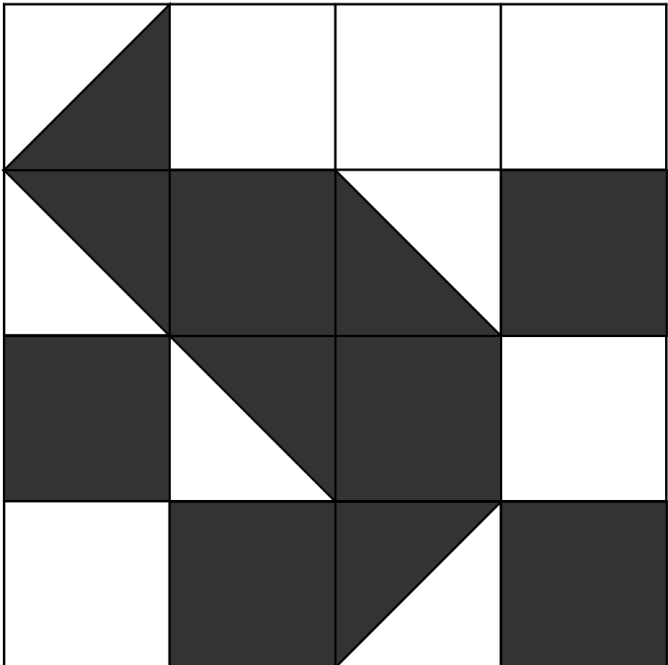
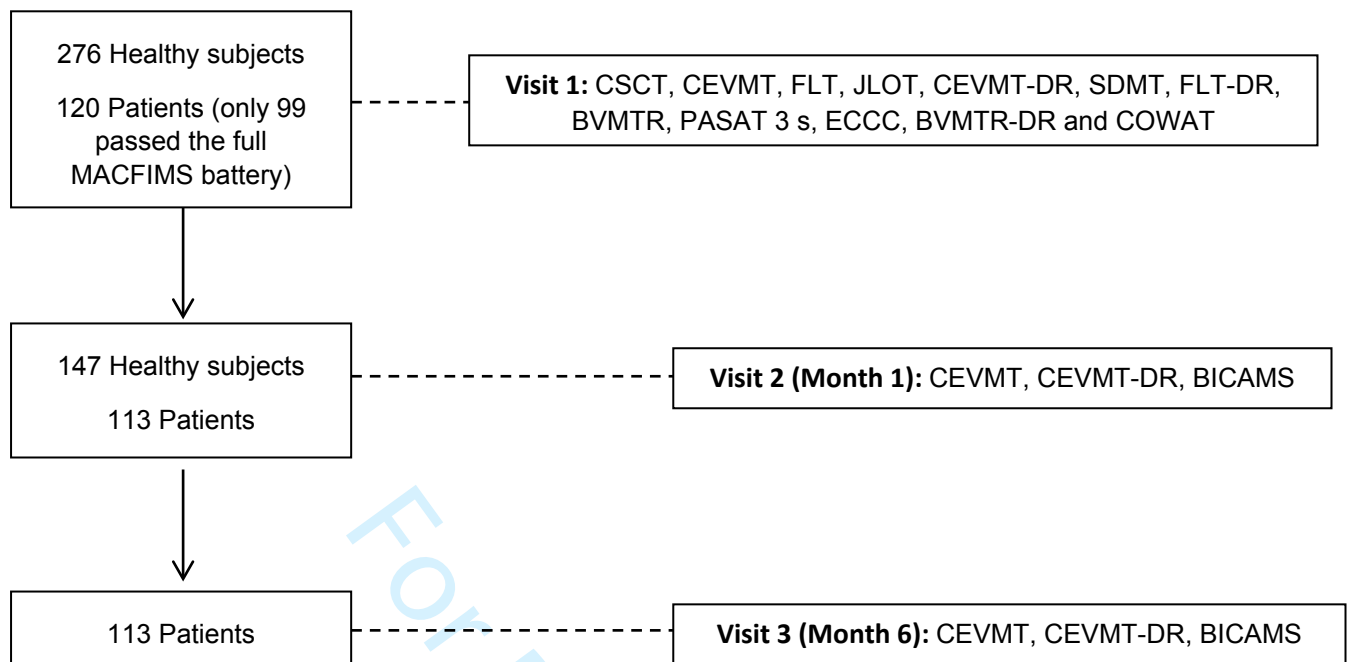


Figure 1: Example of figure of the CEVMT

489x419mm (72 x 72 DPI)



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3 SUPPLEMENTARY MATERIAL
45 1) Regression-based norms methods:
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7 The raw scores for HS were converted to a scaled score metric (mean, 10; SD, 3) based on the
8 cumulative frequency distribution presented in Table 2. Regression was performed on the scaled
9 scores on four variables entered in block, namely, age centered ($agec = age - agemean (43.83)$),
10 $agec^2$, gender (female vs. male), and education. The factor $agec^2$ was added to account for the
11 possible nonlinear effects of age on test performance. Educational level was categorized into four
12 groups, namely, the low educational level (LEL) group (individuals who did not complete secondary
13 education), high educational level (HEL) group (individuals who completed secondary education or
14 graduated with a “baccalauréat” level (high school diploma equivalent to A levels), subjects with two
15 or more years but less than five years of secondary education, and subjects with five or more years of
16 secondary education (HEL-BAC, HEL-BAC+2–4, and HEL-BAC+5).

17 To obtain demographically adjusted z-scores for the MS patients, the study first converted the raw
18 score of each participant to a scaled score based on the raw-to-scaled score conversions derived
19 from the HS (Table 5). Next, predicted scores were calculated using the multiple regression equation
20 based on the β weight values for the four demographic variables and their predictive constants:
21

$$22 \quad \underline{\text{Scaled score predicted}} = \text{constant} + \beta_{agec} (agec) + \beta_{agec^2} (agec^2) + \beta_{gender} (gender) +$$
$$23 \quad \beta_{education} (education).$$

24 Then, the predicted scaled scores were subtracted from the actual obtained scaled score of each
25 participant, and the difference was divided by the root mean squared error (RMSE) of the HS:
26

$$27 \quad Z\text{-score} = (\text{scaled score actual} - \text{scaled score predicted})/\text{RMSE}.$$

28 Tests with a z-score of ≤ -1.5 were considered “impaired.”
29

30 None of the assumptions of regression analyses was violated (i.e., no influential cases, normality of
31 residuals, or homoskedasticity).
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33 2) Example of calculation:
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3 Using this formula and the coefficients in Table 3, the study can, for example, calculate the
4 predicted CSCT score of a 42-year old female MS patient (male: gender = 1; female: gender =
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8 2) with a High School Diploma (1):

9
10 3) $9.511 - 0.100 \times (42-43.83) - 0.002 \times (42-43.83) + 0.051 \times 2 + 0.584 \times 1 = 10.727$.

11
12 The patient's actual score on the CSCT (e.g., 46) can then be converted to a scaled score (i.e.,
13
14 9) using Table 2, which enables the calculation of the difference between predicted and
15
16
17 actual scores. A z-score can be calculated by dividing the difference between the actual
18
19 scaled score and predicted scaled score by the standard error of the residual of the
20
21 regression model (Table 3) as follows:

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23 4) $z\text{-score} = (9 - 10.727)/2.432 = -0.94$.

24
25 Regression analyses revealed that agec and educational level were significant predictors ($p <$
26
27 0.001) of CSCT performance in HS and agec, educational level and gender for CEVMT-IR,
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29 CEVMT-DR, and FLT performances in HS ($p < 0.01$).
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