






## RESEARCH ARTICLE

# Early-onset Alzheimer's disease shows a distinct neuropsychological profile and more aggressive trajectories of cognitive decline than late-onset

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## Introduction

Alzheimer's disease (AD) is the main cause of neurodegenerative dementias and, in addition to the typical late

## Abstract

**Objectives:** Early- and late-onset Alzheimer's disease (EOAD and LOAD) share the same neuropathological traits but show distinct cognitive features. We aimed to explore baseline and longitudinal outcomes of global and domain-specific cognitive function in a well characterized cohort of patients with a biomarker-based diagnosis. **Methods:** In this retrospective cohort study, 195 participants were included and classified according to their age, clinical status, and CSF AD biomarker profile: 89 EOAD, 37 LOAD, 46 young healthy controls (age  $\leq 65$  years), and 23 old healthy controls ( $>65$  years). All subjects underwent clinical and neuropsychological assessment, neuroimaging, *APOE* genotyping and lumbar puncture. **Results:** We found distinct neuropsychological profiles between EOAD and LOAD at the time of diagnosis. Both groups showed similar performances on memory and language domains, but the EOAD patients displayed worsened deficits in visual perception, praxis, and executive tasks ( $p < 0.05$ ). Longitudinally, cognitive decline in EOAD was more pronounced than LOAD in the global outcomes at the expense of these non-amnesic domains. We found that years of education significantly influenced the decline in most of the neuropsychological tests. Besides, the *APOE*  $\epsilon 4$  status showed a significant effect on the decline of memory-related tasks within the EOAD cohort ( $p < 0.05$ ). **Interpretation:** Age of onset is a main factor shaping the cognitive trajectories in AD patients, with younger age driving to a steeper decline of the non-memory domains. Years of education are related to a transversal decline in all cognitive domains and *APOE*  $\epsilon 4$  status to a specific decline in memory performance in EOAD.

onset, it can present with an early onset (age of onset under 65).<sup>1</sup> Early-onset AD (EOAD) and late-onset AD (LOAD) share the same essential neuropathological traits (i.e., amyloid plaques and neurofibrillary tangles) but they

differ in several features.<sup>2–5</sup> For instance, memory loss as presenting symptom is widely common in LOAD, while non-amnesic presentations such as language, visuospatial or executive impairment are rare ( $\approx 5\%$ ).<sup>6</sup> Conversely, non-amnesic variants may occur in 30%–40% of the EOAD patients.<sup>7</sup> These non-amnesic cognitive profiles show domain-specific atrophy and tau spread patterns making EOAD suspicion more challenging and leading to misdiagnosis and diagnostics delay.<sup>8–12</sup>

Several studies have suggested that EOAD could also have a more aggressive course than LOAD at both clinical and neuropathological levels.<sup>13–17</sup> However, how their cognitive trajectories in specific domains differ during the follow-up warrants further research. In addition, many factors could potentially shape this course, so not only the age of onset but also cognitive reserve<sup>18,19</sup> or *APOE* status<sup>20,21</sup> might modulate disease progression. Although some studies have attempted to address this issue, longitudinal data from well-characterized cohorts, including patients with biomarker-based diagnosis and a comprehensive neuropsychological evaluation, is lacking.

To fill this gap, we aimed to (1) describe and compare the neuropsychological profile at diagnosis and its longitudinal trajectories between EOAD and LOAD patients in a biomarker-diagnosed cohort, and (2) evaluate the contribution of the *APOE* status and years of education to the decline of specific cognitive domains.

## Methods

### Participants

One-hundred ninety-five subjects, including 126 AD patients and 69 healthy controls, were selected from different prospective studies carried out in the Alzheimer's disease and Other Cognitive Disorders Unit at Hospital Clínic of Barcelona. All participants self-reported as White Spaniards. The Ethics Committee of Hospital Clínic of Barcelona approved the study. All participants provided signed informed consent. The study was in accordance with the declaration of Helsinki. All included patients and informants were systematically asked about the age of the first symptom onset on the first visit. Time to diagnosis was calculated as the difference from the first reported symptom to baseline. We also collected the first reported (i.e., more predominant) symptom during the baseline visit categorized as memory, language, visual–spatial, executive, and behavioral complaints. Our research protocol included a comprehensive neurological and neuropsychological evaluation, lumbar puncture, blood extraction, and neuroimaging. In cases where lumbar puncture was contraindicated, amyloid-PET was performed instead. Participants were classified into four groups:

- 1 EOAD group ( $n = 89$ ;  $\leq 65$  years): all patients had a typical AD CSF biomarker profile ( $n = 84$ ) or positive amyloid-PET ( $n = 5$ ) and fulfilled the National Institute on Aging–Alzheimer's Association criteria for MCI due to AD ( $n = 75$ ) or mild AD ( $n = 14$ ).<sup>22,23</sup> Subjects with known pathogenic mutations in *PSEN1*, *PSEN2*, or *APP* genes were excluded.
- 2 LOAD group ( $n = 37$ ;  $> 65$  years): patients with a typical AD CSF profile fulfilling criteria for MCI due to AD ( $n = 28$ ) or mild AD ( $n = 9$ ).<sup>22,23</sup>
- 3 Young healthy controls ( $n = 46$ ;  $\leq 65$  years): all subjects performed within the normal range (cutoff 1.5 SD from the normative mean) in all tests on a neuropsychological battery and presented normal AD CSF biomarkers.
- 4 Old healthy controls ( $n = 23$ ;  $> 65$  years): neuropsychological performance within the normal range and normal AD CSF biomarkers.

All the patients included in this study were evaluated at the Alzheimer's Unit at Hospital Clínic de Barcelona because of cognitive complaints. After obtaining neuropsychological battery outcomes and functional assessment as measured by the CDR scores (CDR of 0.5 were classified as MCI, CDR of 1 or above were classified as dementia), 103 individuals met the criteria of MCI and 23 of dementia syndrome.<sup>22,23</sup> Afterward, the etiological study to discern the underlying cause consisted of a blood sampling (including thyroid hormones, B12 vitamin, and folic acid), and an MRI scan to rule out structural causes (i.e., stroke and tumor). Finally, a spinal tap was performed to obtain CSF levels of  $A\beta_{42}$ , P-tau, and T-tau. In cases where the lumbar puncture was contraindicated, amyloid-PET was performed instead. All patients with MCI or dementia syndromes and biological evidence of AD (by CSF biomarkers or amyloid-PET) were diagnosed as MCI due to AD or dementia due to AD respectively in agreement with the current clinical diagnostic criteria.<sup>22,23</sup>

### Neuropsychological assessment

All participants were assessed with a comprehensive neuropsychological battery administered by a trained neuropsychologist. The battery encompassed five cognitive domains. The Free and Cued Selective Reminding Test (FCSRT)<sup>24</sup> was used to assess learning and encoding (free learning and total learning scores) and memory function (delayed free and total recall scores). The Landscape Test<sup>25</sup> evaluated delayed visual recognition memory. The language domain comprised of the Boston Naming Test (BNT),<sup>26</sup> a category fluency test (CFT),<sup>27</sup> and the auditory comprehension subtest from the Boston Diagnostic Aphasia Examination (BDAE).<sup>28</sup> The praxis domain included the ideomotor praxis subtest from the Western

Aphasia Battery (WAB)<sup>29</sup> and the constructional praxis subtest from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery.<sup>30</sup> The visuo-perceptive and visuospatial function was measured by the incomplete letters and number location subtests of the Visual Object and Space Perception (VOSP) battery,<sup>31</sup> respectively. The attention and Executive Functions domain consisted of the Trail Making Test—A,<sup>32</sup> a letter fluency test LFT<sup>33</sup> and the digit span forwards (attention span) and backwards (working memory) subtests from the Wechsler Adult Intelligence Scale WAIS.<sup>34</sup> Global cognition was assessed with the Mini-Mental State Examination (MMSE).<sup>35</sup> Available normative data<sup>36</sup> were used to identify normal/abnormal scores and define the cognitive status and classify the study participants. All subjects completed the baseline neuropsychological battery, and longitudinal data were obtained in 137 subjects (70.2% of the sample) at year 1, and 98 (50.3%) at year 2. By groups (young controls, old controls, EOAD and LOAD), longitudinal data were obtained in 43 (93%), 23 (100%), 44 (49%), and 27 (73%) subjects at year 1, and 42 (91%), 21 (91%), 25 (28%), and 10 (27%) subjects at year 2, respectively. The major reasons for missing data or non-participation in the follow-up were the enrolment of the study participants in clinical trials and, in a few cases, incapacity to complete the neuropsychological assessment due to disease progression or consent withdrawal.

### Determination of CSF, amyloid-PET biomarkers, and APOE analysis

Levels of CSF amyloid- $\beta_{42}$  ( $A\beta_{42}$ ), total tau (T-tau), and phosphorylated tau at Thr181 (P-tau) were measured using Innostest ELISAs following manufacturer's instructions (Fujirebio, Ghent, Belgium). Cut-off values of abnormality for each CSF biomarker were defined according to internal controls: (a)  $A\beta_{42} \leq 550$  pg/mL (CSF samples measured before February 2016) and  $\leq 750$  pg/mL (for those measured after February 2016); (b) T-tau  $>385$  pg/mL, and (c) P-tau  $>65$  pg/mL.<sup>37</sup> Amyloid-PET Florbetapir ( $n = 2$ ) or Florbetaben ( $n = 3$ ) ligands were used for PET acquisition. APOE genotype was determined through the analysis of rs429358 and rs7412 by Sanger sequencing.

### Statistical analyses

Baseline characteristics by diagnostic groups are presented as means (standard deviation) or frequencies (percentages). Differences in demographics, clinical and CSF data at baseline were analyzed by  $\chi^2$  test for categorical data and ANOVA for quantitative data. Analyses involving the amyloid levels did not include the samples measured

before February 2016 ( $n = 26$ ) given the cut-off variability of this variable. Raw neuropsychological scores were converted to Z-scores for all the analyses. In order to obtain the z-scores, we used the automatic tool for that end in SPSS software which takes the mean and standard deviation of the entire baseline sample for normalization, meaning AD groups and healthy controls. APOE  $\epsilon 4$  status was dichotomized as negative/positive. Positive was defined as when at least one allele was present. Baseline neuropsychological performances were compared between patients (EOAD vs. LOAD) and controls (young vs. old) using analyses of covariance (ANCOVA) controlling for years of education and APOE  $\epsilon 4$  status. Mixed effects linear models were used to analyze longitudinal changes in cognitive outcomes from baseline to 1 and 2 years, using the diagnosis as the primary predictor (EOAD vs. LOAD, young vs. old controls) and adjusting for years of education and APOE  $\epsilon 4$  status. As sub-analyses, we performed a mixed effects linear model evaluating the effect of APOE status in each cognitive outcome within EOAD and LOAD cohorts. In all the mixed effects models, a random effect for year within subject was included to adjust for baseline differences. Statistical analyses were conducted using Stata/IC 14.2 (College Station, Texas, USA).

## Results

### Demographics, genetics, clinical data, and AD CSF biomarkers

Demographic, genetic, clinical data, and CSF biomarker levels for each group are reported in Table 1. EOAD showed lower mean age than LOAD (59.8 vs. 74.5 years, respectively). There were no significant differences on syndrome diagnosis (i.e., MCI due to AD/mild AD) between the EOAD and LOAD groups ( $\chi^2 = 3.63$ ;  $p > 0.05$ ). Also, no statistically significant differences were found in years of education, time to diagnosis, or sex between groups. As expected, the APOE  $\epsilon 4$  genotype was more frequent in AD groups than in controls ( $\chi^2 = 19.66$ ;  $p < 0.01$ ). Additionally, control groups had higher CSF  $A\beta_{42}$  ( $F [1,165] = 305.15$ ;  $p < 0.01$ ) and lower CSF T-tau ( $F [1,188] = 81.52$ ;  $p < 0.01$ ) and P-tau ( $F [1,188] = 82.44$ ;  $p < 0.01$ ) levels than AD groups. No differences in APOE  $\epsilon 4$  status, CSF T-tau, or P-tau levels between EOAD and LOAD were found. EOAD and LOAD presented a family history of AD in the 44.8% and 43.7% of the cases, respectively.

### Baseline neuropsychological assessment

The neuropsychological profiles of the study groups are shown in Figure 1. The distribution of the most

**Table 1.** Demographics, clinical data, APOE status, and CSF biomarker levels of the study groups.

Parameters	Young controls (n = 46)	Old controls (n = 23)	EOAD (n = 89)	LOAD (n = 37)
Demographics and clinical data				
Age at baseline	57.4 ± 4.7 <sup>2,4</sup>	69.7 ± 3.7 <sup>1,3</sup>	59.8 ± 4.2 <sup>2,4</sup>	74.5 ± 4.8 <sup>1,3</sup>
Age at onset	—	—	57.1 ± 4.1 <sup>2,4</sup>	71.5 ± 5.6 <sup>1,3</sup>
Sex (% women)	73.9%	65.2%	60.7%	56.8%
Years of education	11.9 ± 4.4	11.9 ± 4.6	11.7 ± 4.9	9.5 ± 4.3
Time to diagnosis	—	—	2.6 ± 1.8	2.9 ± 2.5
CDR	0 ± 0	0 ± 0	0.65 ± 0.2	0.58 ± 0.2
APOE status and CSF levels				
APOE ε4 (%) positive)	19.6% <sup>3,4</sup>	14.3% <sup>3,4</sup>	47.1% <sup>1,2</sup>	59.5% <sup>1,2</sup>
Aβ <sub>1-42</sub>	814.3 ± 211.1 <sup>3,4</sup>	780.1 ± 204.7 <sup>3,4</sup>	404.3 ± 115.6 <sup>1,2</sup>	343.1 ± 73.2 <sup>1,2</sup>
T-tau	237.3 ± 139.0 <sup>3,4</sup>	295.3 ± 179.4 <sup>3,4</sup>	748.5 ± 451.1 <sup>1,2</sup>	765.8 ± 425.4 <sup>1,2</sup>
P-tau	53.0 ± 19.4 <sup>3,4</sup>	58.6 ± 25.9 <sup>3,4</sup>	102.1 ± 37.8 <sup>1,2</sup>	107.5 ± 49.3 <sup>1,2</sup>
Initial symptom at onset				
Memory	—	—	68.6%	86.5%
Language	—	—	11.2%	2.7%
Visual-spatial	—	—	10.1%	8.1%
Executive	—	—	3.4%	2.7%
Behavioral	—	—	6.7%	0%

Data are presented as means ± standard deviation. EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; Aβ<sub>1-42</sub>, Amyloid-beta 42; Tau, total tau; P-tau, phosphorylated tau.

<sup>1</sup>Significantly different from young controls.

<sup>2</sup>Significantly different from old controls.

<sup>3</sup>Significantly different from EOAD.

<sup>4</sup>Significantly different from LOAD.

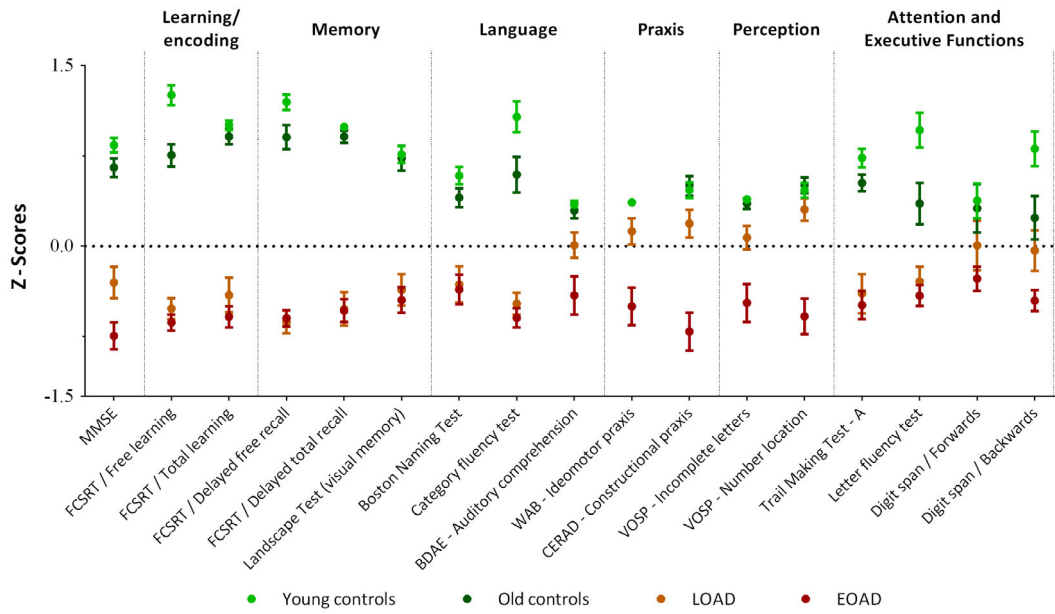
predominant/initial symptom at onset among the EOAD and LOAD groups is shown in Table 1. At diagnosis, patients with EOAD performed worse than patients with LOAD in global cognitive function (measured by the MMSE;  $F [1,115] = 8.56$ ;  $p < 0.01$ ), learning and encoding [free learning ( $F [1,115] = 4.40$ ;  $p < 0.05$ ) and total learning ( $F [1,115] = 3.98$ ;  $p < 0.05$ ) scores from the FCSRT, respectively], ideomotor ( $F [1,115] = 6.36$ ;  $p < 0.05$ ), and constructional ( $F [1,103] = 15.45$ ;  $p < 0.01$ ) praxis, visuoperceptive ( $F [1,113] = 5.09$ ;  $p < 0.05$ ), and visuospatial ( $F [1,111] = 18.97$ ;  $p < 0.01$ ) function, verbal fluency (LFT;  $F [1,110] = 5.10$ ;  $p < 0.05$ ), attention span (digits forwards;  $F [1,108] = 5.43$ ;  $p < 0.05$ ), and working memory (digits backwards;  $F [1,108] = 9.73$ ;  $p < 0.01$ ). None of the measures assessing memory or language were significantly different between EOAD and LOAD.

Regarding the neuropsychological performance between the control groups, the old controls performed worse than the young controls in learning ( $F [1,61] = 12.46$ ;  $p < 0.01$ ), verbal fluency ( $F [1,61] = 4.79$ ;  $p < 0.05$ , for the CFT; and  $F [1,61] = 4.94$ ;  $p < 0.05$ , for the LFT), and

working memory ( $F [1,59] = 4.21$ ;  $p < 0.05$ ). Raw neuropsychological scores of the study groups are shown in Table 2.

### Trajectories of cognitive decline

Trajectories of cognitive decline of the study groups are shown in Figure 2. Detailed results of mixed model effects evaluating the contribution of EOAD vs. LOAD diagnosis to the longitudinal cognitive outcomes are shown in Table 3. Compared with LOAD patients, EOAD declined faster on global cognitive function ( $\beta = 0.653$  [CI 95% (0.311–0.994)]  $p < 0.01$ ), encoding ( $\beta = 0.323$  [CI 95% (0.027–0.618)]  $p < 0.05$ ), verbal fluency ( $\beta = 0.347$  [CI 95% (0.114–0.581)]  $p < 0.01$ , for CFT and  $\beta = 0.382$  [CI 95% (0.117–0.646)]  $p < 0.05$ , for LFT), auditory comprehension ( $\beta = 0.575$  [CI 95% (0.077–1.07)]  $p < 0.05$ ), constructional ( $\beta = 0.869$  [CI 95% (0.422–1.31)]  $p < 0.01$ ), and ideomotor ( $\beta = 0.718$  [CI 95% (0.218–1.21)]  $p < 0.01$ ) praxis, visuoperceptive ( $\beta = 0.605$  [CI 95% (0.130–1.08)]  $p < 0.05$ ) and visuospatial ( $\beta = 0.107$  [CI 95% (0.633–1.51)]  $p < 0.01$ ) function, attention span



**Figure 1.** Baseline neuropsychological scores across the study groups. MMSE, Mini-Mental State Examination; FCSRT, Free and Cued Selective Reminding Test; BDAE, Boston Diagnostic Aphasia Examination; WAB, Western Aphasia Battery; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; VOSP, Visual Object and Space Perception Battery. Error bars represent SEM. TMTA z-scores were inverted (sign change) for visualization purposes.

**Table 2.** Baseline raw neuropsychological scores.

Function	Measure	Young controls	Old controls	EOAD	LOAD
Global	MMSE	28.7 ± 1.6	28.0 ± 1.4	22.6 ± 3.9 <sup>†</sup>	24.3 ± 3.1
Learning/encoding	FCSRT/free learning	29.4 ± 6.1*	23.8 ± 4.7	8.4 ± 6.8 <sup>†</sup>	9.6 ± 5.9
	FCSRT/total learning	43.9 ± 3.9	42.5 ± 4.3	20.2 ± 12.2 <sup>†</sup>	22.9 ± 12.9
Memory	FCSRT/delayed free recall	10.9 ± 2.1*	9.5 ± 2.2	2.3 ± 3.1	2.1 ± 2.7
	FCSRT/delayed total recall	15.1 ± 1.0	14.6 ± 1.3	6.3 ± 4.9	6.4 ± 4.8
	Landscape test (visual memory)	45.9 ± 3.1	45.7 ± 3.1	38.0 ± 6.3	38.5 ± 5.1
Language	Boston naming test	53.6 ± 4.0	52.1 ± 3.1	45.9 ± 9.3	46.2 ± 7.5
	Category fluency test	22.8 ± 5.6*	19.8 ± 4.5	12.2 ± 4.7	12.9 ± 3.5
	BDAE – auditory comprehension	14.9 ± 0.2	14.9 ± 0.3	14.2 ± 1.3	14.6 ± 0.6
Praxis	WAB – Ideomotor praxis	5.0 ± 0.0	5.0 ± 0.0	4.3 ± 1.1 <sup>†</sup>	4.8 ± 0.5
	CERAD – Constructional praxis	10.5 ± 0.8	10.6 ± 0.7	8.2 ± 2.5 <sup>†</sup>	10.0 ± 1.3
Perception	VOSP – incomplete letters	19.6 ± 0.6	19.5 ± 0.7	16.4 ± 5.4 <sup>†</sup>	18.5 ± 2.2
	VOSP – number location	9.2 ± 0.9	9.3 ± 0.6	6.8 ± 3.0 <sup>†</sup>	8.9 ± 1.2
Attention and executive functions	Trail making test – A	37.7 ± 23.4	47.2 ± 14.9	93.9 ± 50.5	89.5 ± 45.8
	Letter fluency test	39.9 ± 12.2*	32.2 ± 9.8	22.4 ± 10.0 <sup>†</sup>	23.9 ± 9.5
	Digit span/forwards	8.1 ± 1.9	8.0 ± 1.8	6.8 ± 1.8 <sup>†</sup>	7.4 ± 2.2
	Digit span/backwards	6.2 ± 1.9*	5.1 ± 1.5	3.8 ± 1.5 <sup>†</sup>	4.6 ± 1.7

Data are presented as means ± standard deviation. EOAD, early-onset Alzheimer’s disease; LOAD, late-onset Alzheimer’s disease; MMSE, Mini-Mental State Examination; FCSRT, Free and Cued Selective Reminding Test; BDAE, Boston Diagnostic Aphasia Examination; WAB, Western Aphasia Battery; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; VOSP, Visual Object and Space Perception Battery.

\*Significantly different from old controls ( $p < 0.05$ ).

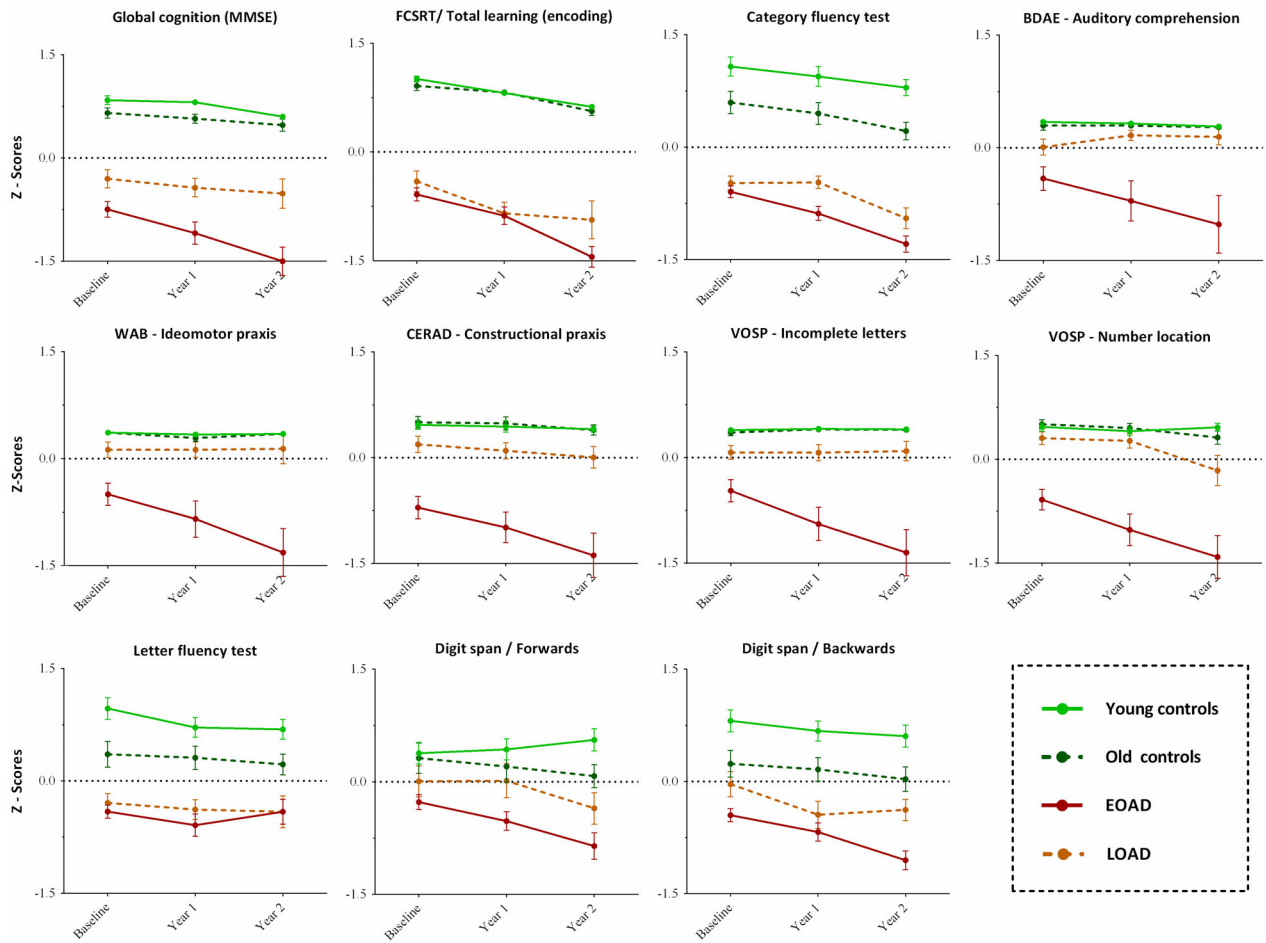
<sup>†</sup>Significantly different from LOAD ( $p < 0.05$ ).

( $\beta = 0.471$  [CI 95% (0.153–0.787)]  $p < 0.01$ ), and working memory ( $\beta = 0.416$  [CI 95% (0.136–0.695)]  $p < 0.01$ ). There were no differences on cognitive decline

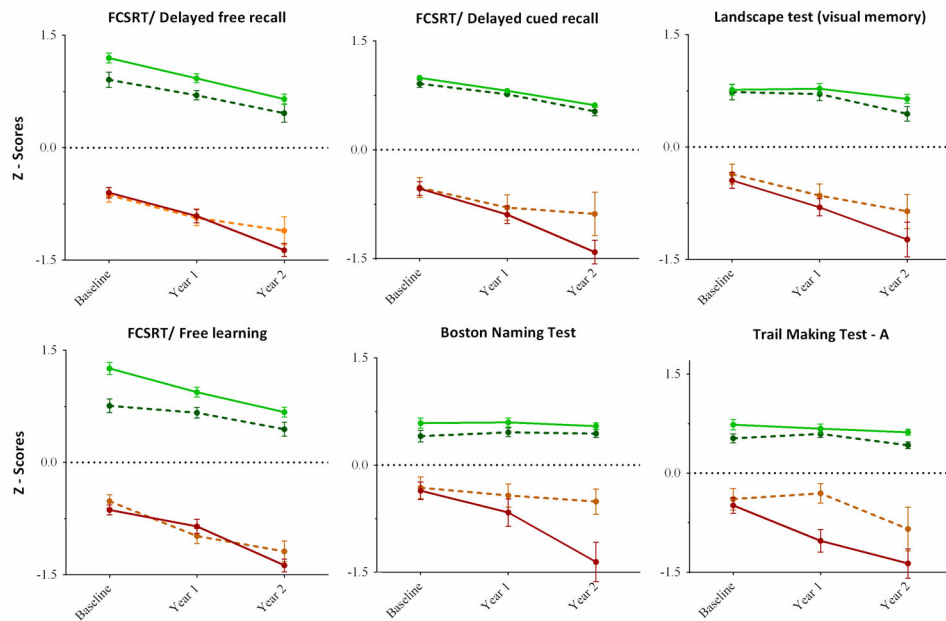
between EOAD and LOAD in verbal memory ( $\beta = 0.122$  [CI 95% (–0.090 to 0.335)]  $p = 0.26$  and  $\beta = 0.259$  [CI 95% (–0.036 to 0.554)]  $p = 0.08$  for delayed free and



**SIGNIFICANT EFFECT OF DIAGNOSIS (EOAD vs LOAD)**



**NON-SIGNIFICANT EFFECT OF DIAGNOSIS (EOAD vs LOAD)**



**Figure 2.** Neuropsychological progression of the study groups. MMSE, Mini-Mental State Examination; FCSRT, Free and Cued Selective Reminding Test; BDAE, Boston Diagnostic Aphasia Examination; WAB, Western Aphasia Battery; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; VOSP, Visual Object and Space Perception Battery. Error bars represent SEM. TMTA z-scores were inverted (sign change) for visualization purposes.

**Table 3.** Effects of diagnosis, years of education, and *APOE*  $\epsilon$ 4 genotype on longitudinal cognitive decline.

Function	Measure	Diagnosis (EOAD vs. LOAD)			Years of education			<i>APOE</i> $\epsilon$ 4 genotype		
		Coef.	(CI 95%)	<i>p</i>	Coef.	(CI 95%)	<i>p</i>	Coef.	(CI 95%)	<i>p</i>
Global	MMSE	0.653	(0.311–0.994)	**	0.067	(0.035–0.099)	**	0.009	(–0.300–0.320)	ns
Learning/ encoding	FCSRT/free learning	0.186	(–0.016 to 0.388)	ns	0.039	(0.020–0.058)	**	–0.236	(–0.418 to –0.054)	*
	FCSRT/Total learning	0.323	(0.027–0.618)	*	0.038	(0.011–0.066)	**	–0.402	(–0.668 to –0.137)	**
Memory	FCSRT/Delayed free recall	0.122	(–0.090 to 0.335)	ns	0.043	(0.023–0.063)	**	–0.245	(–0.436 to –0.054)	*
	FCSRT/Delayed total recall	0.259	(–0.036 to 0.554)	ns	0.043	(0.016–0.071)	**	–0.433	(–0.697 to –0.168)	**
Language	Landscape Test (visual memory)	0.283	(–0.028–0.594)	ns	0.057	(0.027–0.086)	**	–0.220	(–0.502–0.062)	ns
	Boston Naming Test	0.194	(–0.223 to 0.611)	ns	0.075	(0.037–0.113)	**	0.052	(–0.319–0.423)	ns
	Category fluency test	0.347	(0.114 to 0.581)	**	0.038	(0.016 to 0.059)	**	–0.043	(–0.253 to 0.167)	ns
Praxis	BDAE – Auditory comprehension	0.575	(0.077–1.07)	*	0.023	(–0.022 to 0.069)	ns	0.154	(–0.292 to 0.601)	ns
	WAB – Ideomotor praxis	0.718	(0.218–1.21)	**	0.029	(–0.016 to 0.075)	ns	0.242	(–0.205 to 0.689)	ns
Perception	CERAD – Constructional praxis	0.869	(0.422 to 1.31)	**	0.065	(0.019 to 0.110)	**	0.235	(–0.185 to 0.656)	ns
	VOSP – Incomplete letters	0.605	(0.130–1.08)	*	0.046	(0.003–0.090)	*	0.388	(–0.036–0.812)	ns
Attention and executive functions	VOSP – Number location	1.07	(0.633–1.51)	**	0.062	(0.021–0.103)	**	0.131	(–0.265 to 0.527)	ns
	Trail Making Test – A	–0.332	(–0.733 to 0.069)	ns	–0.059	(–0.096 to –0.022)	**	0.152	(–0.207 to 0.512)	ns
	Letter fluency test	0.382	(0.117 to 0.646)	**	0.071	(0.046–0.095)	**	0.104	(–0.134 to 0.343)	ns
	Digit span/forwards	0.471	(0.153–0.787)	**	0.083	(0.054–0.112)	**	0.156	(–128 to 0.440)	ns
	Digit span/backwards	0.416	(0.136–0.695)	**	0.065	(0.039–0.091)	**	0.183	(–0.067–0.433)	ns

Coef., coefficient; MMSE, Mini-Mental State Examination; FCSRT, Free and Cued Selective Reminding Test; BDAE; Boston Diagnostic Aphasia Examination; WAB; Western Aphasia Battery; CERAD; Consortium to Establish a Registry for Alzheimer's Disease; VOSP, Visual Object and Space Perception Battery.

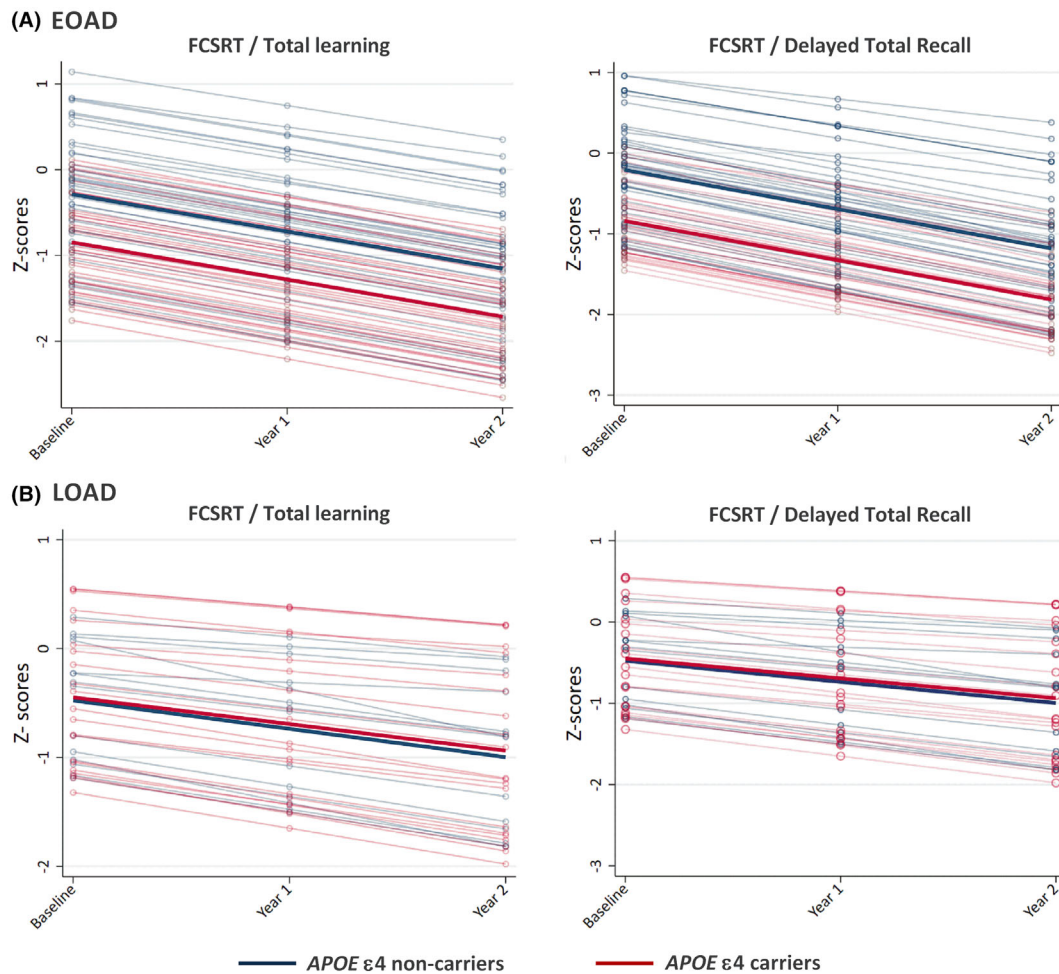
\* $p < 0.05$ ; \*\* $p < 0.01$ ; ns, nonsignificant.

delayed cued recall, respectively), visual memory ( $\beta = 0.283$  [CI 95% (–0.028 to 0.594)]  $p = 0.08$ ), the BNT ( $\beta = 0.194$  [CI 95% (–0.222 to 0.601)]  $p = 0.36$ ), and the TMT-A ( $\beta = –0.332$  [CI 95% (–0.734 to 0.069)]  $p = 0.11$ ).

The effect of years of education was significant on most of the neuropsychological tests. Interestingly, we found that the effect of *APOE*  $\epsilon$ 4 was only significant on learning ( $\beta = –0.236$  [CI 95% (–0.418 to –0.054)]  $p < 0.05$  and  $\beta = –0.402$  [CI 95% (–0.668 to –0.137)]  $p < 0.01$

for free and cued learning, respectively), and memory performance ( $\beta = –0.245$  [CI 95% (–0.436 to –0.054)]  $p < 0.05$  and  $\beta = –0.433$  [CI 95% (–0.697 to –0.168)]  $p < 0.01$  for delayed free and cued recall, respectively), while it had no effect on any of the non-amnesic domains (all  $p > 0.05$ ).

The sub-analyses on the effect of the *APOE* status within EOAD and LOAD groups showed that *APOE*  $\epsilon$ 4 status had a significant effect on learning ( $\beta = –0.536$  [CI 95% (–0.833 to –0.238)]  $p < 0.01$ , for EOAD and



**Figure 3.** Effect of the APOE genotype in memory decline. FCSRT, Free and Cued Selective Reminding Test.

$\beta = -0.0636$  [CI 95% ( $-0.589$  to  $0.461$ )]  $p = 0.812$ , for LOAD) and memory ( $\beta = -0.608$  [CI 95% ( $-0.904$  to  $-0.313$ )]  $p < 0.01$ , for EOAD and  $\beta = 0.001$  [CI 95% ( $-0.530$  to  $0.532$ )]  $p = 0.997$ , for LOAD) performance, with APOE  $\epsilon 4$  positivity contributing to lower outcomes only in the EOAD cohort (Fig. 3).

Compared with the young controls, old controls declined faster on global cognitive function ( $\beta = -0.210$  [CI 95% ( $-0.342$  to  $-0.078$ )]  $p < 0.01$ ), learning ( $\beta = -0.475$  [CI 95% ( $-0.708$  to  $-0.241$ )]  $p < 0.01$  and  $\beta = -0.208$  [CI 95% ( $-0.391$  to  $-0.0255$ )]  $p < 0.05$  for free and cued learning, respectively), and memory function ( $\beta = -0.379$  [CI 95% ( $-0.601$  to  $-0.156$ )]  $p < 0.01$  and  $\beta = -0.226$  [CI 95% ( $-0.385$  to  $-0.067$ )]  $p < 0.01$  for delayed free and cued recall, respectively), naming ( $\beta = -0.194$  [CI 95% ( $-0.384$  to  $-0.004$ )]  $p < 0.05$ ), and verbal fluency ( $\beta = -0.564$  [CI 95% ( $-0.915$  to  $-0.213$ )]  $p < 0.01$  and  $\beta = -0.525$  [CI 95% ( $-0.921$  to  $-0.128$ )]  $p < 0.01$  for CFT and LFT, respectively), psychomotor

speed ( $\beta = 0.172$  [CI 95% ( $0.003$  to  $0.342$ )]  $p < 0.05$ ), and working memory ( $\beta = -0.462$  [CI 95% ( $-0.840$  to  $-0.083$ )]  $p < 0.05$ ).

Again, the effect of years of education was significant on most of the neuropsychological tests. However, APOE  $\epsilon 4$  did not affect cognitive decline in any of the neuropsychological tests (all  $p > 0.05$ ). Trajectories of cognitive decline comparing EOAD and LOAD to their respective reference group are included as supplementary materials (Table S1 and S2).

## Discussion

We performed baseline and longitudinal outcomes of global and specific cognitive domains in a biomarker-based EOAD and LOAD cohort. The main findings of this study are the differential trajectories of cognitive decline observed between EOAD and LOAD patients. The deterioration of EOAD was more pronounced than LOAD in



the global outcomes due to the impairment of certain non-amnestic domains (i.e., visuospatial, praxis, and executive functions). In addition, we found that *APOE* status had a relevant influence on the amnestic domains' decline but not in the non-amnestic, specifically in EOAD patients.

The higher frequency of atypical patterns of cognitive impairment at the baseline evaluation in EOAD compared to LOAD is in concordance with prior literature.<sup>7,13,14,38</sup> While LOAD presented with memory impairment as the primary deficit, early-onset presentations also displayed difficulties in the visuospatial and executive domains. In our AD patients, younger age led to lower performances in all cognitive domains except memory and language. Indeed, higher differences were found in the non-amnestic domains (i.e., praxis and perception). Importantly, the cross-sectional differences observed between the EOAD and LOAD groups were not explained either by demographical variables such as sex or years of education or clinical aspects such as the time to diagnosis or functional status (CDR).

Beyond the differences at the baseline, the cognitive decline observed in AD patients was different when comparing early- and late-onset presentations. Our results indicate that there is a faster decline in the global cognitive performance in EOAD. This may be explained by the fact that EOAD displays a higher burden of tau and amyloid deposition than LOAD,<sup>39–41</sup> leading to more aggressive disease progression in the early-onset cases.<sup>42,43</sup> Our findings also align with the impression of a faster cognitive decline of EOAD patients in the clinical setting and prior literature reporting a worsening on global cognitive and functional outcomes in clinically diagnosed EOAD.<sup>11</sup> Here, it is important to note that, unlike most existing literature, the present study has been conducted on a biomarker-based cohort, thus increasing the possibility of only including in the analyses patients with evidence of AD pathophysiological process.

Our findings are in concordance with a recent autopsy study by Smirnov et al.<sup>44</sup> found that despite having less concomitant non-AD pathology, earlier age of onset in AD patients entails more significant global cognitive decline at the expense of executive and visuospatial domains. However, it is important to note that we did not explore non-AD pathology in the present study. Overall, the results suggest that cognitive heterogeneity may result from age-related differences in cortical tau-spread following a pattern of selective vulnerability rather than an effect of non-AD co-pathologies.<sup>44–46</sup> Our results showing specific trajectories of cognitive decline between EOAD and LOAD support these prior findings.

The faster rate of cognitive decline in EOAD is specially related to the impairment of specific non-amnestic

domains. Even though the trajectory of memory performance is similar in both LOAD and EOAD, the decline in language, visuospatial, and executive domains along the disease course are more pronounced in EOAD. The poor cognitive performance due to non-amnestic impairment in EOAD compared with LOAD aligns with the clinical heterogeneity of AD, being the atypical forms more predominant in early-onset presentations. Recent investigations pointed out a pattern of cortical selective vulnerability in the distribution of AD pathology within AD phenotypes. Non-amnestic presentations of AD are not only presenting higher cortical burden along with the disease progression, but there is also a syndrome-specific distribution of the tau-AD deposition and its consequent atrophy patterns.<sup>9,45</sup> Since the atypical variants are more common in EOAD, this phenotype-dependent spread pattern underlying atypical forms would explain the differential cognitive decline observed during the follow-up. The evidence of differential trajectories of EOAD and LOAD cognitive profiles along the disease course agrees with the cortical phenotype-related selective vulnerability at the initial stages and the disease progression.

An important consideration in EOAD studies is the arbitrarily established criterion used to classify AD patients as early- or late-onset cases (i.e., 65 years). This is particularly interesting since apparently there is no reason to establish this distinction at the age of 65, particularly from a biological point of view. This argument has been extensively discussed in the literature and there are studies addressing the possibility of using different cut-offs. For example, Palasí et al.<sup>13</sup> proposed an age cut-off of 70 years to better differentiate between early- and late-onset AD patients.

The age of onset was the main factor determining the cognitive trajectory in the different cognitive domains. Nevertheless, other factors such as cognitive reserve or *APOE* status may play a role. Our findings highlight years of education, a proxy of cognitive reserve, as a factor influencing transversely all cognitive areas both in healthy aging and AD. These results are relevant since EOAD samples could intrinsically have a higher educational level than LOAD at the group level. There were no statistically significant differences in terms of years of education between the young and old controls or between the EOAD and LOAD groups in our sample. However, the effect of this factor was significant in the cognitive trajectories of both populations. These results suggest that, beyond the age of onset, educational level/cognitive reserve's effect should constantly be considered when assessing cognitive progression in AD.

Although most AD cases are sporadic, they can carry risk polymorphisms such as *APOE*  $\epsilon 4$ . Since *APOE*  $\epsilon 4$  is the major genetic risk factor for sporadic AD, there is

increasing interest in determining how *APOE*  $\epsilon 4$  drives cognitive decline and whether it can influence the disease's clinical expression and progression. Prior studies analyzed the influence of *APOE* status in global cognitive and functional outcomes. Although there is certain evidence supporting a faster decline in those AD patients carrying *APOE*  $\epsilon 4$ , results between them are discordant, which might be explained by the use of different cognitive/functional measures and the use of non-biomarker confirmed cohorts.<sup>20,47</sup> Our findings support *APOE*  $\epsilon 4$  as a predictor determining patients' cognitive trajectories but specifically contributing to the decline of memory performance. A recent study analyzed longitudinally the interaction between *APOE* status and age of onset on the cognitive performance in a cohort of clinically diagnosed AD patients. The results showed that an *APOE*  $\epsilon 4$ -negative status could drive the decline of non-memory domains (i.e., language, executive function) in EOAD patients.<sup>21</sup> Interestingly, this complements the result observed in our cohort, where *APOE*  $\epsilon 4$  had a detrimental effect on the longitudinal performance of memory tasks, particularly in EOAD. Besides, this differential effect of *APOE*  $\epsilon 4$  on EOAD and LOAD's cognitive performance has been previously suggested. In a cross-sectional study, Marra et al.<sup>20</sup> reported lower baseline memory performances in EOAD *APOE*  $\epsilon 4$  carriers over non-carriers. Conversely, they found no differences between *APOE*  $\epsilon 4$  carriers and non-carriers in LOAD. Furthermore, a recent PET neuroimaging study enriched with early-onset and atypical AD phenotypes demonstrated an association between the presence of *APOE*  $\epsilon 4$  and an increased Flortaucipir-SUVR focal uptake in the medial temporal lobe, suggesting once again that *APOE* status could especially modulate memory-related cognitive impairment in AD.<sup>48</sup>

Conversely, in our cohort, the *APOE* status had no influence on the decline of neither memory nor non-memory cognitive domains in healthy adults. Taken together, our findings suggest that beyond the age of onset, *APOE* could drive in part the memory decline only once the symptom onset has started, having no remarkable effect in healthy aging.

The main strengths of this study are the well-characterization of the AD patients included in the cohort, being the diagnosis biomarker confirmed. Also, cognitive function was assessed through a comprehensive neuropsychological battery addressing the five cognitive domains instead of limiting the results to global cognitive and/or functional outcomes. Furthermore, we included two age-matched groups of healthy controls with negative AD CSF biomarkers, excluding the potential bias of pre-clinical participants with a comparing purpose.

As a relevant limitation, the small size of the sample and the proportion of patients not completing the follow-up sessions, particularly in year 2 due to disease progression and patients' enrollment on clinical trials, could hamper data interpretation and generalizability. Nevertheless, to the best of our knowledge, the present sample includes one of the largest reported cohorts of early-onset patients with a biomarker-based diagnosis and comprehensive neuropsychological characterization longitudinally. Other limitations are the reliability of obtaining first symptom at onset of the AD patients in a retrospective informant-reported way and the potential circularity of employing the same neuropsychological measures both as part of the participants' diagnosis and classification and as study outcomes. Finally, the use of years of education as a proxy of cognitive reserve instead of a more accurate measurement could potentially bias its effect in cognitive trajectories. However, the results obtained in this regard are congruent with prior literature.

In conclusion, age of onset is the main factor driving the neuropsychological profile at diagnosis and its longitudinal trajectories in AD. Younger ages of onset (i.e., EOAD) determine the worsening of non-memory domains. In addition, years of education and *APOE* status also contribute to shape this cognitive decline, leading the lower years of education a transversal decline in all domains, and the *APOE*  $\epsilon 4$  a specific decline in memory performance in EOAD. The present findings may have implications on the characterization and tracking of cognitive trajectories of early- and late-onset AD patients both in the clinical and research settings as well as for the design of future clinical trials. Future studies should include larger samples and also explore for non-AD pathology.

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## Conflict of Interest

The authors do not have any competing financial or non-financial interests related to the manuscript.

## Authors' Contributions

ATM, NF, RSV, and AL designed and conceptualized the study. IEA, ATM, NF, and AL analyzed and interpreted the data. ATM, JO, and MC had a major role in the acquisition of data. AT and NF wrote the initial manuscript. AL and RSV supervised and revised the work. All authors read and approved the final manuscript.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Effects of diagnosis, years of education, and APOE  $\epsilon 4$  genotype on longitudinal cognitive outcomes on EOAD vs young controls.

**Table S2.** Effects of diagnosis, years of education, and APOE  $\epsilon 4$  genotype on longitudinal cognitive outcomes on LOAD vs old controls.