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ORIGINAL ARTICLE

Utility of the INECO frontal screening (IFS) in the detection of executive dysfunction in patients with relapsing-remitting multiple sclerosis (RRMS)

D. Bruno[1] · T. Torralva[1,2] · V. Marenco[1] · J. Torres Ardilla[1] · S. Baez[1] · E. Gleichgerrcht[4] · V. Sinay[1,2] · M. Roca[1,2,3,5]

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Abstract Several studies have reported that about 65 % of patients with relapsing-remitting multiple sclerosis (RRMS) suffer from cognitive impairment, with executive dysfunction being the most frequently described. Even if several executive screening tests have been designed to specifically detect executive deficits, few studies have investigated their ability to tackle such dysfunction particularly in multiple sclerosis (MS). The aim of the present study was to evaluate the sensitivity and specificity of the INECO frontal screening (IFS) in the detection of executive dysfunction in patients with relapsing-remitting MS (RRMS). 54 patients with RRMS were included in the study. 34 presented executive dysfunction while 20 did not. 32 control subjects matched for age, sex, and educational level were also included. All were evaluated with the IFS and with a battery of classical executive tests. A patient was considered to have executive dysfunction if he/she scored a one and a half standard deviation below the control mean in at least one of the classical executive tests. Sensitivity and specificity of the IFS in its ability to detect executive dysfunction in MS was analyzed. Using a cut-off of 25.5 points, sensitivity of the IFS was 73.53 %, and specificity 78.13 % in differentiating controls from MS patients with executive dysfunction. The IFS showed excellent concurrent validity with executive tasks. The IFS can be considered a brief, easy-to-administer, cost-less tool for the detection of executive dysfunction in patients with RRMS.

Keywords Multiple sclerosis · Executive screening tests · Cognitive impairment · Executive functions

✉ M. Roca
mroca@ineco.org.ar

[1] Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina

[2] Institute of Neurosciences at Favaloro Foundation, Buenos Aires, Argentina

[3] UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University, Santiago, Chile

[4] Department of Neurology, Medical University of South Carolina, Charleston, USA

[5] National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

Introduction

Multiple sclerosis (MS) is one of the most common chronic neurological disorders affecting young adults worldwide. It is an autoimmune disease of the central nervous system, which is chronic and progressive, most commonly evolving with periods of remission and exacerbation. Patients exhibit focal inflammatory lesions in the cerebral white matter and, even if its pathogenesis is not entirely understood, it is thought that genetic and environmental factors are both involved in disease onset and progression [1, 2].

In spite of the fact that the initial description of the disease made by Charcot in 1968 did not include cognitive symptoms as a central component of MS, as early as 1977, Beatty reported the presence of these symptoms in 50 % of the cases [3]. The latest research reports that up to 65 % of patients display some degree of cognitive impairment [4–6], with executive dysfunction being the most frequent. This clinical population can also exhibit cognitive impairment in other domains, including deficits in attention, visual constructive functions, and memory. In fact, it is observed that memory deficits emerge not during the process of storage, but rather, due to impaired encoding

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and free recall of the new information, revealing the involvement of fronto-subcortical dysfunction typical of this disease [7–12].

Assessments of executive processes are usually included as part of complete neuropsychological batteries and include tests such as backward digit span [13], phonological verbal fluency [14], Trail Making Test part B (TMT-B) [15], PASAT [16], Wisconsin Card Sorting Test (WCST) [17], and Symbol [18], among others. Although the clinical utility of such tests is non-contentious, extensive neuropsychological batteries that include such tests rely on specialized and highly trained professionals, increasing time demands, resources, and costs. Even if brief cognitive batteries—such as BICAMS [19] or BRB-N [20]—have also been validated in patients with MS, they only assess one of multiple executive domains, making it impossible to detect other possible frontal dysfunctions in this population. Moreover, in some cases, these batteries can take much longer than the time expected for a screening tool administered at bedside or during a short clinical interview, and they require specific training for their administration [21]. Thus, despite their utility, such tests may not always be accessible in healthcare setting. It is hence important to develop executive screening instruments that are easy and quick to administer, and that do not require specialized professionals or ad hoc training, all while proving useful to detect the presence of specific executive dysfunction.

Several such executive screening tests have been designed, including the Frontal assessment battery (FAB) [21]; the INECO frontal screening (IFS) [22] and the verbal fluency test [23]. Results using these tests have been mixed. Even if originally it was reported that the FAB was sensitive to detect frontal dysfunction, other studies have shown limited sensitivity and specificity [24, 25] and its utility in MS has not yet been studied. Furthermore, even if the verbal fluency test has been used as a screening of cognitive dysfunction in MS [23], it does not assess different aspects of executive processing, and its ability to detect specifically executive deficits has not yet been established. Consequently, examining the utility of reliable frontal screening instruments in MS is impending in achieving more successful rates of detection of cognitive deficits detection in this population.

The IFS is a brief screening test originally designed to detect executive dysfunction in frontotemporal dementia. This screening tool is characterized by its easy administration, which takes no longer than 10 min, requires no specific material except for the testing protocol (e.g., no physical objects as stimuli), requires no specialized training, and can thus be used by any healthcare provider despite their background with minimal prior instruction. Importantly, this brief screening test probes executive functions in particular, and it provides useful information about frontal functioning by tapping different executive processes, such as verbal and motor inhibitory control, verbal and visual working memory, and abstraction ability, among others. It has also been shown useful in the detection of executive dysfunction in other neurological and psychiatric conditions such as unipolar depression [26], bipolar disorder, and attentional and hyperactivity disorder [27]. Several studies have already reported on the usefulness of this instrument in different populations, reporting relatively high levels of specificity and sensitivity for a screening tool [22], along with a higher ability than other executive screening tools to discriminate between different types of dementia [28], between dementia and depression [26], and to detect executive dysfunction in patients with attention deficit disorder [21, 29]. However, no previous study has investigated its utility in detecting executive dysfunction in patients with MS, who as stated above, tend to primarily and very frequently show this form of cognitive impairment.

Given the aforesaid reasons, the objective of the present study was to evaluate the usefulness of the IFS in the detection of executive dysfunction in patients with MS. We propose this study with the ultimate goal of granting healthcare professionals a brief, clinical screening tool that can be readily administered to patients with MS with the philosophy of any screening tool in medicine: for a positive test (i.e., executive performance below the proposed IFS cut-off score), patients should be referred to specialized neuropsychologists for a more comprehensive assessment of their cognitive functions.

Methods

Permission for the study was initially obtained from the local research ethics committee and all participants signed an informed consent prior to inclusion. A total of 54 patients diagnosed with RRMS fulfilling the Macdonald criteria [30] were recruited. A total of 32 control subjects, matched by age, level of educational, and premorbid intelligence were also included in the study. RRMS patients were grouped as either presenting with (RRMS-ED, $n = 34$) or without executive dysfunction (RRMS-WED, $n = 20$) based on their performance in classical executive tests (see below). It was considered that a patient had executive dysfunction if performance on at least one of four tests of the executive battery was more than 1.5 deviations below the mean of controls. The proportion of patients with executive impairment was 63.93 %, similar to that reported in the literature (e.g., 65 % in Rao 2004 [3] goodness-of-fit $\chi^2 = 0.123$, $df = 1$, $p = .72$, and 70 % in Feinstein et al. 2013 [5] goodness-of-fit $\chi^2 = 2.138$, $df = 1$, $p = .14$).

Neuropsychological Assessment

All participants were assessed with the WAT-BA [31] as a test of premorbid intelligence (similar to the NART [32]), as well as with the IFS [22] and a classical executive battery.

- The IFS has a maximum total score of 30 and includes eight subtests:
  - Motor Programming (MP). Subjects were asked to perform the Luria motor series 'fist, edge, palm.' At the beginning, they had to copy the administrator three times, and then, they had to repeat the series six times in a row on their own. Score: If subjects could carry out six consecutive series by themselves (3); if they performed at least three consecutive series on their own (2); if they failed at achieving at least three consecutive series on their own, but performed three when copying the examiner (1); otherwise the score was 0.
  - Interference (CI). Subjects were asked to hit the table once when the administrator hit it twice, or to hit the table twice when the administrator hit it only once. After a practice trial, the examiner completed 10 series. Score: If subjects made no errors (3); if they made one or two errors (2); for more than two errors (1), and if the subject copied the examiner at least four consecutive times (0).
  - Motor Inhibitory control (MIC). This task was administered immediately after CI test. Subjects were told that this time, when the test administrator hit the table once, they should also hit it once, but when the examiner hit it twice, they should do nothing. After a practice trial, the examiner completed 10 series. Score: If subjects made no errors (3); If they made one or two errors (2); for more than two errors (1), and if the subject copied the examiner at least four consecutive times (0).
  - Backwards Digit Span (BDS). Subjects were asked to repeat a progressively lengthening string of digits in reverse order. Two trials were given at each successive list length, beginning at two and continuing to a maximum of seven. If subjects passed either trial at a given list length, then the next length was administered. Score: number of lengths at which the subject passed either trial, maximum 6.
  - Verbal Working Memory (VWM). Subjects were asked to list the months of the year backwards, starting with December. Score: If subjects made no errors (2); for one error (1); otherwise the score was 0.
  - Spatial Working Memory (SWM). The examiner presented subjects with four cubes and pointed at them in a given sequence. Subjects were asked to repeat the sequence in reverse order. There were four trials, with sequences of two, three, four, and five cubes movements, respectively. Score: number of sequences completed correctly.
  - Abstraction capacity (AC). In this task, three proverbs were read to the subjects and they were asked to explain their meaning. Score: 1 point for each proverb adequately explained, .5 points for a correct example, otherwise the score was 0.
  - Verbal Inhibitory Control (VIC). In this test, six sentences were used. In the three sentences, subjects were asked to read the sentences and were asked to complete each of them correctly, as quickly as possible. In the remaining three sentences, subjects were asked to complete the sentence but with words which had no relation to the meaning of the sentence. Only the second part was scored. For each sentence, a score of two points was given for words which had no relation to the sentence, one point for a word semantically related to the expected completion, and zero point for the expected word itself.

Classical executive battery

The classical executive battery included test commonly used to evaluate executive functions in patients with RRMS such as the phonological verbal fluency task [14], trail making test part B (TMT-B) [15], paced auditory serial addition test (PASAT) [16], and the Wisconsin Card Sorting Test (WCST) [17].

Statistical analysis

Comparisons between groups regarding demographic, clinical information, and neuropsychological test performances were analyzed using one-way ANOVA, followed by Turkey's HSD post hoc tests when significance was reached. Correlations were carried out using Pearson's *r* coefficients. The sensibility and specificity of the IFS to discriminate healthy controls from patients with executive dysfunction were determined using a receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using the SPSS 17.0 software package.

Results

Demographics

No significant differences related to age, gender, premorbid intelligence level, or educational levels were observed

between RRMS-ED, RRMS-WED, and controls (see Table 1).

Classic executive tests

Statistically significant differences between groups in classical executive tests emerged. Significant differences between groups were also found on the trail making test B (F (2, 82) = 26.18; $p < .01$) with both controls ($p < .01$) and RRMS-WED ($p < .01$) performing better than RRMS-ED. Similarly, significant differences between groups were observed on the verbal fluency test (F (2, 83) = 5.64, $p = .05$), for which the RRMS groups did not differ significantly from each other ($p = .31$), but performed worse than controls. On the WCST, significant differences were also found between groups (F (2, 79) = 15.08, $p < .01$), with RRMS-WED ($p < .01$) and controls ($p < .01$) outperforming RRMS-ED patients. Finally, significant differences between groups were also found on the PASAT (F (2, 66) = 22.83, $p < .01$) with controls performing significantly better than RRMS-ED ($p < .01$). Moreover, both RRMS groups differed significantly from each other on this test ($p < .01$) (see Table 1).

INECO frontal screening

Significant differences between the groups were found on the IFS total score (F (2, 83) = 19.30, $p < .01$). The post hoc analysis revealed that controls performed significantly better than RRMS-ED ($p < .01$), and that both RRMS groups differed significantly from one another ($p < .01$), RRMS-WED outperforming RRMS-ED, as revealed by Fig. 1. Significant differences between groups were found on the backward digit span subtest (F (2, 83) = 9.91, $p < .01$) with controls outperforming RRMS-ED ($p < .01$) and with both RRMS groups differing significantly between themselves ($p = .02$,—ED worse than—WED, as expected). Significant differences between groups were also found on the SWM IFS subtest (F (2, 83) = 9.11, $1 < .01$), on which controls performed significantly better than RRMS-ED ($p < .01$). Significant differences between groups were found on the AC IFS subtest (F (2, 83) = 9.30, $p < .01$), on which post hoc comparisons revealed that controls performed significantly better than RRMS-ED ($p < .01$) (see Table 1; Fig. 1).

Correlations

Remarkably, significant correlations were found between the IFS total score and the total number of categories abstracted on the WCST ($r = .477$, $p < .01$), the verbal fluency score ($r = .453$, $p < .01$), the PASAT ($r = .602$, $p < .01$), and the TMT-B ($r = -.683$, $p < .01$), highlighting the high concurrent validity of the IFS in patients with MS.

Sensitivity and specificity of the IFS in the detection of executive dysfunction

A ROC curve analysis on the IFS total score comparing healthy controls and RRMS-ED generated a cut-off score of 25.5 points with a sensitivity of 73.53 % and specificity

Table 1 Neuropsychological performance in RRMS-ED, RRMS-WED, and healthy controls

	RRMS-ED ($N = 34$)		RRMS-WED ($N = 20$)		Controls ($N = 32$)		p
	Mean	SD	Mean	SD	Mean	SD	
Age	40.38	11.44	35.30	7.84	41.66	11.28	.106
Years of formal education	15.26	3.91	16.18	2.64	15.97	2.42	.517
WAT-BA	38.19	7.02	39.40	5.78	38.83	6.19	.805
Verbal fluency	14.09	5.63	18.00	4.15	18.12	5.77	**.005**
Trail making B	147.00	74.77	62.75	17.70	68.90	24.00	**.000**
WCST	4.62	1.55	6.00	.00	5.82	.476	**.000**
PASAT 3′	29.46	14.39	51.80	9.06	47.14	10.93	**.000**
IF_total score	22.84	3.753	26.25	2.227	26.95	1.829	**.000**
IF_MP	2.71	.676	2.90	.316	2.94	.246	.153
IF_CI	2.76	.496	3.00	.000	2.97	.177	.039
IF_MIC	2.56	.746	2.90	.316	2.94	.246	.015
IF_BDS	3.76	1.075	4.80	.919	4.72	.924	**.000**
IF_VWM	1.88	.409	2.10	.316	2.03	.177	.073
IF_SWM	2.12	1.038	2.60	1.174	3.16	.884	**.000**
IF_AC	2.309	.7979	2.750	.2635	2.859	.2613	**.001**
IF_VIC	4.69	1.194	4.70	.823	5.34	.787	.023

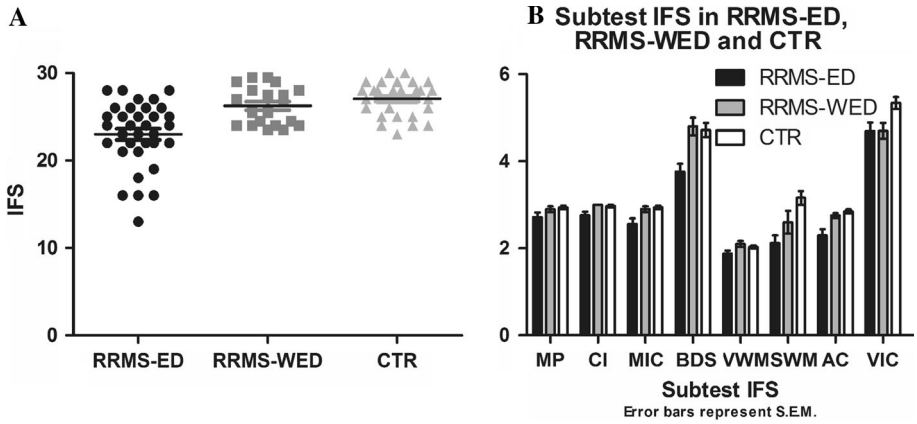

Fig. 1 **a** IFS total score in RRMS-ED, RRMS-WED, and control groups. **b**. IFS subtest scores in RRMS-ED, RRMS-WED, and control groups

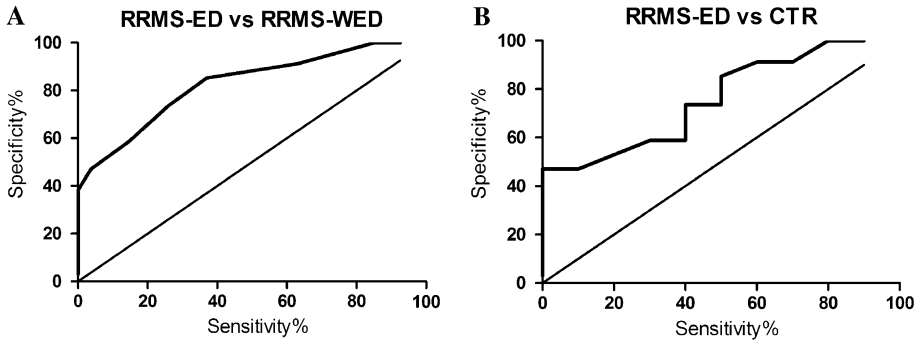

Fig. 2 IFS receiver operating characteristic (ROC) curve. A ROC curve analysis (**a**) between RRMS-ED and control groups, and (**b**) between RRMS-ED and RRMSW-ED. In both cases, the *diagonal* represents the reference line

of 78.13 % (Fig. 2a). With an IFS score of 25.5, 78.12 % of the RRMS-ED patients, 60 % of the RRMS-WED patients, and 76.47 % of the controls were correctly classified. The area under the ROC curve was .85 (CI .76–.94; $p < .01$). Furthermore, a ROC curve analysis aimed at distinguishing both RRMS groups based on the total IFS score generated a cut-off score of 24.5 points, with a sensitivity of 58.82 % and a specificity of 70 %, and an area under the curve of .76 (CI .63–.88; $p < .01$) (Fig. 2b).

Discussion

Deficits in executive functions are usually reported in MS, and these have been related to the involvement of circuits within the prefrontal cortex. However, the heterogeneity of the disease makes the symptomatic presentation varied, particularly at the cognitive level. For this reason, systematic cognitive assessment in MS allows to describe cognitive impairment in an objective and quantifiable manner, which is essential for the clinical management and longitudinal follow-up of the disease.

In most cases, cognitive examinations include extensive batteries that must be conducted by a highly trained and specialized professional. These batteries can thus be remarkably expensive and time consuming. Even if brief cognitive batteries have been validated in patients with MS, most of such tests require training, ad hoc equipment, and take anywhere 15–60 min. As a consequence, these tests are not always an option for patients in many healthcare settings. In addition, they are mostly designed to assess general cognitive abilities, and they do not examine executive functioning in particular. Hence, the study of executive screening instruments that are able to detect executive dysfunction in patients with MS is of the essence, especially because of the high frequency with which executive impairments are reported in this population.

Several studies have demonstrated the usefulness of one screening tool specifically designed to probe executive functions: the IFS [22, 26, 27, 29]. Here, we examine the properties of the IFS as an executive screening test for patients with RRMS.

The IFS showed good psychometric properties for a short screening test of a cognitive domain as complex as executive functioning, including: excellent concurrent validity (as evidenced by the strong correlations with performance on classical executive tests), a good discriminatory validity to successfully differentiate MS patients with executive dysfunction from controls (a 25.5 score detected 73.52 % of MS patients with executive dysfunction), and adequate specificity in its ability to accurately differentiate patients with and without dysfunction.

As previously mentioned, several tests have been used as general cognitive screening tools in patients with MS. These tests include the Verbal fluency test [23], the PASAT [33, 34], Symbol Digit Modalities test [35–37], the test of drawing a clock [38], and the MoCA [39], among others. These tests show good psychometric properties to discriminate between patients with MS who suffer from cognitive impairments and those who do not. For example, while the Verbal Fluency Test showed a sensitivity of 84.6 % and specificity of 85.5 %, the PASAT evidenced a sensitivity of 57.7 % and specificity of 74.2 %. Again, however, such tests examine only one specific sub-domain at a time, while the IFS taps several executive processes in a short period of time, allowing the professional to obtain a more detailed executive profile to determine whether the patient's performance warrants further neuropsychological testing by a specialist.

We believe the results from the present study show that the IFS is a brief screening test able to detect executive deficits in MS in a practitioner-friendly and readily available manner. It is not only simple in its structure, easily administrable and a cost-free tool, but it is also exhaustive in its capacity to evaluate various subdimensions of the executive sphere. In particular, these dimensions include motor programming, inhibition of predominant responses, visual and verbal work memory, motor and verbal inhibitory control, and abstraction ability. Patients with MS particularly showed deficits in backwards digit span, visual working memory, and abstraction ability.

Several limitations must be noted regarding the present study. First, only patients with RRMS were studied and the utility of the IFS should be further explored in other types of MS patients. On the other hand, even if our study shows that the IFS is sensitive for the detection of executive dysfunction, further studies should directly compare its utility with that of other executive screening tests, such as the verbal fluency test, the PASAT, and the FAB.

Conclusion

Our study shows that the IFS can be considered a useful tool for detecting executive dysfunction in patients with MS. The use of this sensitive, specific, and at the same time, brief and costless screening tool may be helpful in clinical practice, especially when time and resources are limited and complete neuropsychological assessments are not readily available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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