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LAM Test: A New Cognitive Marker for Early Detection in Preclinical Alzheimer's Disease

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Abstract.
Background: With the arrival of disease-modifying treatments, it is mandatory to find new cognitive markers that are sensitive to Alzheimer's disease (AD) pathology in preclinical stages.
Objective: To determine the utility of a newly developed Learning and Associative Memory face test: LAM test. This study examined the relationship between AD cerebrospinal fluid (CSF) biomarkers and performance on LAM test, and assessed its potential clinical applicability to detect subtle changes in cognitively healthy subjects at risk for AD.
Methods: We studied eighty cognitively healthy volunteers from the Valdecilla cohort. 61% were women and the mean age was 67.34 years (±6.416). All participants underwent a lumbar puncture for determination of CSF biomarkers and an extensive neuropsychological assessment, including performance on learning and associative memory indices of the LAM-test after 30 min and after 1 week, and two classic word lists to assess verbal episodic memory: the Rey Auditory Verbal Learning Test (RAVLT) and the Free and Cued Selective Reminding Test (FCSRT). We analyzed cognitive performance according to amyloid status (A+ versus A–) and to ATN model (A–T–N–; A+T–N–; A+T+N–/A+T+N+).

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Results: Performance on the LAM-test was significantly correlated with CSF Aβ ratio. A+ participants performed worse on both learning (mean difference = 2.19, $p = 0.002$) and memory LAM measures than A– (mean difference = 2.19, $p = 0.004$). A decline in performance was observed along the Alzheimer's continuum, with significant differences between ATN groups.
Conclusions: Our findings suggest that LAM test could be a useful tool for the early detection of subjects within the AD continuum, outperforming classical memory tests.

Keywords: Alzheimer's disease, associative memory, cognitive markers, early detection, long-term forgetting, neuropsychological assessment, preclinical Alzheimer's disease

INTRODUCTION

Classical word list tests such as the Rey Auditory Verbal Learning Test (RAVLT) or the Free and Cued Selective Reminding Test (FCSRT) are able to identify subjects with mild cognitive impairment (MCI) at risk of progression to Alzheimer's disease (AD) [1, 2]. However, they are not sensitive enough to detect pathology in preclinical stages in functionally and cognitively normal subjects in whom such tests usually have a ceiling effect [3, 4]. Hence, there is a need to continue the search for new cognitive markers sensitive to early-stage pathology to promote accurate identification of those at risk for the disease. In this regard, the focus has broadened to explore other aspects of memory which have been proposed to be altered in preclinical stages of AD [3–6], such as associative learning and recall (i.e., the association in memory of two previously unrelated items, such as a scene and an object or a name and a face), and deficits in long-term memory consolidation which are thought to be related to the underlying pathophysiological processes of AD [7] and are often underestimated in everyday clinical practice due to the lack of memory assessments beyond 20–30 min [8].

An increasing amount of research is being conducted with cognitive tests that have been demonstrated to be highly sensitive to early AD pathology. In fact, recent studies have proven the utility of a modified version of the RAVLT to detect accelerated long-term forgetting after one week in subjects with preclinical autosomal dominant AD [9] and asymptomatic *APOE* ε4 carriers at risk for the sporadic form of the disease [7]. Likewise, an increasing number of new tests based on cross-modal associative memory paradigms, such as the Online Repeatable Cognitive-Assessment-Language Learning Test (ORCA-LLT) [10], the Ancient Farming Equipment Test (AFE-T) [4] or the FNAME [3] and its Spanish version, the S-FNAME [11] have found a clear relationship between AD pathology and cognitive performance in patients with AD in preclinical stages.

We therefore created a single cognitive instrument that would address both cross-modal associative learning and memory: the Learning and Associative Memory face test (LAM test), a new, simplified, and gamified version of the face-name test that includes measures of associative learning as well as association memory at standard and extended delays.

In this study, we analyzed the relationship between the LAM test and cerebrospinal fluid (CSF) biomarkers of AD pathology in a cohort of cognitively healthy, older volunteers. In addition, we compared the cognitive performance on this test with that of two of the most widely used standard episodic memory assessment tests in the clinic: the RAVLT (modified version) and the FCSRT. Finally, we determined the clinical utility of these tests in terms of their sensitivity and specificity for detecting individuals harboring amyloid pathology across the AD continuum.

METHODS

Participants

We conducted a cross-sectional study at the Cognitive Impairment Unit (UDC), Marqués de Valdecilla University Hospital-IDIVAL (Santander, Spain). Participants were recruited from the Valdecilla Study for Memory and Brain Ageing, a prospective cohort whose main objective is to expand existing knowledge of AD in the preclinical phase [12, 13]. All participants were adults over 55 years, residents of the Community of Cantabria (Spain), with a minimum of 8 years of formal education, Mini-Mental State Examination (MMSE) score of 26 or more, and objective cognitive performance within the normal range (1.5 SD cut-off from the normative mean) on a series of standardized neuropsychological tests validated in the Spanish population [14]. Screening and baseline assessment were performed as previously described [12]. We extensively phenotyped all participants, including CSF analysis of significant AD biomarkers and a comprehensive neuropsychological battery on each participant [13]. The institutional

ethics committee of the HUMV approved the study, and all volunteers signed an informed consent form according to the Declaration of Helsinki.

Neuropsychological assessment

Two expert neuropsychologists (MGM and AP) assessed all participants using a comprehensive neuropsychological battery that covered all cognitive areas. The neuropsychological assessment for the area of memory included: FCSRT [15, 16], RAVLT (modified version) [17], Logical Memory Test of the Wechsler Memory Scale-III (WMS-III LM) [18], CERAD Figure recall [19] and Rey Figure recall [16]. For language, we used the Boston Naming Test [20] and letter fluency test [21]. Likewise, to assess visuoconstructive praxis, we used the Rey-Osterrieth Complex Figure Copy [16]. Poppelreuter complex figures test [22] and the Number Location subtest of the Visual Object and Space Perception Battery [23] were used for the visuoperceptual/visuospatial domain. Finally, executive function assessment included the Trail Making Test (Parts A and B) [24] and subtests of the WAIS III-R battery [25] including Digit Span subtest (forward and backward) [24] and Digit Symbol subtest [24].

Learning and Associative Memory face test (LAM test)

We developed a new, cognitively highly demanding, associative memory test to measure both learning and long-term memory with a single instrument. We based it upon a pre-existing test, the FNAME, in which the participant has to learn and retrieve associations between images of unfamiliar faces and common first names and occupations [3, 5, 26]. As a new approach, we implemented a similar protocol to one previously used to assess learning and long-term episodic memory in at-risk individuals [7, 9]. Thus, in addition to the standard 30-min delay, we employed a one-week delay to assess both recall and long-term recognition (Supplementary Figure 1).

The task was created in collaboration with a graphic designer (PV) who was commissioned to draw a series of original and realistic faces based on different facial features and characteristics. We placed these drawings on a white background and dressed them in neutral-colored to avoid giving additional clues that might facilitate associations and thus make the task more challenging. Regarding the food items, they were selected from among the most common and frequent ones within the Mediterranean diet, a diet that is widespread not only in Spain but also around the world [27]. The LAM test was developed as a computerized task in collaboration with the Photonics Engineering Group (GIF) of the University of Cantabria (Santander, Spain). A GIF engineer (PA) then integrated it on a web platform to facilitate standardization, optimize data collection process, and facilitate its remote application if needed.

Subjects had to learn certain information about a set of faces. The test includes two versions related to real-life situations to contextualize the task: "party" and "meal" (Supplementary Figures 2 and 3). Participants were randomly assigned to receive one or the other and both versions included a series of associations each: the "party" version comprised six faces, each of which was associated with a name and an age. The "meal" version similarly comprised six faces, each associated with a name and a food. In both versions, there was an initial learning phase in which each triad (face-name-age or face-name-food) was displayed for 6 s. Once all six triads had been shown, the subject was sequentially presented with each of the six faces again without any other information and asked to recall the other two items (name-age or name-food) previously associated with each face. The triads were then displayed again, and this was followed by another cued recall trial. All participants performed a minimum of two and a maximum of three trials until they reached a learning criterion of 80% correct. The test was administered with the support of an examiner on a desktop computer, although both the context and the instructions for what to do are written on the screen. The duration of exposure to the stimuli in the learning phase is fixed at 6 s each. Participants progress at their own pace through the response phase, although there is a maximum allowed response time of 60 s for each trial. The learning phase lasts a total of 8 min; the delayed recall phase lasts about 4 min and the free recall and recognition phase after one week lasts about 5 min.

We recorded the number of correct answers and errors in each learning trial and a further cued recall trial was conducted after a 30-min filled delay (30 min recall). We then administered a further, unannounced delayed cued recall probe after a seven day delay (1 week recall) on the pretext that the participant had to return to the hospital a week later to complete other study procedures. We also measured recognition with a four-alternative forced-choice response procedure in each of the six cases. Because the test was comput-

erized, we could assess by video call seven subjects who could not attend the hospital in person due to various circumstances (COVID pandemic, commuting difficulties, work, etc.).

Outcome measures

LAM test

Subjects receive one point for each correct answer (name, food or age), which must be accurate even in the case of age. All measures were calculated for each version: "meal" (name/food) and "party" (name/age). We measured performance for each association as follows: i) learning as the average of the maximum number of hits across learning trials in each association, ii) standard-delay memory as recall after 30 min, and iii) long-term memory as recall after one week. Recognition memory was measured as the difference between hits and errors (d'=(hit rate) – (error rate)) after one week.

Finally, we calculated a score based on the total number of associations made for each learning and memory measure corresponding to each version (meal and party).

RAVLT

All participants had to learn a list of 15 words that were read aloud by the rater (one per second) with a minimum of four and a maximum of 10 learning trials. We recorded the raw scores for each trial. We measured performance as follows: i) learning as the average of the maximum number of correct words across learning trials, ii) standard-delay memory as free recall after 30 min, and iii) long-term memory as free recall after one week.

FCSRT

We administered the FCSRT in the standard way and selected the following performance measures: i) learning as the total number of words recalled freely over the three trials and ii) standard-delay memory as free recall of the word list after 30 min.

Biomarker studies and APOE test

Both procedures were performed as previously described [12, 13]. Evaluation of CSF biomarkers included the determination of amyloid-β_{1-42} ($A\beta_{42}$), amyloid-β_{1-40} ($A\beta_{40}$), total tau (t-tau), and phosphorylated-tau_{181} (p-tau). Biomarker levels were quantified by chemiluminescent enzyme immunoassay (Lumipulse G600 II, Fujirebio Europe, Belgium) following the manufacturer's instructions. Cut-off levels were calculated for our cohort through Gaussian Mixture Models [28]: ratio $A\beta_{42/40} \leq 0.076$, t-tau ≥ 543 and p-tau ≥ 73.2. Also, $A\beta_{42}$ and $A\beta_{40}$ were used to calculate Aβ ratio. The ATN nomenclature was applied to interpret the CSF findings, considering A+ those cases with an abnormal Aβ ratio, $T+$ when abnormal levels of p-tau_{181} and $N+$ when abnormal levels of total tau [29]. According to this, participants were divided into three groups: normal CSF biomarkers (A–T–N–), Alzheimer's pathologic change (A+T–N–), and Preclinical AD (Pre-AD) (A+T+N–/A+T+N+). This way, we considered that all individuals with abnormal values of Aβ (A+T–N–, A+T+N– y A+T+N+) were inside the AD continuum.

APOE was genotyped using TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, USA). Participants with one copy or more of the $\varepsilon 4$ allele were considered $\varepsilon 4+$. All others were considered $\varepsilon 4-$.

Statistical analysis

We carried out partial correlations, controlling for age between the above-mentioned measures of learning and memory and CSF levels of the three core AD biomarkers ($A\beta_{42/40}$, t-tau, and p-tau). We used Student's t-test to compare the A–/A+groups performance only on those learning and memory indices that correlated most significantly with CSF amyloid ratio and p-tau. Moreover, following the NIA-AA ATN classification [30], we also used Student's t-test to compare performance between groups on those cognitive measures that proved to be most sensitive: "Normal AD Biomarkers" (A–T–N–) versus "Alzheimer´s pathologic change" (A+T–N–), and "Normal AD Biomarkers" (A–T–N–) versus "Preclinical Alzheimer´s disease" (A+T+N–/A+T+N+).

We employed general linear models (GLM) for multivariate analysis, including those selected learning and memory indices as dependent variables with age, gender, years of education and interval between lumbar puncture and test performance (months) as covariates, and ATN group as independent variable. We also performed a linear regression model to analyze the relationship between Aβ ratio and tests performance (LAM, RAVLT, and FCSRT), in which we included age as a covariate. *APOE* status was not related to any outcome measure in univariate analysis, so we decided not to included it in the model as a covariate.

Differences between groups were considered significant when $p < 0.05$. Furthermore, we used ROC

curves to assess the clinical utility of LAM indices for the detection of amyloid-positive (*A+*) versus amyloid-negative (A–) subjects, and for the detection of subjects with Alzheimer´s pathologic change (A+T–N–) versus those with a normal biomarker profile (A–T–N–). We did the same with the RAVLT and the FCSRT. Then, we selected the LAM test measures with an AUC greater than 0.7 to compare them to the AUCs of the RAVLT and FCSRT using the DeLong test. We performed all statistical analyses with SPSS (Statistical Package for Social Sciences, 25).

RESULTS

We recruited 80 cognitively healthy subjects between November 19, 2021, and December 15, 2022. All participants scored 0 on the global Clinical Dementia Rating scale, 61% were women, and the mean age was 67.34 years (SD = 6.416). The average educational level was 13.38 years (SD = 3.813), MMSE mean was 29 (SD = 1.322), and the proportion of *APOE* ε4 carriers was 31.3%. Amyloid positive subjects (A+T–N–/A+T+N–/A+T+N+) constituted half of the sample and carried *APOE* ε4 in a higher percentage than amyloid negative (52.5% versus 10%), and were also significantly older than those with normal CSF marker values (A–T–N–) (mean = 69.08, SD = 5.699 versus mean = 65.60, SD = 6.686, $p = 0.014$) (Table 1). Following the ATN model, 33.7% ($N = 27$) had Alzheimer's pathologic change (A+T–N–) and 16.2% ($N = 13$) belonged to the preclinical AD group (A+T+N–/A+T+N+).

LAM test indices correlate with CSF biomarkers

Correlation analyses between the main biomarkers of AD in CSF and the performance in the LAM test for each version ("meal" or "party"), revealed that most of the learning indices of the meal version were significantly correlated with Aβ ratio but not with tau: *Names*-$A\beta_{42/40}$ ratio ($r = 0.366$, $p = 0.020$), *Food*-$A\beta_{42/40}$ ratio ($r = 0.424$, $p = 0.006$), and *Total*-$A\beta_{42/40}$ ratio ($r = 0.440$, $p = 0.004$) (Fig. 1). The standard memory index (30 min recall) was also correlated with Aβ ratio: *Names*-$A\beta_{42/40}$ ratio ($r = 0.329$, $p = 0.038$) and *Total*-$A\beta_{42/40}$ ratio ($r = 0.329$, $p = 0.038$). Long-term memory index (1 week recall) associations also correlated significantly with Aβ ratio: *Names*-$A\beta_{42/40}$ ratio ($r = 0.399$; $p = 0.011$), *Food*-$A\beta_{42/40}$ ratio ($r = 0.328$, $p = 0.039$), and *Total*-$A\beta_{42/40}$ ratio ($r = 0.402$, $p = 0.010$) (Fig. 1). Recognition measures correlated only moderately with Aβ ratio and not with other CSF biomarkers: *Food* and *Total* ($r = 0.336$, $p = 0.034$ and $r = 0.322$, $p = 0.043$, respectively) (Supplementary Table 1).

In the party version, the only measurement that correlated with biomarkers was a learning index: *Names*-$A\beta_{42/40}$ ratio ($r = 0.328$, $p = 0.044$) (Supplementary Table 2).

Classic memory tests and CSF AD biomarkers

First, we studied the relationship between LAM test and classic memory tests, and we observed a high correlation between them (Supplementary Table 3). However, when we analyzed the relationship between the RAVLT measures and the CSF biomarkers, we observed that the RAVLT learning measure (average maximum number of correct answers) did not correlate with any of the CSF biomarkers. In addition, memory measures, correlated with tau but not with amyloid. Only delayed free recall at 30 min correlated modestly with p-tau and t-tau ($r = –0.264$, $p = 0.019$ and $r = –0.274$, $p = 0.015$, respectively).

Regarding the FCSRT, the learning measure (learning free recall) only correlated weakly with p-tau ($r = –0.227$, $p = 0.044$), while the memory measure (delayed free recall at 30 min) correlated weakly with t-tau and p-tau ($r = –0.258$, $p = 0.022$ and $r = –0.304$, $p = 0.006$, respectively).

Finally, to compare the performance of the three tests (LAM, RAVLT and FCSRT) in terms of their association with CSF biomarkers, we run an age-adjusted linear regression model. We found a statistically significant association between LAM meal version and the amyloid ratio: learning measure *Total* ($\beta = 0.005, p = 0.011$). Regarding measures of long-term memory, LAM was the only test that showed a significant association with amyloid *Total* ($\beta = 0.004$, $p = 0.015$). Conversely, the association between RAVLT memory measures: 30' ($\beta = 0.001$, $p = 0.532$) and one week ($\beta = <–0.001$, $p = 0.574$), and FCSRT memory measures: delayed free recall ($\beta = 0.001, p = 0.337$) was not statistically significant.

Differences between amyloid positive (A+) and healthy subjects (A–) in LAM test

Of the 40 subjects included in the amyloid-negative group (A–), 22 were given the meal version and 18 were given the party version. Regarding the amyloid positive (A+) group, 21 were administered the party version and 19 the meal version (Table 2). After performing the correlation analysis between

Table 1
Participants' characteristics

	Global sample ($n = 80$)	Amyloid negative (A–T–N–) ($n = 40$)	Amyloid positive (A+T–N–/A+T+N–/A+T+N+) ($n = 40$)	p A– versus A+
Demographics and education level				
Age (y), mean (SD)	67.34 ± 6.416	65.60 ± 6.686	69.08 ± 5.699	**0.014**
Females no. (%)	49 (61.3%)	23 (57.5%)	26 (65%)	0.647
Education (y), mean (SD)	13.38 ± 3.813	13.20 ± 3.891	13.55 ± 3.775	0.684
MMSE (0–30), mean (SD)	29 ± 1.322	29.33 ± 0.797	28.68 ± 1.639	**0.028**
APOE-ε4 carrier, no. (%)	25 (31.3%)	4 (10%)	21 (52.5%)	**<0.001**
Difference between CSF and test (mo) mean (SD)	11.45 ± 16.953	3.95 ± 13.991	18.95 ± 16.464	**<0.001**
CSF Biomarkers				
Ratio $A\beta_{42/40}$, mean (SD)	0.071 ± 0.023	0.092 ± 0.006	0.051 ± 0.013	**<0.001**
Total-Tau, mean (SD), pg/ml	380.98 ± 184.759	308.67 ± 99.421	453.27 ± 220.317	**<0.001**
P-Tau, mean (SD), pg/ml	53.827 ± 34.258	38.497 ± 11.566	69.158 ± 41.969	**<0.001**

Statistically significant values are shown in bold. SD, standard deviation; y, years; mo, months; Aβ, amyloid-β; P-Tau, phosphorylated-tau.

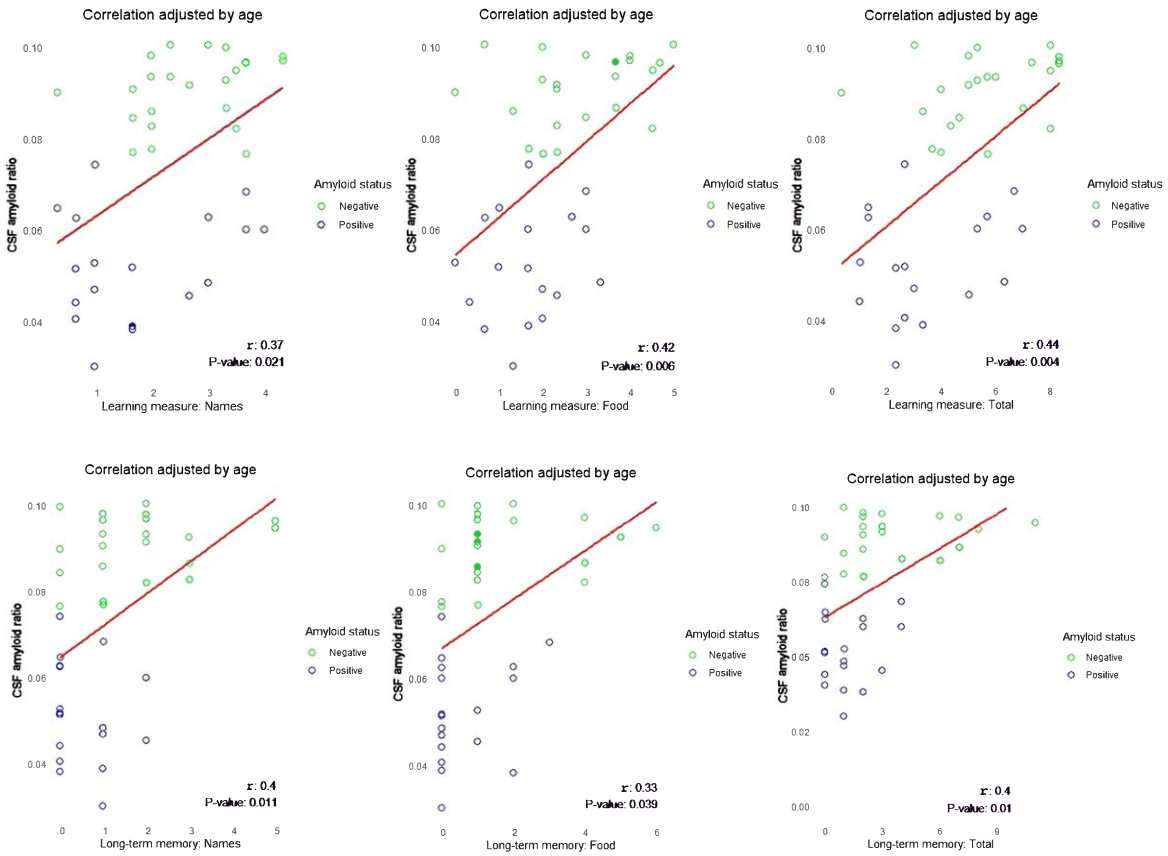

Fig. 1. Relationship between CSF biomarkers and LAM test indices (meal version). Scatter plot showing the distribution of values for performance in LAM test indices for meal version: Learning measures *names, food, total* (above) and Long-term memory measures (after one week) *names, food, total* (below) (X-axis) and the Alzheimer's biomarkers in CSF (pg/ml) (Y-axis). The dots represent a pair of values of both variables for each observation. The green ones are those corresponding to amyloid-negative subjects and the blue ones represent the amyloid-positive subjects. The red line is the regression line. In the upper right corner of each graph is the partial correlationcoefficient (R) adjusting by age. CSF, cerebrospinal fluid; Aβ, amyloid-β.

Table 2
LAM test (meal version). Amyloid status (A– versus A+)

	Amyloid negative (A–) ($n = 22$)	Amyloid positive (A+) ($n = 19$)	p* A– versus A+
LEARNING INDICES			
Names (0–6) (SD)	2.757 ± 1.002	1.771 ± 1.186	**0.015**
Food (0–6) (SD)	2.909 ± 1.348	1.701 ± 0.942	**0.002**
Total (0–12) (SD)	5.666 ± 2.115	3.473 ± 1.960	**0.002**
STANDARD MEMORY INDICES			
30 minutes delayed recall			
Names (0–6) (SD)	3.14 ± 1.642	1.89 ± 1.823	**0.018**
Food (0–6) (SD)	3.23 ± 1.798	2.05 ± 1.580	**0.024**
Total (0–12) (SD)	6.36 ± 3.185	3.95 ± 3.291	**0.013**
LONG-TERM MEMORY INDICES			
One-week delayed recall			
Names (0–6) (SD)	1.77 ± 1.412	0.63 ± 0.761	**0.008**
Food (0–6) (SD)	1.73 ± 1.723	0.63 ± 0.955	**0.016**
Total (0–12) (SD)	3.50 ± 2.858	1.26 ± 1.327	**0.004**
Recognition			
Names (SD)	–3.45 ± 2.241	–4.74 ± 2.766	0.058
Food (SD)	–1.91 ± 1.797	–3.26 ± 2.766	0.493
Total (SD)	6.64 ± 3.346	4 ± 4.899	0.121

Statistically significant values are shown in bold. *Adjusted for age, sex, education, difference in months of testing/lumbar puncture. SD, standard deviation.

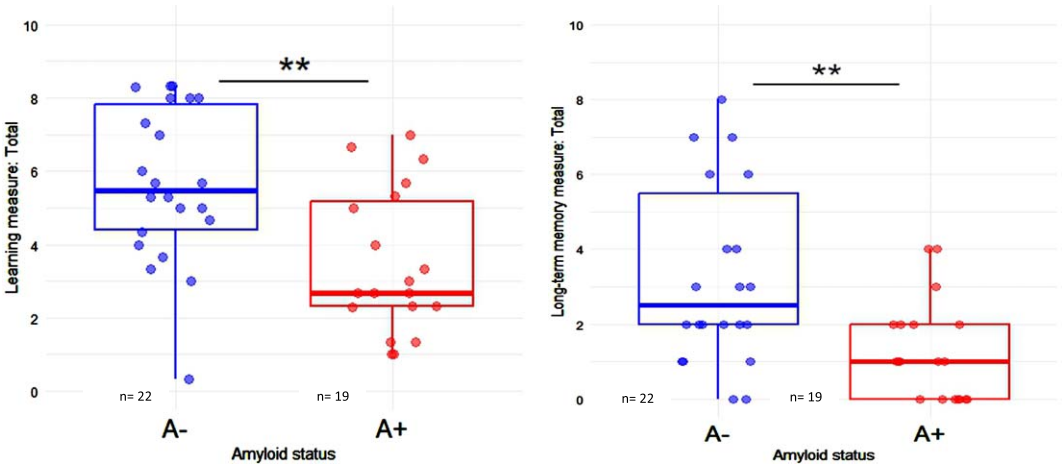

Fig. 2. Differences between amyloid positive (A+) and amyloid negative (A–) on LAM test (meal version). Distribution of Total indices shows that A+ individuals perform significantly worse both in learning and memory (measured after one week) than A– individuals. The boxes show the interquartile range (the upper boundary is the Q3, and the lower boundary is the Q1). The line inside the box corresponds to the median of the sample and the whiskers represent the maximum (upper) and minimum (lower) values. The dots indicate individual values. Significant differences are indicated with a horizontal line and two asterisks between the boxes.

CSF biomarkers and the different LAM indices of learning and memory, we observed that only the meal version indices correlated significantly with amyloid. In fact, after a brief analysis to directly compare Total learning performance across the different types of associations, we found that only 26.8% of the subjects were able to correctly make more than six associations (out of 12) with food (Supplementary Figure 4), while in the case of age, the percentage increased to 59% ($\chi^2 = 8.45$, $p = 0.006$). When we measured Total recall after one week, the percentages were 9.8% versus 23.1%, respectively ($\chi^2 = 2.60$, $p = 0.135$).

Based on these results, we decided to analyze only the indices of the food version in order to find out whether or not they could be used to distinguish amyloid status (A– versus A+). After adjusting for age, gender, education, and difference in the interval between cognitive testing and lumbar puncture, we observed that A+ subjects learned significantly less information than A– subjects in all learning measures.

Table 3
LAM test (meal version). Alzheimer's disease continuum

	Normal AD Biomarkers (A–T–N–) ($n=40$)	Alzheimer's pathologic change (A+T–N–) ($n=27$)	p* A–T–N– versus A+T–N–	Preclinical AD A+T+N–/ A+T+N+($n=13$)	p* A–T–N– versus A+T+N–/ A+T+N+
LEARNING INDICES					
	($N=22$)	($N=15$)		($N=4$)	
Names (0–6) (SD)	2.757 ± 1.002	1.933 ± 1.267	0.084	1.166 ± 0.577	**0.015**
Food (0–6) (SD)	2.909 ± 1.348	1.733 ± 0.985	**0.006**	1.583 ± 0.876	0.172
Total (0–12) (SD)	5.666 ± 2.115	3.666 ± 2.096	**0.011**	2.750 ± 1.287	**0.039**
STANDARD MEMORY INDICES					
30 minutes delayed recall	($N=22$)	($N=15$)		($N=4$)	
Names (0–6) (SD)	3.14 ± 1.642	2.13 ± 1.959	0.072	1.00 ± 0.816	0.068
Food (0–6) (SD)	3.23 ± 1.798	2.20 ± 1.656	0.080	1.50 ± 1.291	0.177
Total (0–12) (SD)	6.36 ± 3.185	4.33 ± 3.519	0.058	2.50 ± 1.915	0.090
LONG-TERM MEMORY INDICES					
One-week delayed recall	($N=22$)	($N=15$)		($N=4$)	
Names (0–6) (SD)	1.77 ± 1.412	0.67 ± 0.816	**0.019**	0.5 ± 0.577	0.192
Food (0–6) (SD)	1.73 ± 1.723	0.73 ± 1.033	**0.036**	0.25 ± 0.500	0.219
Total meal (0–12) (SD)	3.50 ± 2.858	1.4 ± 1.404	**0.013**	0.75 ± 0.957	0.167

Statistically significant values are shown in bold. *Adjusted for age, sex, education, difference in months of testing/lumbar puncture. SD, standard deviation.

At the 30-min delay, A+ subjects also forgot significantly more information than A– subjects. The A+ group also showed greater forgetting at the 1 week delay (Table 2, Fig. 2).

Differences between amyloid positive (A+) and healthy subjects (A–) in RAVLT and FCSRT tests

We analyzed the performance on each of the RAVLT and FCSRT cognitive measures to see if there were significant differences between groups (A+ versus A–). We found no significant differences on any of the selected measures, even when adjusting for age, gender, and education (Supplementary Table 4).

Alzheimer's continuum groups analysis in LAM test

Because there were significant differences in both learning and memory measures between A– and A+ (except for recognition), we decided to analyze the differences between groups according to the ATN model. In general, we observed a tendency to obtain lower scores in all indices along the AD continuum, with worse performance in the A+T–N– group compared to A–T–N– and the lowest scores in the A+T+N–/A+T+N+ group (Table 3).

We found that previously observed differences in learning and long-term (one-week delay) memory scores were maintained between the normal AD biomarkers group (ATN–) and those with Alzheimer's pathologic change (A+T–N–). However, differences disappeared in standard memory measurements (30 min delay).

Significantly lower performance was also observed in the A+T–N– group after one week in: *Names* (mean difference = 1.1, $p = 0.019$), *Food* (mean difference = 0.99, $p = 0.036$) and *Total* (mean difference = 2.1, $p = 0.013$).

In the preclinical AD group (A+T+N–/A+T+N+), we noted that, despite significance only remaining in two learning measures: *Names and Total*, worse performance was observed compared to the healthy group (ATN–). No differences were found in the other memory measures after adjustment (Fig. 3).

Clinical utility for the identification of individuals within the Alzheimer's continuum

ROC analysis for the discrimination between subjects with amyloid (A+) and without amyloid (A–) with the LAM test revealed several significant AUCs. Among the highest were two of the learning measures: *Food* which showed an AUC of 0.768 (95% CI 0.62–0.91) and *Total* which showed an AUC of 0.782 (95% CI 0.63–0.92). Regarding long-term memory measures (one week delay) we found two measures with the most significant AUCs: *Names*, which revealed an AUC of 0.755 (95% CI 0.61–0.90) and *Total,* which revealed an AUC of 0.763 (95% CI 0.62–0.91) (Table 4).

Finally, we also compared the AUCs between LAM, RAVLT and FCSRT. LAM had the highest AUCs in every case. More specifically, we

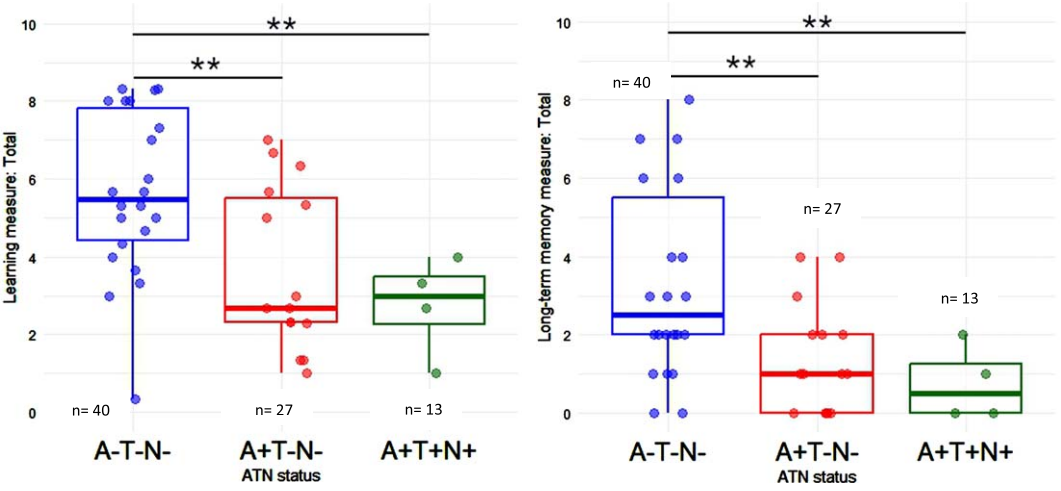

Fig. 3. Distribution of LAM test (meal version) across the "ATN" NIA-AA classification. Plots show significant differences in both learning and memory (after one week) between groups: a clear decrease in performance is observed along the continuum, especially between the biologically healthy (A–T–N–) and the pre-clinical (A+T–N–) groups.The boxes show the interquartile range (the upper boundary is the Q3, and the lower boundary is the Q1). The line inside the box corresponds to the median of the sample and the whiskers represent the maximum (upper) and minimum (lower) values. The dots indicate individual values. Significant differences are indicated with a horizontal line and two asterisks between the boxes.

Table 4
LAM test (meal version). Clinical utility for the identification of individuals in the Alzheimer's disease continuum

	Classification of A+ individuals	
	AUC (CI 95%)	*p*
LEARNING INDICES		
Names (0–6)	0.744 ***(0.58–0.90)***	***0.008***
Food (0–6)	0.768 ***(0.62–0.91)***	***0.003***
Total (0–12)	0.782 ***(0.63–0.92)***	***0.002***
MEMORY INDICES	**AUC (CI 95%)**	***p***
30 MINUTES		
Names (0–6)	0.701 ***(0.53–0.86)***	***0.028***
Food (0–6)	0.691 ***(0.53–0.85)***	***0.036***
Total (0–12)	0.711 ***(0.55–0.87)***	***0.021***
ONE WEEK		
Names (0–6)	0.755 ***(0.61–0.90)***	***0.005***
Food (0–6)	0.719 ***(0.56–0.88)***	***0.017***
Total (0–12)	0.763 ***(0.62–0.91)***	***0.004***

Bold values indicate $p < 0.05$. *p*, level of significance; CI, confidence interval.

observed that there were significant differences between AUCs in one of the LAM learning measures: *Food* and RAVLT memory measures: 30 min delay (AUC difference = 0.239, $p = 0.013$) and one week delay (AUC difference = 0.193, $p = 0.015$). Regarding another LAM learning measure: *Total,* we also found significant differences between its AUC and the same RAVLT memory measures: 30 min delay (AUC difference = 0.254, $p = 0.004$) and one week delay (AUC difference = 0.207, $p = 0.007$) (Fig. 4).

Furthermore, we also found significant differences between one of the LAM test memory measures: *Total,* and the former RAVLT memory measurements: 30 min delay (AUC difference = 0.224, $p = 0.025$) and one week delay (AUC difference = 0.177, $p = 0.047$) (Fig. 4).

We found no significative differences between any of the LAM and FCSRT AUCs (Supplementary Figure 5).

DISCUSSION

The main objective of this work was to capture early associative learning and memory deficits that can help to detect people at risk for AD in a cohort of cognitively normal individuals. Classical verbal episodic memory tasks based on word lists are clinically sensitive for the detection of MCI subjects at risk of progression to AD [1, 2, 31, 32], but not for detecting disease in preclinical stages [3, 4, 33]. We designed a novel paradigm that combines associative learning and memory with extended testing intervals to overcome this limitation of classical tests. Our main finding is that the performance on the LAM test is related to AD pathology in CSF, revealing alterations in performance more accurately and earlier than widely-used, classical verbal episodic memory tests.

We found that most of the LAM learning and memory indices correlated with CSF amyloid biomarker,

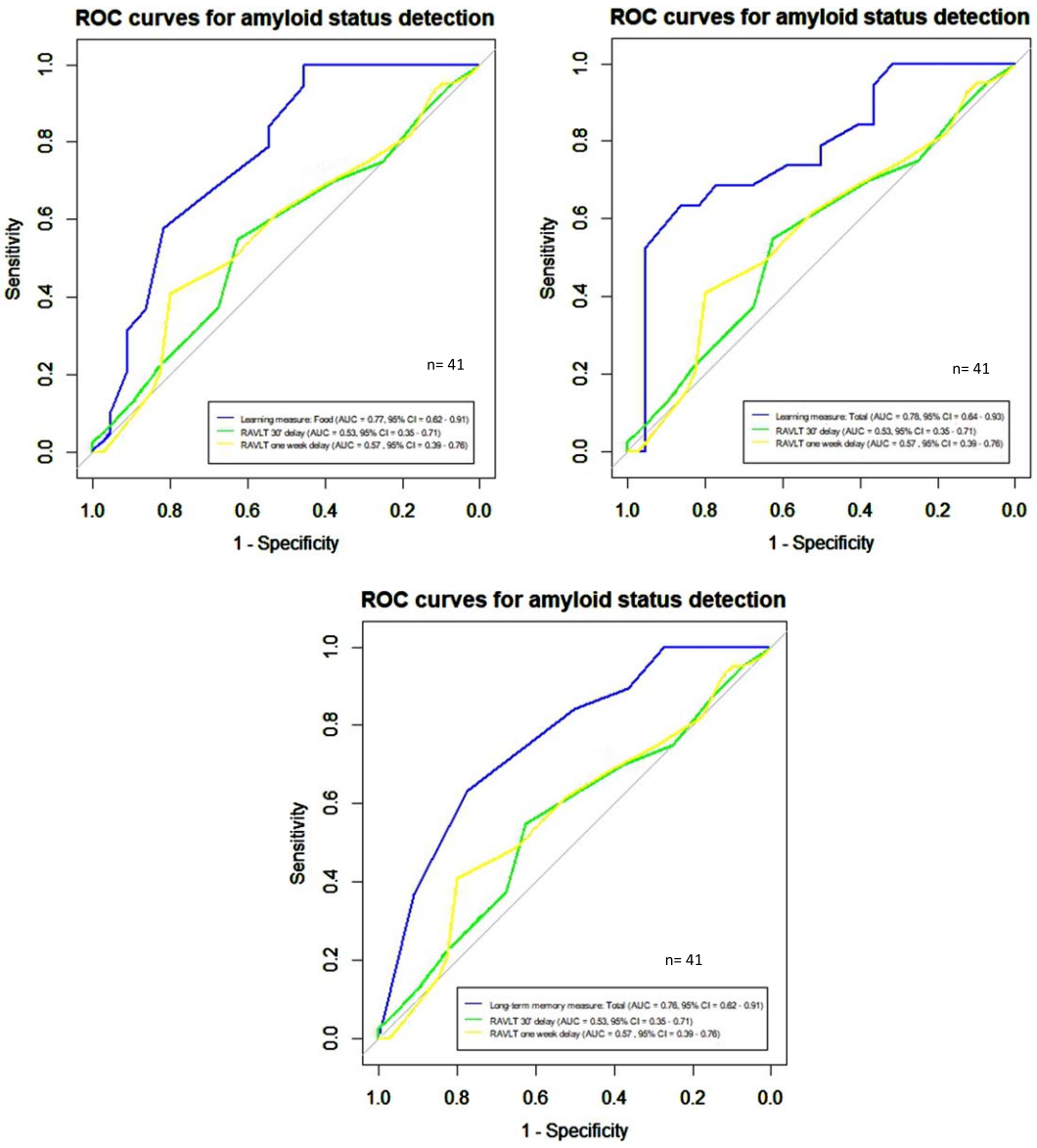

Fig. 4. ROC curves comparison between LAM and RAVLT measures.The graphs show significant differences between the AUCs of LAM and RAVLT tests. The abscissa axis shows 1-specificity, and the ordinate axis shows sensitivity. The curves are based on the results of a logistic regression in which different measures and their combinations have been considered (see colours in the legend of each plot); RAVLT, Rey Auditory Verbal Learning Test

so we were able to confirm that the test was sensitive to amyloid pathology. We observed that the association with *food domain* was particularly strong. We can hypothesize that it is the most arbitrary, the least affected by previous experience and, therefore, the most difficult to learn and remember. Previous literature reported the complexity of the name-face association as a function of its randomness and uniqueness [3, 34, 35]. However, we argue that perhaps the association with food is even more difficult. We have observed when using other face tasks such as the S-FNAME test [3, 11] that participants often tell us that they remember the name of one of the pictures because they have a family member or a close friend with the same name, reminds them of someone familiar or their image fits them with a certain profession, all of which makes it easier for them to create an associative link. In the case of food, since they had no prior knowledge of the face presented and could not relate this information to a previous experience,

face-food might be the most sensitive association of all.

When we compared subjects' performance on the LAM test based on their amyloid status (negative versus positive), we observed that A+ subjects performed significantly worse in both learning and memory than amyloid-negative subjects, even in memory measured over the longer term (after one week). This is consistent with previous research associating amyloid burden with worse performance on episodic memory tests in cognitively healthy older subjects with brain amyloidosis [36] and with the fact that memory tested at longer-than-usual intervals (e.g., 1 week) may be an early sign related to AD pathology [7, 8].

It is recognized that 20–30% of cognitively normal subjects older than 65 years living in the community have brain amyloid accumulation [37, 38], although we do not know when the transition to a definite AD pathological state, defined by CSF biomarkers, occurs [39, 40]. For this reason, we decided to analyze test performance according to the ATN classification [30], to determine which stage of the AD continuum the subjects were in and whether there were any cognitive changes once tau protein became detectable.

We found that the differences between the biologically normal (A–T–N–) and the group with Alzheimer's pathologic change (A+T–N–) were significant in almost all LAM indices. The subjects in the (A+T–N–) group learned less information and were able to remember fewer associations than the healthy ones. They also forgot more after one week. These results suggest that memory deficits can be caused by amyloid accumulation independently of the presence of tau. On the other hand, when comparing those with preclinical AD (A+T+N–/A+T+N+) with the biologically healthy (A–T–N–), we found that the aspect that most differentiated them was a lower learning capacity. Notably, however, the A+T+group was composed of only 13 subjects (4 for the meal version and 9 for the party version), so we believe the sample sizes are too small to observe significant differences. Our results are in line with recent research demonstrating a relationship between amyloid deposits and learning difficulties in early stages of AD, while, although a disposition to decline in memory performance was detected, forgetting rates seemed to stabilize [4, 41]. This might support a relationship between the presence of tau protein and longitudinal memory impairment [42], most likely based on the severity of the pathology.

In this study, testing at an extended delay (one week) was valuable in detecting amyloid positivity. We found relationships between long-term memory measures after one week *Food* and *Total* and the amyloid ratio. However, the learning measure was the most sensitive and earliest cognitive measure for detecting those already on the continuum. This suggests that difficulty in learning new information might be the earliest sign for detecting at-risk subjects in the early stages, even before the interaction with tau is present.

We further tested whether classical word list tests for assessing verbal episodic memory were also related to the presence of AD pathology in CSF and whether, at the same time, they could detect significant differences between groups in an equivalent way. We employed two of the most widely used tests to assess verbal episodic memory in AD: the Rey Auditory Verbal Learning Test (RAVLT) (modified version) and the Free and Cued Selective Reminding Test (FCSRT) [1, 33, 43, 44]. The 30-min delayed free recall of the FCSRT was the only measure that correlated with CSF amyloid and tau levels. Concerning the RAVLT, free recall after one week only correlated with tau but not with amyloid, in contrast to what we observed in the LAM test.

We found no significant differences in performance on the classical memory tests (RAVLT and FCSRT) depending on amyloid status (A– versus A+), which may indicate that they are not sensitive enough to detect amyloid pathology at such early stages, at least in our cohort. We therefore took the decision not to analyze performance along the ATN continuum. One possible explanation is that classical word list tasks are easier to compensate for in the preclinical stages of the disease, where cognitive impairment is very subtle and factors such as attentional capacity and individual learning and retrieval strategies play an important role in performance [33, 45]. However, in the case of more challenging associative memory tasks such as LAM test, these compensatory strategies would not be sufficient to overcome the effects of pathology on performance even as early in the continuum as in the A+T–N– stage.

Finally, we studied the clinical utility of LAM test measures to discriminate amyloid (A+) from non-amyloid (A–) subjects. Two learning measures and two long-term recall measures (with greater delay than those commonly used) yielded the highest AUCs. *Food* and *Total* were the two learning indexes that most sensitively detected A+, while for the long-term memory indexes (after one week) there were *Names* and *Total.* Given that our findings occur in a sample of cognitively healthy individuals who are

within the normal range on standardized neuropsychological tests [14], we believe that these indices could be considered potential neuropsychological markers of the earliest stages of the AD continuum, particularly, one learning measure, *Total,* and one long-term memory measure*, Total*, with the learning index being of great utility in terms of cost/benefit in daily clinical practice. None of the RAVLT or FCSRT AUCs measures were significant, suggesting a lower sensitivity of the classical tests for the detection of pathology at such early stages in clinical practice. Moreover, we did find significant differences between the AUC of the LAM test and the RAVLT test. Although there were no significant differences with the FCSRT, we think this is probably related to the lower sample size.

The fact that learning indices were the most significantly different, after adjusting for covariates, between the biologically healthy and those in the AD continuum suggests that learning impairment, rather than excessive forgetting, is the earliest detectable phenomenon as AD pathology develops. However, the question of whether a learning problem or a memory problem comes first in AD is not one that can be easily answered since performance will depend on the sensitivity of the tests used, the resources demanded by the tasks and the strategies available for each subject, as well as the underlying pathology.

Limitations

Limitations of this work are that it is a cross-sectional analysis and that the samples are small, so it is necessary to test the findings in a larger sample with repeated assessments over time to establish the relationship between poor performance in LAM and the presence of pathology at preclinical stages. We are aware that the RAVLT and FCSRT analyses have twice as many participants as we have for the LAM (meal version versus party version). Although it is clear that this may affect the results, it should be noted that despite this, the LAM test proves to be sensitive to amyloid pathology while the classical memory tests do not. In addition, it will also be important to study the relationships of LAM with other AD biomarkers that are known to be altered at preclinical stages [46].

We consider that another potential limitation is related to the timing of test application, which due to the COVID-19 pandemic was altered, resulting in a difference between the time when the LAM was performed and the time when the lumbar puncture was done. For this reason, we decided to include it as a co-variable in the model. We believe that this does not diminish the value of the data since the difference is larger in the amyloid positive group and the amyloid status would not have changed at the time the test was administered, since it is positive and within the continuum, which is what we are interested in at the time of evaluation.

Moreover, we understand that the test being applied on a website may provide an advantage concerning the administration, not only because of the benefits of digital cognitive assessment in terms of cost-effectiveness and sensitivity [47], but also because of the ease of conducting assessments at different times. However, we also notice that this could be a source of variability, as several factors, such as experience in using new technologies or the assessment scenario (face-to-face versus online), may play a role and is something we will need to explore further in our data.

Furthermore, given that the LAM is a newly developed test, we understand that it will need to be validated to confirm its reliability. No corrections have been made for multiple comparisons, so we are aware that these analyses are exploratory. They should be taken with caution and await replication. It is noteworthy, however, that it is sensitive to amyloid pathology and that it detects differences between groups even though only six face-name/food associations are presented, while in other tests on which it is based, the number of pairs to be associated is greater [11, 35, 48].

Our results showed that learning and associative memory performance in LAM test is significantly associated with *in vivo* CSF Aβ biomarker in a prospective cohort of cognitively healthy older adults. These findings imply the potential clinical applicability of several indices, especially, the *Total* learning measure as sensitive cognitive marker for the identification of subjects with AD pathology in preclinical stages of the disease. Our results raise the possibility that they could become helpful for early detection, with the advantage of low cost and easy administration. Further longitudinal study of these data will be necessary to understand their relevance by analyzing the relationship of the test to other known biomarkers and to discover the underlying neurological correlates of these processes.

AUTHOR CONTRIBUTIONS

María García-Martínez (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing; Assess subjects); Ana Pozueta-Cantudo (Data curation; Investigation; Assess subjects); Carmen Lage (Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – review & editing); Francisco Martínez-Dubarbie (Data curation; Formal analysis; Investigation; Visualization); Sara López-García (Data curation; Investigation; Assess subjects); Marta Fernández-Matarrubia (Data curation; Investigation; Assess subjects); Andrea Corrales-Pardo (Data curation; Investigation; Assess subjects); María Bravo (Data curation; Investigation); Nadia C. Cavada (Data curation; Investigation); Pedro Anuarbe (Data curation; Software); Jon Infante (Writing – review & editing); José Miguel López-Higuera (Resources); Luis Rodríguez-Cobo (Resources; Writing – review & editing). Eloy Rodríguez-Rodríguez (Investigation; Visualization; Writing – original draft; Writing – review & editing; Assess subjects); Christopher R Butler (Conceptualization; Investigation; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing); Pascual Sánchez-Juan (Conceptualization; Investigation; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-240067.

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