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Validation of the Spanish Version of the LASSI-L for Diagnosing Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Background: The Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L) is a novel cognitive test that measures recovery from proactive semantic interference, which may be an early cognitive marker of Alzheimer's disease (AD).

Objective: To generate normative data for a Spaniard population and to validate the LASSI-L for the diagnosis of amnesic mild cognitive impairment (aMCI) and mild AD.

Methods: We performed a cross-sectional study in which 97 healthy participants, 34 with aMCI, and 33 with mild AD were studied with LASSI-L and a comprehensive neuropsychological protocol. The overlapping strategy analysis was used to maximize the sample size and to provide age- and education-adjusted normative data using a logistic regression analysis.

Results: Internal consistency was 0.932. Convergent validity with the Free and Cued Selective Reminding Test was moderate. LASSI-L raw scores were correlated with age and years of education, but not gender. The area under the curve for discriminating between healthy controls and aMCI was 0.909, and between healthy controls and mild AD was 0.986. LASSI-L sub-scores representing maximum storage capacity, recovery from proactive interference, and delayed recall yielded the highest diagnostic accuracy.

Conclusions: The LASSI-L is a reliable and valid test for the diagnosis of aMCI and mild AD. The age and education influences on the performance of the test and normative data are provided. LASSI-L merits further studies to evaluate its ability to detect preclinical AD and predict progression to aMCI and early dementia.

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DISCLOSURE STATEMENT

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SUPPLEMENTARY MATERIAL

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Keywords

Alzheimer's disease; LASSI-L; memory; mild cognitive impairment; neuropsychological assessment; proactive interference; validation

INTRODUCTION

Neuropsychological assessment is an essential tool in the diagnosis of Alzheimer's disease (AD) [1]. Due to the aging population, the incidence and prevalence of AD has increased in recent years and is on the rise [2]. Given that developing therapies will likely be more effective in the preclinical disease stages, early diagnosis is becoming increasingly necessary.

In this regard, the term mild cognitive impairment (MCI) was suggested to herald the onset of a possible neurodegenerative process before clinical dementia can be diagnosed [3]. Thus, MCI, representing an intermediate stage between the typical cognitive decline associated with aging and dementia, is without substantial observable functional impairments in daily living [4]. The amnesic subtype in particular (aMCI) often precedes the early dementia stage of AD, and is considered a high-risk condition that progresses to dementia in 10–20% of cases per year [5, 6].

Memory impairment is a hallmark feature of MCI and early AD due to the onset of neurodegeneration in hippocampus and entorhinal cortex. Patients with incipient AD show learning and retrieval deficits characterized by poor encoding, rapid forgetting, impaired recognition memory due to defective storage, poor delayed recall, and sensitivity to proactive and retroactive interference [1]. Traditional and widely used cognitive tests are often employed to diagnose memory impairment, including the Rey Auditory Verbal Learning Test, California Verbal Learning Test, the Free and Cued Selective Reminding Test (FCSRT), and the Wechsler Memory Scales. Of these, the FCSRT has been specifically recommended due to its ability to control encoding using semantic cues, and its ability to distinguish between storage and retrieval deficits [7, 8]. In general, these tests achieve high diagnostic accuracy in mild AD and detect amnesic mild cognitive impairment in approximately 80% of cases [5, 9]; however, more sensitive cognitive tests are needed to capture the disease in its presymptomatic stages [10].

To this end, the development of novel tools has been encouraged, such as the Memory Capacity Test [11], Face Name Associative Memory Exam [12, 13], and the Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L). The last is based on a new paradigm to assess memory that capitalizes on semantic interference effects [14, 15]. Previous research found a high vulnerability to semantic interference in AD patients using the Semantic Interference Test (SIT), a memory task using real objects in which the patient has to recall 10 semantically related objects [16]. In MCI patients, semantic interference measured by the SIT was associated to a higher risk of progression to dementia [17] and to amyloid load [18]. The LASSI-L was subsequently developed using a verbal list learning paradigm. It was initially validated in 121 subjects (47 healthy controls, 34 aMCI, and 40 AD) with a sensitivity of 87.9% and a specificity of 91.5% in discriminating between

healthy controls and aMCI [18]. The LASSI-L's ability to measure proactive interference, particularly release from proactive interference, has been associated to amyloid load in the brain and was more sensitive than traditional memory measures. The LASSI-L uses free and cued recall, measures proactive and retroactive interference, and, uniquely, recovery from the proactive interference [18].

The aim of our study was two-fold: first, to adapt the LASSI-L to the Spaniard population and to obtain normative data and second, to validate the test for the diagnosis of aMCI and mild AD.

METHODS

Subjects

The study was performed with 164 participants recruited from the Department of Neurology at Hospital Clinico San Carlos, in Madrid, Spain. The enrollment period was between September 2015 and April 2016. Three diagnostic groups included: healthy older adults ($n = 97$), aMCI ($n = 34$), and mild AD ($n = 33$). In all cases Spanish was the native and dominant language. For the entire sample, the mean age was 73.4 ± 10.0 years and 102 (62%) were women. A common protocol was administered, comprising of a clinical interview, Mini-Mental State Examination (MMSE), Functional Activities Questionnaire [19], and Clinical Dementia Rating (CDR) [20]. The ethics committee of our hospital approved the study.

Healthy participants were volunteers. We used the following inclusion criteria: 1) 50–99 years old, 2) absence of any cognitive and functional impairment, using the MMSE adjusted for age and education >24 [21], a global Clinical Dementia Rating equal to 0, and Functional Activities Questionnaire (FAQ) of 0 [19, 20], 3) absence of depression according to the Hamilton Depression Scale [22], 4) absence of subjective memory or cognitive complaints. The exclusion criteria were as follows: 1) neurological disease (e.g., history of stroke, epilepsy, brain tumor, movement disorder, etc.), 2) systemic disease potentially associated with cognitive impairment, 3) psychiatric disease (e.g., history of major depression, psychosis, bipolar disorder, personality disorder, etc.), 4) substance abuse, and 5) visual or auditory impairment that may impair test performance.

Only participants with memory complaints suggestive of AD were included in our cognitively impaired groups and were classified as either amnesic mild cognitive impairment (aMCI) or mild AD. Current diagnostic criteria used for aMCI [4] were as follows: 1) memory complaints by the patients and/or confirmed by an informant, 2) a global CDR equal to 0.5, 3) memory impairment demonstrated using age- and education-adjusted scaled scores on the FCSRT [23]: specifically, a scaled-score equal to or less than 6 in total recall and/or delayed recall (suggestive of a storage deficit), and 4) absence of functional impairment in daily living activities. The criteria for mild AD were as follows: 1) probable AD dementia of the National Institute on Aging-Alzheimer's Association 2011 [24] and 2) a global CDR equal to 1. All patients were studied with structural neuroimaging (CT or MRI) to exclude other non-neurodegenerative causes.

In a subgroup of 62 cases (12 healthy controls, 33 aMCI, and 17 AD) a neuropsychological battery was administered and included: verbal span (forward and backward digit span), the Corsi block-tapping test, Trail Making Test, Symbol Digit Modalities Test, Boston Naming Test, Visual Object and Space Perception Battery (subtests for object decision, progressive silhouettes, position discrimination, and number location), Judgement of Line Orientation, Tower of London-Drexel version, FCSRT, Rey-Osterrieth Complex Figure Test (copy and memory at 3 and 30 minutes), and Stroop Color-Word Interference Test.

Loewenstein-Acevedo scales for semantic interference and learning (LASSI-L)

The LASSI-L was administered independently from the other cognitive tests and scales, and was not used for the diagnostic workup. The test was administered according to the following procedure: first, the examiner presents a list of 15 common words that are fruits, musical instruments and articles of clothing (five words of each category) (List A). The participant reads aloud the words, which are presented one at a time at 4-s intervals. After the 15 words are read, the examiner asked the participant to recall the words. After the free recall (60 s) (Free Recall 1A, FRA1), the semantic cue is provided (e.g., “Now I want you tell me all the words from the list that are fruits” (20 s for each category) (Cued Recall A1, CRA1). Then, List A is presented again using the same procedure, and cued recall is performed again (CRA2). Thereafter, a semantically related list (List B) with 15 common words (fruits, musical instruments and articles of clothing) is presented in the same manner. Again, a free recall (FRB1) and cued recall (CRB1) is performed. Then, the presentation of List B is once more followed by a second cued recall attempt (CRB2). After that, participants are asked to free recall the words belonging to List A (Short-delay free recall, SdFRA). This is followed by a category-cued recall trial (SdCRA). Finally, a delayed recall of all words (List A and List B) is performed 20 min later (Delayed Recall, DR). Words correctly remembered, intrusions from other list, and intrusions unrelated to the presented words were registered.

The Spanish version of the LASSI-L used in United States was adapted to a Spaniard population. Three words were changed due to being largely unknown in Spain: “*banana*” was replaced by “*plátano*”, “*mango*” was replaced by “*melón*”, and “*suéter*” was replaced by “*jersey*”. The replaced words represent the same concept and/or have the same or a very similar length. A pilot study was conducted in 10 subjects to ensure understanding and applicability.

The following indices were calculated:

- FRA1 – FRB1, to assess the proactive interference in free recall (PI-FR).
- CRA1 – CRB1, to assess the proactive interference in cued recall (PI-CR).
- FRA1 – SdFRA, to assess the retroactive interference in free recall (RI-FR).
- CRA1 – SdCRA, to assess the retroactive interference in cued recall (RI-CR).
- CRB2 – CRB1, to assess the recovery from proactive interference (RPI).
- Intrusions CB1 – Intrusions CB2, to assess the recovery of the intrusions from proactive interference (ti-RPI).

Statistical analysis

Statistical analysis was conducted using IBM®SPSS Statistics 20.0 and MedCalc® 16.4.3. Results are shown as frequency (percentage) and mean $\pm$ standard deviation. Internal consistency was measured with Cronbach's alpha. Demographic variables (age, years of education, and gender) were evaluated using Pearson's correlation coefficient (r) as well as the coefficient of determination (r^2). Convergent validity with the FCSRT was estimated using Pearson's correlation coefficient in a subgroup of 62 cases (12 healthy controls, 33 aMCI, and 17 AD).

We used the overlapping interval strategy to provide the norms, in order to maximize the sample size [23, 25]. Age intervals of 11 years (for instance, 68–78) were generated to provide normative ranges of three years (for instance, age range 72–74, midpoint 73). Subsequently, raw scores were converted to percentile ranks for each age interval, and then to scaled scores (mean 10, standard deviation 3). Linear regression analysis was used to study the influence of education, according to the following formula:

$$SS_{AE} = SS_A - (\beta^*[\text{Education} - 12])$$

where SS_{AEG} was Scaled Score adjusted by age and education; SS_A was the scaled score adjusted only by age; β was the regression coefficient for education. Education was measured as years of formal schooling.

To study the validity of the test to discriminate between groups, only cases in which an individual was at least 65 years were selected. ANOVA analyses and *post hoc* Tukey procedure were performed to test for differences between the three groups. A p -value < 0.05 was considered statistically significant. We also estimated ROC (Receiver Operating Characteristic) curves for discriminating between groups. The best cutoff values were estimated according to the Youden index J . The ROC curves were compared using the method proposed by DeLong et al. [26].

RESULTS

Psychometric properties

Internal consistency measured by the Cronbach's alpha was 0.932. Convergent validity, assessed using correlations with FCSRT, was moderate to substantial. Correlation was $r = 0.541$ ($p < 0.01$) between FRA1 and FCSRT (free recall 1) and $r = 0.656$ ($p < 0.01$) between CRA2 and FCSRT (total recall). Regarding DR, the correlation with FCSRT (free delayed recall) was 0.595 ($p < 0.01$).

Normative data

Age and years of education correlated with all the raw scores of the LASSI-L measure. Regarding gender, the influence was lower and only correlated with two scores (FRA1 and DR). Correlations between age, years of education, and gender with each score of the test in healthy controls are shown in Table 1. In contrast, as indicated in Table 1, ratios in which subjects own scores performance on initial learning were accounted for using indices

measuring proactive and retroactive interference, there was no statistically significant correlations between these measures and demographic factors.

Age-adjusted scaled score and age- and education-adjusted scaled scores are provided in the Supplementary Material.

Test performance and intrusions between groups

There were significant differences between the three groups in all the scores of the LASSI-L (Table 2). *Post hoc* analysis using Tukey's method revealed significant differences between healthy controls versus aMCI and healthy controls versus AD on all scores. In contrast, the comparison between aMCI versus AD showed significant differences on all the scores except the FRB1, CRB1 and CRB2. When controlling for FRA1 (strength of initial learning), significant differences between groups were also observed in all scores except for SdFRA.

Regarding intrusions from other list, there were significant differences between groups in FRB1, CRB2, and SdFRA. When totaling all intrusions, there were significant differences in FRA1, CRA1, CRA2 and CRB2 (Table 3). *Post hoc* analyses using the Tukey procedure showed that aMCI made a greater number of intrusions from the other list than healthy controls in CRB2 and total intrusions in FRA1, CRA1, CRA2, and CRB2. Furthermore, aMCI made more intrusions from the other list than AD in FRB1 and CRB2 and AD than healthy controls in SdFRA and CRA2 (total intrusions).

As shown in Table 4, there were significant differences between groups on some of the indices of proactive interference, but not retroactive interference. In this regard, PI-FR and PI-CR were higher in healthy controls than AD. In contrast, recovery from proactive interference (RPI) was higher in healthy controls than aMCI and AD. There were no significant group differences between aMCI and AD on these indices.

Diagnostic properties

ROC curves and areas under the curve (AUC) were estimated for the discrimination between the diagnostic groups with the different scores (Fig. 1). All ROC curves were statistically significant ($p < 0.001$). For the distinction between healthy controls versus aMCI and AD, FRA1 (AUC 0.896), CRA2 (AUC 0.921), CRB2 (AUC 0.884), and DR (AUC 0.947) achieved the highest discrimination (Fig. 1A). The AUC of the other scores was lower (CRA1 = 0.877; FRB1 = 0.822; CRB1 = 0.779; SdFRA = 0.778; SdCRA = 0.813).

Regarding the classification between healthy controls versus aMCI, CRA2 (AUC 0.874), CRB2 (AUC 0.841), and DR (AUC 0.909) obtained the highest discrimination capacity (Fig. 1B), in comparison to the other scores (FRA1 = 0.835; CRA1 = 0.825; FRB1 = 0.764; CRB1 = 0.731; SdFRA = 0.699; SdCRA = 0.720) (Table 5).

Concerning the discrimination between healthy controls versus AD, the AUC was high with almost all scores (FRA = 0.958; CRA1 = 0.931; CRA2 = 0.970; FRB1 = 0.883; CRB1 = 0.829; CRB2 = 0.928; SdFRA = 0.860; SdCRA = 0.909; DR = 0.986) (Fig. 1C, Table 5).

The best cutoff points to discriminate between groups and size effect are shown in Tables 6 and 7, respectively.

DISCUSSION

The Spanish-language version of LASSI-L is a reliable memory test with high diagnostic accuracy. It demonstrated very good internal consistency using Cronbach's alpha and had acceptable convergent validity with the FCSRT, which measures similar processes (encoding, learning, and delayed retrieval).

Significant effects of both age and education were observed on all raw scores of the LASSI-L. In contrast, the influence of the gender was not significant.

These results are consistent with normative studies conducted with other memory tests that showed the influence of education while gender has a weak or absent influence [23, 27–30]. The influence of age in verbal memory performance has been previously demonstrated in both longitudinal and cross-sectional studies, suggesting a decline, especially in encoding [31], but also on other processes (e.g., learning, recall) [32]. Importantly, in the current investigation, indices measuring proactive interference, retroactive interference, and recovery from proactive interference (after accounting for initial leading) did not correlate with demographic factors. For example, RPI was not associated with age and education. This may allow for the process of recovery from proactive interference to be interpreted independently from demographic factors.

Both aMCI and AD had worse performance on all the subtests of the LASSI-L as compared to healthy controls. When comparing aMCI and AD participants, there were also significant differences in all scores but three: FRB1, CRB1, and CRB2. This suggests that encoding, learning, and recall follow a linear pattern of impairment, from healthy controls (unimpaired), aMCI (moderate impairment), and AD (major impairment). When semantic interference ratios were examined, healthy controls actually had a greater degree of proactive interference compared to AD participants in free (PI-FR) and cued recall (PI-CR) conditions. This likely reflects the fact that the AD group had insufficient encoding of the initial List A targets to result in proactive interference effects when List B targets were presented. In contrast, despite greater proactive interference effects, healthy controls were able to recover from proactive interference effects (RPI) after an additional learning trial whereas both aMCI and AD patients were not able to benefit from the additional List B learning trial. Another notable observation was the rate of intrusive errors, which were particularly evident in CRB2 in aMCI, as was a lack of recovery from the proactive interference. In this regard, the inability to recover from the proactive interference effect has been observed in a cohort of patients with Pre-MCI and subjective memory complaints and has been linked to amyloid deposition in AD signature brain regions. This unique early cognitive impairment may be very useful in that it can address a major problem in the diagnosis of aMCI: having to define memory impairment according to standard deviations (>1 , >1.5 or >2) below the norm of a particular cognitive test or neuropsychological battery [33]. This subscale of the LASSI-L in contrast can potentially allow the individuals to serve as their own control by measuring their ability to recover from proactive interference.

Regarding the ROC curves analyses, several scores evidenced a robust capacity to discriminate between diagnostic groups. In discriminating between healthy controls and aMCI, the scores that obtained a greater AUC were CRA2 (indicative of maximum storage), CRB2 (susceptible to recovery from proactive interference), and DR (delayed recall of all items learned). This is consistent with the findings of Crocco and colleagues (2014) in which CRA2 and CB2 yielded a correct classification rate between healthy controls and aMCI of 88.8% and 90.0%, respectively [15]. Almost all scores obtained an AUC superior than 0.90 when discriminating between healthy individuals and those with mild AD. In general, FRB1, CRB1, SdFRA, and SdCRA obtained a lower AUC in comparison to CRB2 and the other scores, especially CRA2 and DR. This suggests that learning, recovery from proactive interference, and delayed recall are generally better discriminators than the initial proactive interference or retroactive interference.

Our study has some limitations. Firstly, the diagnosis of aMCI was mainly based on the results of FCSRT, and this test may potentially have false positive results. However, subjects were required to have a global CDR of 0.5, which makes this less likely. Nonetheless, there were some aMCI patients who had no difficulties with proactive interference (PSI) or recovery from PSI effects while others had one or more of these deficits. In this regard, the comparison of the progression to dementia between patients only impaired in learning and recall but not in semantic interference and those with high susceptibility to semantic interference should be investigated in future studies. Similarly, the direct comparison of previous memory tests (such as FCSRT) with LASSI-L may be of great interest. Secondly, despite strict inclusion and exclusion criteria for healthy controls, they were not studied with amyloid or tau biomarkers, so we cannot exclude the possibility of persons with high amyloid and/or tau load who may have had subtle cognitive impairments that were not detected by our initial screening evaluation. Although asymptomatic deposition of amyloid in brain does not seem to significantly impair traditional memory tests [34, 35], the influence in semantic interference in the presence of elevated amyloid and tau levels has not been adequately studied.

In conclusion, this study validated the LASSI-L for diagnosing aMCI and mild AD in a Spaniard population averaging less than nine years of education. The findings that maximum storage and the ability to recover from proactive semantic interference (but not retroactive interference) are the best discriminators are also consistent with previous work [15, 18]. The LASSI-L provides information about several important processes involved in memory, such as encoding, learning, proactive and retroactive interference, recovery from proactive interference, and delayed recall. Overall, our study provides further evidence about the usefulness of LASSI-L in the early stages of AD. Further studies are necessary to evaluate the role of LASSI-L in the detection of preclinical AD as well as to predict the progression from subjective memory complaints and aMCI to dementia over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
ROC curves analysis of the pairwise comparison between groups. A) Healthy controls versus aMCI and AD. B) Healthy controls versus aMCI. C) Healthy controls versus AD.

Table 1Correlation (r) and determination (r^2) coefficients

	Age		Years of education		Gender	
	r	r ²	r	r ²	r	r ²
FRA1	-0.519 **	0.269	0.367 **	0.134	0.228 *	0.051
CRA1	-0.451 **	0.203	0.379 **	0.143	0.163	–
CRA2	-0.440 **	0.193	0.414 **	0.171	0.119	–
FRB1	-0.399 **	0.159	0.320 **	0.102	0.091	–
CRB1	-0.433 **	0.187	0.353 **	0.124	0.039	–
CRB2	-0.506 **	0.256	0.415 **	0.172	0.159	–
SdFRA	-0.407 **	0.165	0.343 **	0.117	-0.032	–
SdCRA	-0.413 **	0.170	0.339 **	0.114	0.115	–
DR	-0.491 **	0.241	0.223 **	0.049	0.243 *	0.059
PI-FR	-0.157	–	0.073	–	0.152	–
PI-CR	0.041	–	-0.024	–	0.105	–
RI-FR	-0.041	–	-0.027	–	0.230 *	0.052
RI-CR	-0.038	–	0.039	–	0.045	–
RPI	-0.037	–	0.032	–	0.144	–

**
 p -value <0.01;*
 p -value <0.05.

Table 2

Analysis of variance of the performance among the three diagnostic groups

	Healthy controls (<i>n</i> = 71)	aMCI (<i>n</i> = 33)	AD (<i>n</i> = 32)	F (<i>p</i> -value)
Age	76.23±5.72	77.70±6.52	78.16±6.57	1.34 (0.263)
Gender (number of women, %)	42 (59.2%)	15 (45.4%)	24 (75%)	5.89 (0.052)
Years of education	8.52±4.98 (0–18)	7.61±4.79 (0–18)	7.06±4.20 (0–18)	1.15 (0.320)
MMSE (adjusted)	27.07±1.53 ^{a,b}	25.03±3.28 ^c	20.43±3.94	50.59 (<0.001)
FRA1	6.79±2.19 ^{a,b}	3.97±1.87 ^c	2.50±1.27	61.45 (<0.001)
CRA1	8.11±2.37 ^{a,b}	5.03±2.20 ^c	3.13±2.19	57.74 (<0.001)
CRA2	10.92±2.04 ^{a,b}	7.21±2.38 ^c	4.63±2.37	97.04 (<0.001)
FRB1	5.31±2.29 ^{a,b}	3.21±1.49	2.22±1.09	33.80 (<0.001)
CRB1	5.85±2.50 ^{a,b}	3.76±1.87	2.91±1.59	23.74 (<0.001)
CRB2	9.14±2.46 ^{a,b}	5.42±2.69	4.13±2.10	56.21 (<0.001)
SdFRA	4.49±2.65 ^{a,b}	2.61±2.38 ^c	1.19±1.42	23.43 (<0.001)
SdCRA	6.31±2.16 ^{a,b}	4.09±3.10 ^c	2.16±2.05	34.90 (<0.001)
DR	15.15±3.81 ^{a,b}	5.88±5.29 ^c	2.38±3.58	123.84 (<0.001)

^a Healthy controls versus aMCI – *p*-value <0.05;^b Healthy controls versus AD – *p*-value <0.05;^c aMCI versus AD – *p*-value <0.05. In gender, chi-square test was performed.

Table 3

Analysis of variance of intrusions among the three diagnostic groups

	Healthy controls	aMCI	AD	F (p-value)
i-FRB1	1.52±1.53	2.00±1.52 ^c	1.06±0.94	3.55 (0.031)
i-CRB1	3.34±2.26	4.03±2.44	2.88±1.99	2.19 (0.115)
i-CRB2	2.25±2.05 ^a	3.64±2.42 ^c	2.22±1.53	5.80 (0.004)
i-SdFRA	1.58±1.53 ^b	1.33±1.38	0.78±1.33	3.29 (0.040)
i-SdCRA	3.04±2.21	3.09±2.40	2.25±2.21	1.59 (0.207)
ti-FRA1	0.18±0.48 ^a	0.76±1.17	0.41±0.94	5.62 (0.005)
ti-CRA1	0.89±1.31 ^a	2.00±2.59	1.38±1.71	4.39 (0.014)
ti-CRA2	0.59±1.03 ^{a,b}	2.03±2.50	1.78±2.63	8.08 (<0.001)
ti-FRB1	1.69±1.68	2.39±1.80	1.69±1.61	2.14 (0.121)
ti-CRB1	3.89±2.62	4.97±3.43	3.78±2.76	1.90 (0.153)
ti-CRB2	2.58±2.48 ^a	4.88±3.72	3.25±2.34	7.58 (0.001)
ti-SdFRA	1.72±1.64	1.72±1.52	1.16±1.68	1.45 (0.238)
ti-SdCRA	3.48±2.42	3.88±2.78	3.63±3.81	0.21 (0.804)
ti-DR	0.59±1.05	1.21±1.81	1.03±2.08	2.11 (0.124)

i, intrusions from the other list. ti, intrusions from the other list and non-presented.

^aHealthy controls versus aMCI – *p*-value <0.05.^bHealthy controls versus AD – *p*-value <0.05^caMCI versus AD – *p*-value <0.05

Table 4

Analysis of variance of indices of proactive and retroactive interference among the three diagnostic groups

	Healthy controls	aMCI	AD	F(<i>p</i> -value)
PI-FR	1.47±2.67 ^b	0.75±1.69	0.28±1.61	3.42 (0.036)
PI-CR	2.26±2.87 ^b	1.27±2.18	0.21±1.91	7.54 (0.001)
RI-FR	2.29±3.18	1.36±2.70	1.31±1.85	1.97 (0.143)
RI-CR	1.80±2.97	0.93±2.66	0.96±2.20	1.63 (0.200)
RPI	3.29±2.18 ^{a,b}	1.66±2.24	1.21±1.66	13.69 (<0.001)
ti-RPI	1.30±2.29 ^a	0.09±2.21	0.53±1.58	4.11 (0.018)

^aHealthy controls versus aMCI – *p*-value <0.05;^bHealthy controls versus AD – *p*-value <0.05;^caMCI versus AD – *p*-value <0.05.

Table 5

Pairwise comparison of ROC curves (healthy controls versus aMCI, and healthy controls versus AD)

		HC versus aMCI									
		FRA1	CRA1	CRA2	FRB1	CRB1	CRB2	SdFRA	SdCRA	DR	
HC versus AD	FRA1		0.755	0.311	0.146	0.051	0.873	0.028	0.069	0.064	
	CRA1	0.297		0.173	0.189	0.065	0.705	0.028	0.052	0.041	
	CRA2	0.424	0.072		0.028	0.005	0.391	0.008	0.015	0.316	
	FRB1	0.027	0.168	0.003		0.523	0.105	0.278	0.507	0.009	
	CRB1	0.000	0.006	0.000	0.225		0.014	0.546	0.825	0.000	
	CRB2	0.227	0.901	0.042	0.124	0.005		0.003	0.082	0.077	
	SdFRA	0.007	0.040	0.001	0.588	0.504	0.064		0.647	0.003	
	SdCRA	0.128	0.485	0.048	0.541	0.039	0.578	0.214		0.001	
	DR	0.132	0.019	0.253	0.000	0.000	0.008	0.000	0.011		

The *p*-values of the comparison between ROC curves for discriminating healthy controls (HC) versus MCI are shown below the diagonal; the *p*-values for ROC curves to distinguish HC versus AD are shown above the diagonal.

Table 6

Best cutoff values to discriminate between groups

	CRA2			CRB2			DR		
	Value	Se/Sp	J	Value	Se/Sp	J	Value	Se/Sp	J
HC versus MCI/AD	9/10	90.7/81.6	0.724	6/7	75.3/85.9	0.613	9/10	84.6/92.9	0.77
HC versus aMCI	9/10	81.8/81.6	0.635	8/9	90.1/64.7	0.577	9/10	75.7/92.9	0.687
HC versus AD	7/8	90.6/94.3	0.849	6/7	90.6/85.9	0.765	9/10	93.7/92.9	0.867

Se, sensitivity; Sp, specificity; J, Youden's index J; HC, healthy controls.

Table 7Effect size (Cohen's *d*) between groups

	HC versus MCI/AD	HC versus MCI	HC versus AD
FRA1	1.78	1.38	2.39
CRA1	1.69	1.34	2.18
CRA2	2.08	1.67	2.84
FRB1	1.36	1.08	1.72
CRB1	1.15	0.94	1.40
CRB2	1.76	1.44	2.19
SdFRA	1.08	0.74	1.55
SdCRA	1.27	0.83	1.97
DR	2.52	2.01	3.45