



Validation of an iPad version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)[☆]

Teresa Costabile^a, Elisabetta Signoriello^a, Francesca Lauro^b, Manuela Altieri^d, Antonio Rosario Ziello^e, Alessandro D'Ambrosio^c, Alvino Biseco^c, Giorgia Maniscalco^e, Simona Bonavita^a, Antonio Gallo^c, Vincenzo Brescia Morra^b, Giacomo Lus^a, Francesco Saccà^{b,*}, Cinzia Valeria Russo^b

^a Multiple Sclerosis Center, II Division of Neurology, University of Campania "Luigi Vanvitelli", Naples, Italy

^b Department of Neurosciences, Reproductive and Odontostomatological Sciences, University Federico II, Naples, Italy

^c Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

^d Department of Psychology, University of Campania "Luigi Vanvitelli", Caserta, Italy

^e Multiple Sclerosis Center "A. Cardarelli" Hospital, Naples, Italy

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ABSTRACT

Background: The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is the most widely used screening tool for cognitive impairment in Multiple Sclerosis (MS). However, the administration and scoring procedures of the paper version are time consuming and prone to errors. Aim of our study was to develop a tablet version of BICAMS (iBICAMS), and to assess its reliability compared to the paper version.

Methods: We administered both BICAMS and iBICAMS to 139 MS patients in two different sessions. We compared scores on both versions using a paired *t*-test. We used a repeated measures ANOVA to test the impact of rater, order of administration and test-retest time on test-retest performances. We used the Intraclass Correlation Coefficient (ICC) to assess the reliability between BICAMS and iBICAMS.

Results: All three sub-tests of the BICAMS (SDMT, CVLT-II and BVMT-R) were different between the paper and the tablet versions. Order of administration influenced test-retest performances at the SDMT ($p < 0.001$), CVLT-II ($p < 0.001$) and BVMT-R ($p < 0.001$). Intraclass coefficient correlation (ICC) revealed a high level of agreement between the paper BICAMS and the iPad version for all three tests: SDMT (0.92), CVLT-II (0.83) and BVMT-R (0.82).

Conclusions: We found a high reliability between BICAMS and iBICAMS. Considering the inherent advantages of automated scoring, digital storage of data, standardized timing, the iBICAMS could become a standard in clinical practice.

1. Introduction

Multiple Sclerosis (MS) is a chronic, neurodegenerative and inflammatory disease of the Central Nervous System (CNS), resulting the leading cause of disability amongst young adults (Thompson et al., 2018). MS includes a wide range of motor, sensory, autonomic and cognitive symptoms, depending on the location, the extent, the number and the degree of inflammatory demyelination.

Cognitive impairment affects about 40%–60% of MS population (Amato, Zipoli, and Portaccio, 2008; Moccia, Lanzillo, and Palladino,

2016; Zipoli, Goretti, and Hakiki, 2010), tends to progress over time and can negatively impact patients' quality of life, independently of physical disability (Kavaliunas, Manouchehrinia, and Stawiarz, 2017). Most affected cognitive functions are memory, attention, executive functioning, information processing speed (IPS), verbal fluency and visuo-spatial abilities.

The assessment of cognitive functioning is crucial as standard neurological examinations (Romero, Shammi, and Feinstein, 2015) or Magnetic Resonance Imaging (MRI) (Rocca, Amato, and De Stefano, 2015) are not sensitive enough to detect cognitive impairment. The Brief

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* Corresponding author.

E-mail address: francesco.sacca@unina.it (F. Saccà).

Repeatable Battery (BRB) (Rao, 1990) and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict, Cookfair, and Gavett, 2006) are the most used instruments to evaluate cognitive dysfunction in MS patients. They require about 45 and 90 minutes to be completed and can only be administered by a trained neuropsychologist.

In 2012 Langdon et al. (2012) designed the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), that includes the Symbol Digit Modalities Test (SDMT) (Smith, 1982), the California Verbal Learning Test-II (CVLT-II) (Delis, Kramer, and Kaplan, 2000) and the Brief Visuospatial Memory Test-Revised (BVM-T-R) (Benedict, 1997). They measure IPS, immediate verbal recall and immediate visual recall.

BICAMS can be completed in 15 minutes, requires paper, pencil and a stopwatch and can be administered by most healthcare professionals. Nevertheless, some critical issues may arise during administration. These include the exposure time for the BVM-T-R stimuli, the correct pace and tone for the CVLT-II, scoring computation for the SDMT, thus affecting results. This risk may be considerable in those centers in which BICAMS is largely used as a screening tool for MS population, or when it is used to evaluate the Cerebral Functional Score and its impact on the EDSS (Saccà, Costabile, and Carotenuto, 2017).

The aim of the present study was to develop and validate an iPad based BICAMS version (iBICAMS), that could automate several processes and try to overcome previously described issues, still maintaining a high degree of reliability and overlap with the paper version.

2. Method

2.1. Study design

We designed a multicenter, prospective study, involving four MS centers located in Italy. The trial was approved from the local Ethics Committee. Inclusion criteria were a) a confirmed MS diagnosis (Thompson, Banwell, and Barkhof, 2018); b) age between 18 and 70 years; c) written informed consent to neuropsychological assessment and collection of clinical variables; d) ability to perform cognitive tests despite their physical disability (i.e. the ability to hold the pencil/apple pencil). Exclusion criteria were: patient on relapse or less than 90 days from the last relapse. Patients were recruited through our outpatient services. Enrollment was open for 6 months and we aimed at enrolling at least 120 patients.

2.2. Study Procedures

Tests were administered in a standardized manner, during daytime, in a quiet room, and in a fixed order: Orientation Tests (OTs), SDMT, CVLT-II, BVM-T-R.

We tested each patient with BICAMS and iBICAMS in randomized order, such that a group performed BICAMS first and iBICAMS after, while the other group was exposed to the reverse order. Centers were instructed to re-test patients after a minimum of 14 days to a maximum of 120 days, based on patients' availability.

2.3. iBICAMS

The electronic version of BICAMS for iPad was created using the Filemaker Pro software (Clarif Inc, Cupertino, CA, USA; version 19.4.2.204) running on MacOS. The software was chosen based on the ability to be cross platform (MacOS, Windows, Linux), immediate portability on mobile devices, native cloud storage. Graphical layout was optimized to run on 12.9" iPads due to the very similar size as an A4 paper sheet.

Patient section collected information such as date of birth, gender, education. A unique identification code was generated by the neuropsychologist at enrollment and informed consent stage, to capture

pseudonymized data. The test window contained two sections: the first to investigate patient's orientation, the second for BICAMS administration. The height and width of visual stimuli (SDMT and BVM-T-R) were the same as those of the paper version.

2.4. Symbol Digit Modalities Test

For the iBICAMS we decided to administer the SDMT as a paper stimulus and use the iPad as a back end for neuropsychologists to record the answers given orally by patients. The software would visualize the correct answers on the screen, based on the selected alternate form, and neuropsychologists would tap on the single symbol-to-digit conversion in case of a correct answer or would not tap in case of a wrong answer. Alternate versions of the SDMT were uploaded in the system, and alternate versions were printed and laminated for patient use. A 90 second timer was added to the system to avoid using a stopwatch, and automatically terminated the procedure. A 10-symbol trial was made available, as currently used in the classic SDMT version. Total score was automatically recorded and converted in a corrected score (Goretti, Niccolai, and Hakiki, 2014).

2.5. California Verbal Learning Test – II

The CVLT-II words were pre-recorded using an appropriate pace and tone and avoiding prosody inflections that would suggest the position of the word within the list (i.e., the second to last word). The examiner was given the choice of five different forms, and a button allowed to play the word list through the iPad speakers. A dropdown list, linked to the corresponding alternate form, allowed the examiner to highlight the correct answers as the patients recalled as many words as possible. The procedure was repeated across five trials. Single trials and total score were automatically recorded and converted in a corrected score (Goretti, Niccolai, and Hakiki, 2014).

2.6. Brief Visuospatial Memory Test – Revised

For the BVM-T-R, the examiner was free to choose between 6 alternate forms. The application automatically showed the drawings for 10 seconds, and then switched to a drawing pad. Patients were provided with an apple pencil to draw directly on the iPad. The three trial drawings were stored for subsequent scoring by the examiner. Patients could easily erase drawings and restart from scratch.

2.7. Statistical analysis

We performed a descriptive analysis of all included variables. Global scores of BICAMS and iBICAMS were compared using a paired *t*-test.

As significant differences emerged between single scores, we performed three separate repeated measures ANOVAs (one for each test), using a general linear model with test-retest performances as within-subjects factor and rater, order of administration and test-retest time as between-subjects factors. We considered the Greenhouse-Geisser correction as scores lacked sphericity. *P* values less than 0.05 were considered statistically significant.

Finally, to assess test-retest, intrarater, and interrater reliability we used the Intraclass correlation coefficient (ICC) with a two-way mixed alpha model with absolute agreement. We used SPSS version 27.0.1.0 running on MacOS ver. 12.2.

3. Results

We included 139 MS patients that fulfilled all inclusion and no exclusion criteria. Sample and study features are shown in Table 1.

Global mean scores from both BICAMS and iBICAMS are shown in Table 2. We found significant differences for all three subtests at the pairwise comparison. Paper SDMT was the only test where patients

Table 1

Demographics of enrolled patients and test-retest features.

Parameter	Value
Age at enrollment, years $\pm$ SD (range)	36.6 $\pm$ 10.7 (19 - 64)
Female, n (%)	98 (70)
Education, years $\pm$ SD (range)	13 $\pm$ 4 (4 - 21)
EDSS, median (range)	2.0 (0 - 7.5)
Disease form RR, n (%)	117 (84.2)
OA, iPad - Paper, n (%)	83 (60)
Test - Retest time, median (range in days)	35 (14 - 105)

SD: Standard Deviation; EDSS: Expanded Disability Status Scale; RR: Relapsing-Remitting; OA: order of administration.

Table 2

Scores to paper and iPad BICAMS versions.

Test		Mean $\pm$ SD	Mean difference	CI 95%	p
SDMT	Paper	50.85 $\pm$ 13.98	-2.72	-4.07, -1.37	<0.001
	iPad	53.57 $\pm$ 15.94			
CVLT-II	Paper	55.57 $\pm$ 11.45	1.71	0.338, 3.09	0.015
	iPad	53.86 $\pm$ 10.43			
BVMT-R	Paper	24.86 $\pm$ 8.41	2.25	1.21, 3.29	<0.001
	iPad	22.60 $\pm$ 8.16			

SD: Standard Deviation; CI: Confidence Interval; SDMT: Symbol-Digit Modalities Test; CVLT-II: California Verbal Learning Test II; BVMT-R: Brief Visuospatial Memory Test - Revised.

showed lower performances compared to the iPad test.

Order of administration was the only factor influencing test-retest performances for all tests: SDMT $F(3, 126) = 11.790$, $p < 0.001$, CVLT-II $F(3, 126) = 28.684$, $p < 0.001$ and BVMT-R $F(3, 126) = 12.682$, $p < 0.001$. For CVLT-II, we also found a significant interaction between order of administration and rater ($F(3, 126) = 3.256$, $p = 0.024$). Mean test-retest scores according to the order of administration are shown in Fig. 1.

Intraclass coefficient correlation showed that iBICAMS has a high similarity compared to the paper version. SDMT resulted the most reliable test, followed by CVLT-II and BVMT-R, as shown in Table 3.

4. Discussion

The aim of our study was to build an iPad version of the BICAMS with a good level of reliability compared to the paper/pencil version. To our knowledge, this is the first electronic conversion and validation of the entire BICAMS. One previous study (Beier et al., 2020) validated an iPad version of the BICAMS, but the used the Rey Auditory Verbal Learning Test (RAVLT) instead of the CVLT-II leading to not comparable results. Also, participants were tested only once with responses being recorded simultaneously using both administration procedures. Other studies have swapped the CVLT-II for the RAVLT during local validation studies (Filser et al., 2018), and it could be easily substituted for ease of use, availability of alternate forms, and local choices. The CVLT-II still remains the standard for an international BICAMS administration.

Table 3

Reliability levels between paper and iPad BICAMS.

Test	Cronbach's alpha	ICC	CI 95%	p
SDMT	.922	.915	0.869, 0.943	<0.001
CVLT-II	.837	.832	0.764, 0.881	0.015
BVMT-R	.836	.820	0.724, 0.879	<0.001

ICC: Intra-Class Correlations (average measures); CI: Confidence Interval; SDMT: Symbol-Digit Modalities Test; CVLT-II: California Verbal Learning Test II; BVMT-R: Brief Visuospatial Memory Test - Revised.

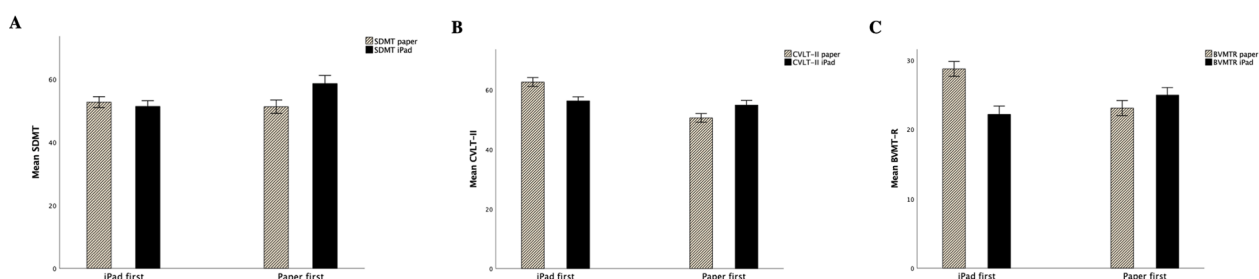
Despite some differences in performances arose, results on the intraclass coefficient correlation demonstrated a high reliability between the original paper BICAMS and the tablet-based one, thus suggesting that the two versions are comparable, with the addition of the advantages in the case of the digital format. We observed an order effect at the test-retest analysis as patients included in the iPad/paper condition showed a greater learning effect at the CVLT-II and BVMT-R, compared to the reverse order group.

For the CVLT-II this effect was worsened by the interaction with a different examiner. We would like to impute this to the scarce reliability that several tests show when administered in paper version. For example, during CVLT-II administration, the constant reading speed, the absence of prosody or other paraverbal clues at the iBICAMS are unlikely to favor learning, and patients can only rely on cognitive strategies. The CVLT-II iPad interface also helps the examiner to record correct answers that may be missed for those patients that report target stimuli quickly. A similar effect may have occurred for the BVMT-R, where timing is crucial and stimulus exposure can be different between raters. The iPad version can show stimuli for exactly 10 seconds and shift patients instantaneously to the drawing area.

Finally, the SDMT was administered through a paper stimulus in both groups and recording alone took place through the iPad. This may be the reason why we both did not observe a learning effect in the iPad/paper condition and a greater reliability between the electronic and paper versions of the SDMT, compared to CVLT-II and BVMT-R.

Administering a computerized BICAMS, avoiding self-administered versions, brings different potential advantages. First, administration procedures are more standardized than in the paper and pencil version, thus reducing interrater differences and examiner dependent errors (i.e., stimuli exposure). Second, automated scoring of both raw and normative data is accurate and immediate. Third, some interfering factors can be contained, thus it is possible to adjust the brightness or the volume of the device to favor a better administration of the tasks. Finally, large MS centers require neuropsychologists to repeatedly administer tests with resulting high stress levels. This can be avoided with an automated reading of the CVLT word list.

The iBICAMS also allows for a definite and instantaneous integration of cognitive tests with the EDSS. We previously demonstrated that calculating the cerebral functional score with the use of BICAMS and orientation questions, lead to a more accurate rating in 25% of EDSS scores. With the iBICAMS it would be possible to have patients undergo neuropsychological testing and shortly after to the EDSS neurological

**Figure 1.** Interaction between test-retest and order of administration

A) Symbol-Digit Modalities Test (SDMT), B) California Verbal Learning Test II (CVLT-II) and C) Brief Visuospatial Memory Test - Revised (BVMT-R).

examination (Saccà, Costabile, and Carotenuto, 2017). BICAMS results could be instantaneously used to calculate an integrated EDSS on the neurologist's back end.

The study has some limitations. We did not enroll subjects with high disability levels that were unable to perform the BVMT-R using the apple pencil. A separate study could validate finger drawing at the BVMT-R section. A fully automated SDMT version for iPad has been proposed and currently used, allowing patients to select the correct answer through a screen tap. In support to our choice, we strongly suggest using the oral version of the SDMT, as it will accommodate more MS patients. Future developments of the iBICAMS could include an integration with a speech recognition software, allowing for a fully automated use.

CRedit authorship contribution statement

Teresa Costabile: Validation, Formal analysis, Conceptualization, Software, Investigation, Writing – original draft, Writing – review & editing. **Elisabetta Signoriello:** Investigation, Writing – review & editing. **Francesca Lauro:** Investigation, Writing – review & editing. **Manuela Altieri:** Investigation, Writing – review & editing. **Antonio Rosario Ziello:** Investigation, Writing – review & editing. **Alessandro D'Ambrosio:** Investigation, Writing – review & editing. **Alvino Biseco:** Investigation, Writing – review & editing. **Giorgia Maniscalco:** Investigation, Writing – review & editing. **Simona Bonavita:** Investigation, Writing – review & editing. **Antonio Gallo:** Investigation, Writing – review & editing. **Vincenzo Brescia Morra:** Resources, Writing – review & editing, Funding acquisition, Project administration. **Giacomo Lus:** Writing – review & editing. **Francesco Saccà:** Validation, Formal analysis, Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Supervision. **Cinzia Valeria Russo:** Investigation, Writing – review & editing, Visualization.

Declaration of Competing Interest

F.S. received public speaking honoraria from Alexion, Argenx, Biogen, Mylan, Novartis, Roche, Sanofi, Teva; he also received compensation for Advisory boards or consultation fees from Alexion, Almirall, Argenx, Avexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Novatek, Roche, Sanofi, Takeda. The other authors report no conflict of interest.

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