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RESEARCH ARTICLE

Decreased practice effects in cognitively unimpaired amyloid betapositive individuals: a multicenter, longitudinal, cohort study

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Abstract

INTRODUCTION: We aimed to determine whether cognitively unimpaired (CU) amyloid- beta-positive (Aβ+) individuals display decreased practice effects on serial neuropsychological testing.

METHODS: We included 209 CU participants from three research centers, 157 Aβ– controls and 52 Aβ+ individuals. Participants underwent neuropsychological assessment at baseline and annually during a 2-year follow-up. We used linear mixed-effects models to analyze cognitive change over time between the two groups, including time from baseline, amyloid status, their interaction, age, sex, and years of education as fixed effects and the intercept and time as random effects.

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RESULTS: The Aβ+ group showed reduced practice effects in verbal learning ($\beta = -1.14$, SE = 0.40, $p = 0.0046$) and memory function ($\beta = -0.56$, SE = 0.19, $p = 0.0035$), as well as in language tasks ($\beta = -0.59$, SE = 0.19, $p = 0.0027$).
DISCUSSION: Individuals with normal cognition who are in the Alzheimer's continuum show decreased practice effects over annual neuropsychological testing. Our findings could have implications for the design and interpretation of primary prevention trials.

KEYWORDS
Alzheimer's disease, cognition, early detection, neuropsychological assessment, practice effects, subtle cognitive decline

Highlights

- This was a multicenter study on practice effects in asymptomatic Aβ+ individuals.
- We used LME models to analyze cognitive trajectories across multiple domains.
- Practice-effects reductions might be an indicator of subtle cognitive decline.
- Implications on clinical and research settings within the AD field are discussed.

1 | BACKGROUND

Early detection of Alzheimer's disease (AD), particularly in the asymptomatic stage when intervention holds the greatest promise, is a major challenge in the field. The comprehensive characterization of subtle changes in cognitive trajectories of cognitively unimpaired (CU) individuals with biological evidence of AD pathology is critical in order to track this population and will be of paramount importance for the interpretation of primary prevention trials on new disease-modifying therapies.

Practice effects are a well-known phenomenon referring to the improvement in performance on a cognitive task that occurs as a result of prior exposure or practice with that same task.[1–4] Practice effects have been extensively studied in normal aging and in cognitively impaired individuals. Several studies have reported that patients with mild cognitive impairment (MCI) and mild AD show practice-effects reductions.[5–9]

Practice effects have also been assessed in CU individuals at increased risk of developing AD.[10–15] The absence of practice effects in annual cognitive testing within the first 3 years of follow-up has been associated with the risk of progression to symptomatic stages of the disease.[10] More recently, Machulda et al. examined practice effects in 190 CU individuals with different biomarker profiles (ie, neuroimaging measures of amyloid and neurodegeneration) at 15- and 30-month intervals and found that those individuals with abnormal biomarkers of amyloid and neurodegeneration or neurodegeneration alone displayed worse performances when compared with individuals with no biomarker abnormalities or only amyloidosis.[12] Thus, some researchers have attempted to address several issues involving the identification, monitoring, and interpretation of practice effects in CU populations at risk of developing AD. However, further studies, particularly those involving international cohorts, are essential to expand the existing evidence and enhance the generalizability of these findings.

To fill this gap, we aimed to assess practice effects in a large sample of CU individuals recruited from three research centers to (1) explore longitudinal cognitive trajectories in terms of practice-related gains of cognitive function and (2) investigate whether CU individuals who are in the Alzheimer's continuum display reduced practice effects when compared with controls.

2 | METHODS

2.1 | Participants

We retrospectively included 209 CU individuals from three Spanish research centers (Figure 1): Hospital Clinic de Barcelona (HCB) and Hospital de la Santa Creu i Sant Pau (HSP) in Barcelona and Hospital Universitario Marqués de Valdecilla (HUMV) in Santander. All participants provided signed informed consent before enrolling in the different projects in accordance with the Declaration of Helsinki and met the following inclusion criteria: (a) age > 45 years and at least 3 years of formal education, (b) Mini-Mental State Examination (MMSE)[16] score > 24 and objective cognitive performance within the normal range (cutoff 1.5 standard deviations from normative mean) in the verbal memory measure (gold standard) from a specific neuropsychological battery (see below), (c) preserved daily functioning, assessed through either the Clinical Dementia Rating,[17] the Functional Activities Questionnaire,[18] or clinical criteria, (d) completion of baseline evaluation and procedures and two follow-up sessions, and (e) remained CU throughout whole study period. The following exclusion criteria were applied: (a) presence of any neurological diagnosis that may affect cognitive performance, (b) presence of a serious or unstable medical condition, and (c) diagnosis of a major psychiatric disorder including schizophrenia, major depression, or substance abuse. Participants were classified into the following groups:

1. Control group (n = 157): CU individuals with a normal AD cerebrospinal fluid (CSF) biomarker profile defined as normal levels of amyloid beta (Aβ) and phosphorylated tau (p-tau).
2. Aβ+ group (n = 52): CU individuals with reduced levels of CSF Aβ or abnormal CSF Aβ and p-tau.

Additionally, we explored the role of p-tau by dividing the Aβ+ group into two subgroups: individuals positive only for the amyloid biomarker (A+; n = 31) and those positive for both amyloid and p-tau (A+T+; n = 13).

2.2 | Study design

This was a multicenter, longitudinal, cohort study. The cohort included participants from different projects from HCB, HSP, and HUMV that shared the same design and procedures: a baseline visit including neurological and neuropsychological evaluation, blood sampling and CSF extraction, and two annual visits for neuropsychological assessment follow-up. Participants from HSP and HUMV were recruited as part of a multicenter study called "SIGNAL Project." Importantly for the present research, all participants completed the baseline visit and two follow-up sessions at years 1 (FU_1) and 2 (FU_2) from baseline.

2.3 | Neuropsychological assessment

All participants were assessed with a comprehensive neuropsychological battery encompassing five cognitive domains that was administered by trained neuropsychologists.

Learning and memory function were evaluated using the Free and Cued Selective Reminding Test (FCSRT).[19] From the FCSRT, we analyzed the free learning score (range 0 to 48), total learning score (0 to 48), delayed free recall (0 to 16), and delayed total recall (0 to 16). Recall of the constructional praxis subtest from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[20] (0 to 11) was used to assess visual memory. This specifically assesses the recall of previously drawn figures from the constructional praxis subtest. The language domain composed of the Boston Naming Test (BNT)[21] (0 to 60) and a category fluency test (CFT).[22] The praxis domain included the constructional praxis subtest from the CERAD battery[20] (0 to 11). Visuospatial function was measured by the number location subtest of the Visual Object and Space Perception (VOSP)

Research in context

1. **Systematic review**: We searched the literature (PubMed) for "practice effects" in (preclinical) AD. The absence or attenuation of practice effects in cognitively unimpaired (CU) individuals who are at risk of developing AD symptoms have been associated with risk of progression to clinical stages of the disease.
2. **Interpretation**: Our findings indicate that practice effects over serial neuropsychological testing are decreased in CU individuals with abnormal Aβ levels, suggesting that these reductions might be an indicator of subtle cognitive decline in the earliest phase of the Alzheimer's continuum.
3. **Future directions**: Further studies are needed to explore practical implications of the present findings for the design and interpretation of primary and secondary prevention trials on disease-modifying therapies.

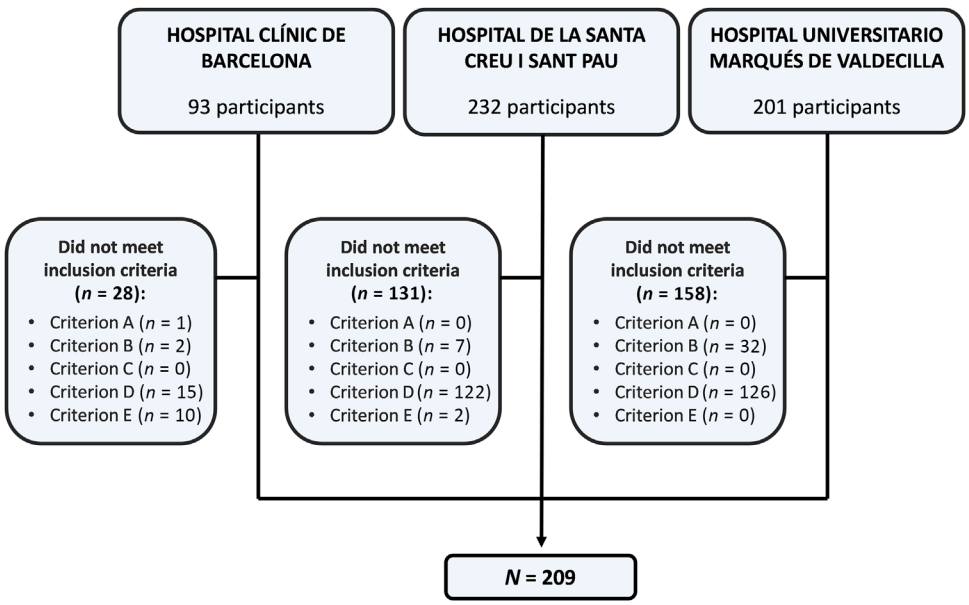

FIGURE 1 Sample composition flowchart.

battery[23] (0 to 10) (see specifications in the Supplementary Material). The attention and executive functions domain consisted of the Trail Making Test (TMT) – forms A and B[24] – and the digit span forward (attention span [0 to 9]) and backward (working memory [0 to 9]) subtests from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV).[25] Global cognition was assessed through the MMSE[16] (0 to 30). Importantly, participants completed the same neuropsychological assessment at baseline and in the follow-up visits in terms of test procedures, forms, and items employed.

2.4 | Determination of CSF biomarkers and apolipoprotein E (*APOE*) analysis

All participants underwent a lumbar puncture to analyze CSF AD biomarkers and blood extraction for *APOE* status determination following international consensus recommendations.[26] Individuals were then classified based on each center's cutoffs for the amyloid biomarker[27–29] (see details in the Supplementary Material). The three research centers participate in the Alzheimer's Association quality control program for CSF biomarkers.[30]

2.5 | Statistical analyses

Statistical analyses were conducted using R, version 4.2.1 (https://www.r-project.org).

Baseline characteristics by group are presented as means (standard deviation) or frequencies (percentages). Differences in demographics, clinical, and CSF data at baseline were analyzed by X^2 tests for categorical data and ANOVA for quantitative data. *APOE* ε4 status was dichotomized as negative/positive. Positive was defined as when at least one ε4 allele was present. Baseline neuropsychological performances were compared between controls and Aβ+ using analyses of covariance (ANCOVA) controlling for age and years of education.

For the longitudinal analyses, we used linear mixed-effects (LME) models to study the evolution of time according to the two groups (control vs Aβ+) at the three available time points. The fixed effects were time from baseline, amyloid status, amyloid status by time interaction, baseline age, sex, and years of education, and the random effects were the intercept and time (see equation in the Supplementary Material). Further longitudinal analyses using LME models, with the same fixed and random effects, were conducted to explore the role of p-tau (controls vs A+ vs A+T+). We applied Bonferroni corrections to account for multiple comparisons, ensuring stricter control of Type I errors across analyses.

3 | RESULTS

3.1 | Demographics, biological, and clinical data

Demographic, biological, and clinical data are reported in Table 1. The Aβ+ group was slightly older, had fewer years of education, and had a higher frequency of the *APOE* ε4 allele compared to the control group. There were no differences in sex distribution or MMSE scores. Frequency of CSF p-tau positivity among Aβ+ individuals was 25%.

TABLE 1 Demographic, biological, and clinical data among study groups.

	Control ($n = 157$)	Aβ+ ($n = 52$)	T	p
Sex (% women)	66.8%	69.2%	0.98[a]	0.75
Age	60.8 ± 7.5	64.6 ± 6.8	−3.24	0.001
Years of education	13.7 ± 4.4	12.1 ± 4.5	2.33	0.021
MMSE	28.9 ± 1.2	28.8 ± 1.1	0.53	0.59
***APOE* ε4 (% positive)**	18.4%	61.5%	35.05[a]	<0.001
p-tau positivity	3.1%	25%	−3.51	<0.001

Abbreviation: MMSE, Mini-Mental State Examination.
[a]χ^2 test.

3.2 | Cross-sectional neuropsychological performance among study groups

There were no cross-sectional differences between the control and Aβ+ groups in any of the neuropsychological scores at baseline or follow-up sessions. Baseline neuropsychological performance is shown in Figure 2 and Table 2. Cross-sectional neuropsychological performance at baseline and follow-up sessions are included in Table S1 and Figure S1.

3.3 | LME models

When comparing the results of the LME models for amyloid status by time interaction, the control group showed higher practice effects in learning and verbal memory measures, such as the free learning score ($\beta = -1.14$, SE = 0.40, $p = 0.0046$) and the delayed free recall ($\beta = -0.56$, SE = 0.19, $p = 0.0035$) from the FCSRT, as well as in language tasks (ie, BNT; $\beta = -0.59$, SE = 0.19, $p = 0.0027$). These results remained significant after applying Bonferroni corrections for multiple comparisons. See Table 3 for the LME model coefficients and Figure 3 for the plots for the significant variables of the model (see Figure S2 for the remaining plots).

3.3.1 | LME models on the effect of p-tau

Overall, the A+T+ group exhibited the lowest performance compared with controls and A+ participants. Regarding practice effects, the A+T+ group displayed lower slopes in free learning measures than both the control ($p < 0.001$) and the A+ ($p = 0.013$) groups. On the other hand, the A+ group showed lower slopes than the control group in the delayed free recall of the FCSRT ($p = 0.0021$) and in the BNT ($p = 0.0070$). Figure 4 shows the performance of these groups for the significant variables of the model. The remaining plots and the LME coefficients are also included in Figure S3 and Table S2.

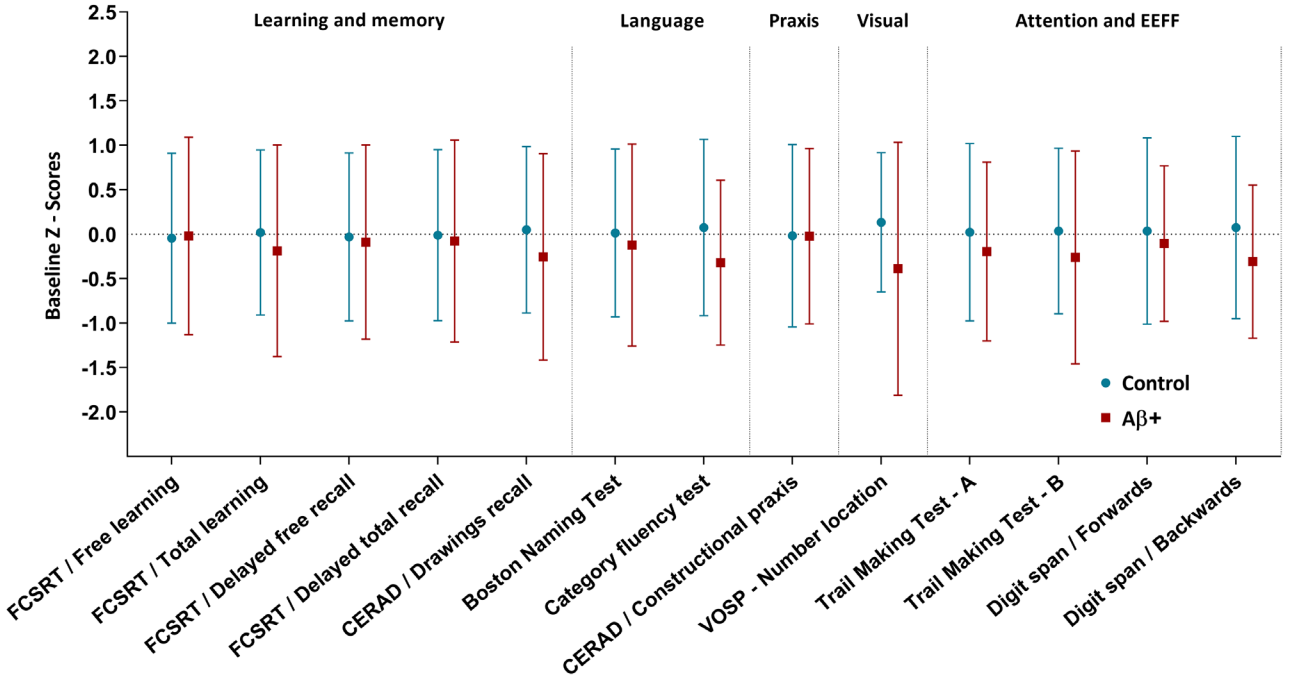

FIGURE 2 Baseline neuropsychological performance among the study groups. Data are presented in z-scores for visualization purposes to standardize performance across all tests and present them on a common scale (error bars represent SD). Trail Making Test scores are shown inverted. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FCSRT, Free and Cued Selective Reminding Test; VOSP, Visual Object and Space Perception Battery.

TABLE 2 Baseline neuropsychological performance among study groups.

Function	Measure	Control	Aβ+	*F*	*p*
Learning/encoding	FCSRT/free learning	26.8 ± 5.4	26.9 ± 6.3	2.292	0.13
	FCSRT/total learning	43.5 ± 3.7	42.7 ± 4.7	0.007	0.98
Verbal memory	FCSRT/delayed free recall	10.8 ± 2.1	10.7 ± 2.4	0.733	0.39
	FCSRT/delayed total recall	15.1 ± 1.1	15.0 ± 1.2	0.645	0.42
Visual memory	CERAD—drawings recall	9.4 ± 2.0	8.75 ± 2.4	0.847	0.36
Language	Boston Naming Test	54.1 ± 3.7	53.6 ± 4.5	0.483	0.49
	Category fluency test	21.5 ± 5.1	19.5 ± 4.7	1.36	0.24
Praxis	CERAD—constructional	10.6 ± 0.7	10.6 ± 0.7	0.895	0.35
Perception	VOSP—number location	9.4 ± 0.8	9.2 ± 0.9	2.58	0.11
Attention/executive functions	Trail Making Test—A	41.1 ± 18.2	45.1 ± 18.3	0.128	0.72
	Trail Making Test—B	90.4 ± 40.8	103.5 ± 52.5	0.106	0.75
	Digit span—forward	6.4 ± 1.8	6.1 ± 1.5	0.291	0.59
	Digit span—backward	4.8 ± 1.5	4.2 ± 1.2	2.551	0.11

Note: Data are presented as means ± standard deviation.
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FCSRT, Free and Cued Selective Reminding Test; VOSP, Visual Object and Space Perception Battery.

4 | DISCUSSION

In a large multicenter CU sample, individuals with evidence of Aβ pathology displayed reduced multidomain practice effects over annual neuropsychological testing compared with controls. The association found between amyloid deposition and the longitudinal decline of practice effects in CU individuals reinforces the need to consider this common cognitive phenomenon for the identification of individuals who are at increased risk of developing AD and in the design and interpretation of primary prevention trials of disease-modifying therapies.

Our study demonstrates that practice effects over annual neuropsychological testing are reduced in CU individuals with an abnormal Aβ biomarker. The higher differences in terms of performance gain

TABLE 3 Linear mixed-effects model coefficients.

	B	SE	*p*
FCSRT/Free learning			
Time	1.968	0.199	**<0.001**
Amyloid status	2.371	1.067	**0.027**
Age at baseline	−0.254	0.044	**<0.001**
Sex	2.604	0.668	**<0.001**
YOE	0.149	0.072	**0.039**
Time × amyloid status	−1.141	0.399	**0.0046**
FCSRT/total learning			
Time	0.885	0.135	**<0.001**
Amyloid status	−0.419	0.784	0.59
Age at baseline	−0.131	0.028	**<0.001**
Sex	0.670	0.428	0.12
YOE	0.072	0.046	0.12
Time × amyloid status	−0.068	0.271	0.80
FCSRT/delayed free recall			
Time	0.604	0.094	**<0.001**
Amyloid status	0.842	0.455	0.066
Age at baseline	−0.092	0.017	**<0.001**
Sex	0.814	0.256	**0.0017**
YOE	0.100	0.028	**<0.001**
Time × amyloid status	−0.556	0.188	**0.0035**
FCSRT/delayed total recall			
Time	0.209	0.049	**<0.001**
Amyloid status	0.268	0.245	0.27
Age at baseline	−0.033	0.008	**<0.001**
Sex	0.215	0.120	0.076
YOE	0.046	0.013	**<0.001**
Time × amyloid status	−0.168	0.098	0.088
CERAD—drawings recall			
Time	0.053	0.088	0.55
Amyloid status	0.073	0.422	0.86
Age at baseline	−0.072	0.016	<0.001
Sex	−0.129	0.245	0.60
YOE	0.060	0.026	0.023
Time × amyloid status	−0.163	0.174	0.35
Boston naming test			
Time	0.654	0.096	**<0.001**
Amyloid status	1.211	0.687	0.079
Age at baseline	−0.178	0.034	**<0.001**
Sex	−1.069	0.516	**0.040**
YOE	0.242	0.056	**<0.001**
Time × amyloid status	−0.587	0.193	**0.0027**
Category fluency test			
Time	−0.042	0.182	0.82
Amyloid status	−1.653	0.946	0.082
Age at baseline	−0.233	0.040	**<0.001**
Sex	0.082	0.611	0.89
YOE	0.156	0.066	**0.019**
Time × amyloid status	0.580	0.364	0.11
CERAD – constructional praxis			
Time	0.040	0.037	0.29
Amyloid status	0.283	0.167	0.091
Age at baseline	−0.013	0.006	**0.034**
Sex	−0.088	0.090	0.33
YOE	0.052	0.010	**<0.001**
Time × amyloid status	−0.095	0.074	0.20
VOSP—number location			
Time	−0.139	0.050	**0.0059**
Amyloid status	−0.212	0.200	0.29
Age at baseline	−0.012	0.007	0.099
Sex	−0.197	0.111	0.078
YOE	0.017	0.012	0.15
Time × amyloid status	0.008	0.100	0.94
Trail Making Test—A			
Time	−1.107	0.551	**0.046**
Amyloid status	−1.605	3.429	0.64
Age at baseline	0.818	0.119	**<0.001**
Sex	0.910	1.802	0.61
YOE	−0.893	0.194	**<0.001**
Time × amyloid status	1.479	1.117	0.19
Trail making test—B			
Time	−0.118	1.454	0.94
Amyloid status	−1.736	7.768	0.82
Age at baseline	2.531	0.346	**<0.001**
Sex	7.809	5.217	0.14
YOE	−2.386	0.593	**<0.001**
Time × amyloid status	2.140	3.018	0.48
Digit span – forward			
Time	−0.014	0.053	0.79
Amyloid status	−0.017	0.342	0.96
Age at baseline	−0.020	0.016	0.22
sex	−0.129	0.246	0.60
YOE	−0.006	0.027	0.82
Time × amyloid status	−0.021	0.109	0.85
Digit span – backward			
Time	0.083	0.053	0.12
Amyloid status	−0.316	0.279	0.26
Age at baseline	−0.028	0.013	**0.027**
Sex	−0.087	0.191	0.65
YOE	0.035	0.021	0.094
Time × amyloid status	0.099	0.108	0.36

Note: Linear mixed-effects model coefficients for cognitive trajectories by visit according to amyloid status. In bold, significant *p* values and variable names with time × amyloid status significant. The significance was set at $p < 0.05$.
Abbreviation: YOE, years of education.

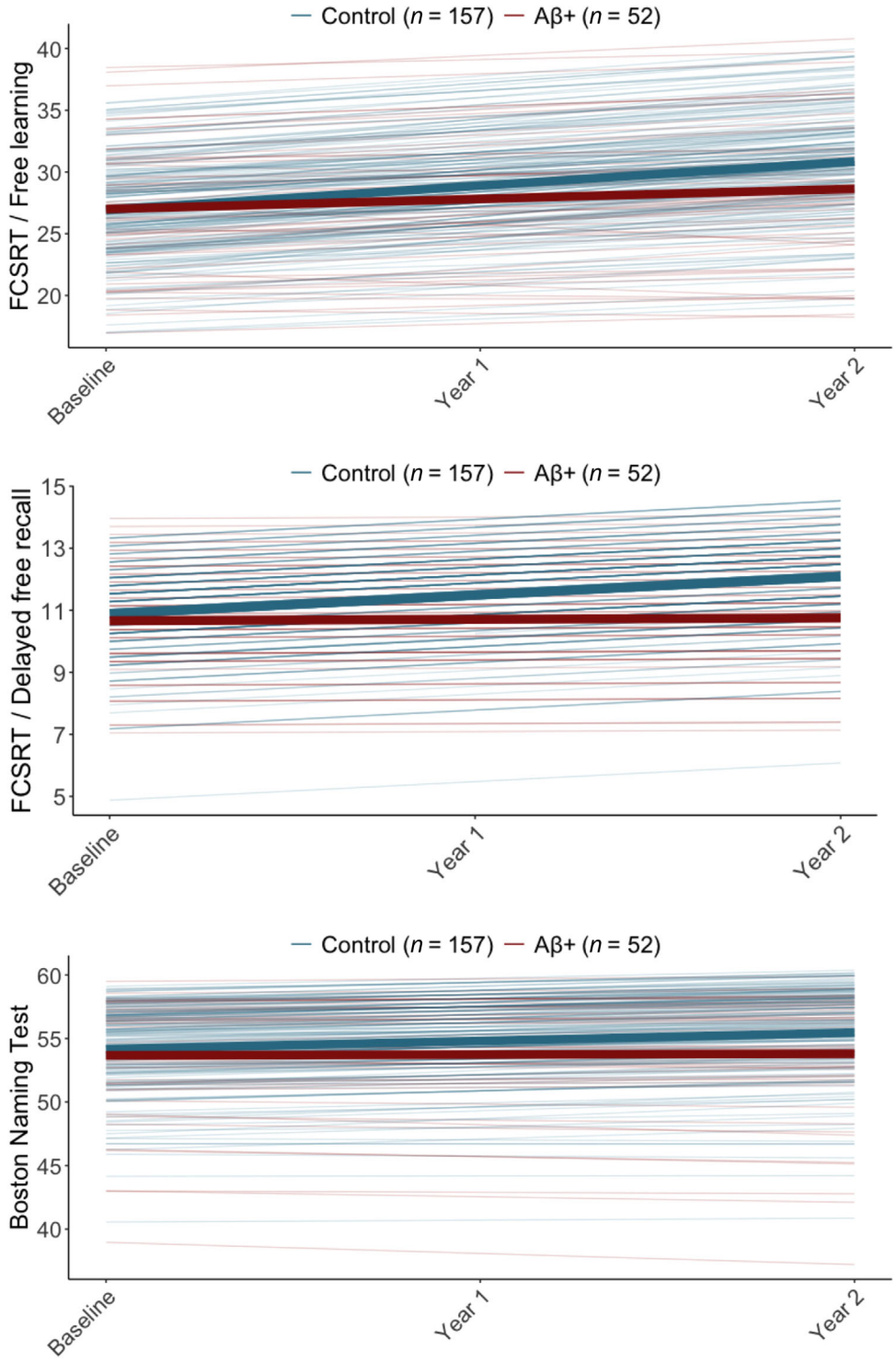

FIGURE 3 Linear mixed-effects model plots at individual and population levels. Linear mixed-effects model plot showing predicted population tendency (thick line) and predicted individual trajectories (thin line) according to amyloid status. Individual lines are lighter/darker depending on number of observations with the same results. FCSRT, Free and Cued Selective Reminding Test.

across the first three annual assessments were found in several verbal memory outcomes. The findings are in line with prior literature examining practice effects through serial neuropsychological testing in CU individuals with increased risk of developing AD, where memory measures are found to be particularly sensitive to these early cognitive changes.[8,10,13,14,31,32] Our results also align with recent studies highlighting the utility of computerized cognitive testing for detecting diminished practice effects in Aβ+ CU individuals.[33,34] We replicate and expand these previous works by showing that practice effects in verbal learning and memory measures are the most consistent in these

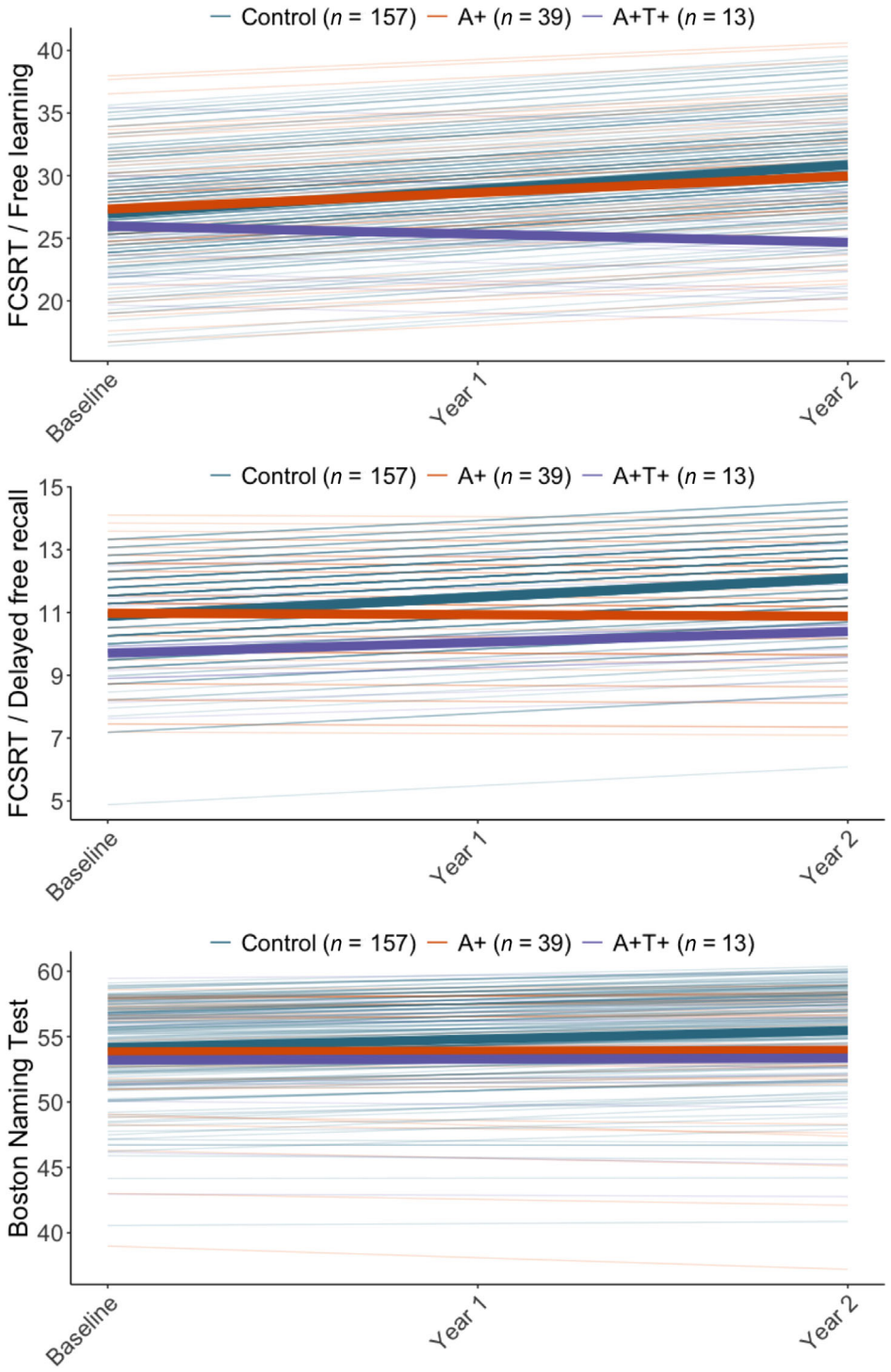

FIGURE 4 Linear mixed-effects models on effect of phosphorylated tau. Linear mixed-effects model plot showing predicted population tendency (thick line) and predicted individual trajectories (thin line) according to amyloid status. Individual lines are lighter/darker depending on number of observations with the same results. FCSRT, Free and Cued Selective Reminding Test.

populations and that other non-memory domains such as language or attention and executive functions could also play an important role. In this regard, a recent work developed standardized regression-based change norms across multiple cognitive tests. By accounting for the influence of practice effects, the study provides a clinically valuable tool to detect meaningful cognitive changes.[35]

Practice effects in non-memory domains over longitudinal cognitive assessments have also been reported.[8,12,15,36,37] In the present study, we found that the Aβ+ group performance on the BNT remained stable throughout the study period, while the control group showed an improvement over time. In normal aging, while there are functions such as memory, processing speed, and attention that show a clear

decline, other cognitive abilities such as vocabulary and general knowledge remain stable or even improve.[38,39] Given the expected stability of this function over time, naming performance could be considered an interesting variable when assessing practice effects as an indicator of subtle cognitive difficulties. Our results on the BNT are also in agreement with a clinicopathologic study,[36] where individuals without biological evidence of AD improved longitudinally on this measure while a group with AD neuropathologic characteristics did not. Taken together, our findings highlight the need to include comprehensive neuropsychological assessments when studying CU populations for the characterization and monitoring of the earliest cognitive changes in individuals who are at risk of developing AD.

A critical question in the field of AD is whether the presence of amyloidosis alone could drive to (subtle) cognitive dysfunction. Several studies have suggested that only the co-occurrence of amyloidosis and neurodegeneration accelerates cognitive decline in CU individuals.[40,41] However, some studies employing highly demanding neuropsychological measures or more sensitive methods have shown that it is possible to identify subtle difficulties in CU Aβ+ individuals, even at the cross-sectional level.[42–44] In the specific field of practice effects, Machulda et al. showed that individuals with both amyloidosis and neurodegeneration had worse cognitive trajectories at a 30-month follow-up than individuals with amyloidosis alone.[12] Conversely, in our cohort we found a reduction of practice effects in a group of Aβ+ individuals where the frequency of CSF p-tau positivity was only 25%. Furthermore, our additional analyses revealed that the group with amyloidosis alone continued to perform worse than the controls in delayed recall measures and naming tasks. However, given the small sample size of this subgroup, these findings should be interpreted with caution. Overall, considering the temporal evolution of AD biomarkers throughout the asymptomatic phase of the disease, where tau abnormalities are presented prior to neurodegeneration,[45] our results suggest that practice-effects reductions might be detected in the earliest stage of the AD continuum.

Moreover, neuropathological studies have established that tau pathology emerges in the earliest stages of AD, initially affecting small subcortical structures such as the locus coeruleus, even before reaching the entorhinal cortex.[46] This early involvement likely contributes to the onset of subtle neuropsychiatric and cognitive symptoms.[47–49] In line with this, our findings on the impact of p-tau on longitudinal cognitive trajectories revealed that the A+T+ group exhibited the poorest performance, particularly in the free learning measures. Therefore, the observed reduction in practice effects may not be solely due to amyloid deposition but could also be influenced by early tau pathology. This is particularly relevant given that tau pathology confined to these subcortical regions might be undetectable by traditional AD biomarkers. Supporting this view, recent studies[50–52] suggest that early locus coeruleus tau pathology could play a significant role in these subtle cognitive changes in asymptomatic stages.

This work has important implications not only in the clinical field but also within the framework of clinical trials and observational research. Recent studies point to the need to consider practice effects when establishing outcome measures in clinical trials.[53] It is important to emphasize that, while we assessed practice effects over annual neuropsychological testing, shorter time intervals may have even greater utility in this context. For example, Duff et al.[54] evaluated 1-week practice effects in a sample of non-demented, amyloid-positive individuals and proposed that measuring practice effects over such brief intervals could significantly improve participant selection for prevention trials. This approach highlights the potential for shorter-term assessments to enhance recruitment processes and identify at-risk individuals more effectively.

A report based on data from the Dominantly Inherited Alzheimer Network (DIAN) by Aschenbrenner et al.[55] explored the role of practice effects in AD prevention trials, presenting three key insights. First, practice effects were influenced by clinical status in CU individuals, with non-carriers of mutations showing better performance than carriers. Our findings are in line with these observations, suggesting that the rate of improvement over time might be an indicator of subtle cognitive changes also in sporadic presentations of the disease. Second, alternative forms and randomized stimuli in computerized measures reduced, though did not eliminate, practice effects, reflecting the impact of learning strategies. Lastly, cognitive trajectories were consistent between clinical trial and observational cohorts. Taken together, these results highlight the need to consider practice effects when statistically modeling cognitive endpoints in both clinical trials and observational studies.

Regarding the effect of sex on practice effects, we observed some variability across cognitive domains. While males were associated with lower practice effects in learning and memory measures, this pattern reversed for naming tasks. Notably, our findings are consistent with previous literature suggesting that women tend to perform better in verbal memory.[56] More specifically, a recent study showed that women outperformed men in the memory test employed in our study.[57] These results contribute to a better understanding of the role of sex in practice effects, with potential implications for the early detection of cognitive decline and the development of targeted intervention strategies.

Our work has some limitations. First, the multicentric nature of the study implies several constraints, such as variability in data collection (eg, order of test administration, inter-rater reliability). Regarding participants' characteristics, the Aβ+ group was slightly older and less educated than the controls. Also, the study design only included two longitudinal assessments, precluding the possibility of assessing practice effects trajectories beyond. However, previous evidence suggests that practice effects seem to be most pronounced during the first two retests.[10,58] We also acknowledge the potential limitation of using the same measure for both participant classification and as a study outcome, as this may introduce some circularity at baseline. Another important limitation is the potential ceiling effects observed in the constructional praxis and number location tests, which may have restricted our ability to fully assess practice effects within these measures. Finally, due to the small sample size of the A+T+ group, our analyses on the impact of p-tau on practice effects should be interpreted with caution.

In conclusion, our research provides important data on the study of practice effects in CU populations and has significant implications in both clinical and research settings within the AD field. We showed that individuals with normal cognition who are in the Alzheimer's continuum display decreased practice effects over annual neuropsychological testing compared to controls. Our findings suggest that the reduction of practice effects, particularly in memory measures, might be an indicator of early cognitive dysfunction in the earliest phase of the Alzheimer's continuum. Considering the influence of practice effects in cognitive trajectories is particularly relevant for the design and interpretation of primary prevention trials on disease-modifying therapies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in connection with this paper. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants included in the present study provided signed informed consent.

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REFERENCES

1. Dodge HH, Wang CN, Chang CCH, Ganguli M. Terminal decline and practice effects in older adults without dementia: the MoVIES project. *Neurology*. 2011;77(8):722-730. doi:10.1212/WNL.0b013e31822b0068
2. Duff K, Beglinger LJ, Moser DJ, Paulsen JS, Schultz SK, Arndt S. Predicting cognitive change in older adults: the relative contribution of practice effects. *Arch Clin Neuropsychol*. 2010;25(2):81-88. doi:10.1093/arclin/acp105
3. Wilson RS, Beckett LA, Bennett DA, Albert MS, Evans DA. Change in cognitive function in older persons from a community population: relation to age and Alzheimer disease. *Arch Neurol*. 1999;56(10):1274. doi:10.1001/archneur.56.10.1274
4. Wilson RS, Li Y, Bienias JL, Bennett DA. Cognitive decline in old age: separating retest effects from the effects of growing older. *Psychol Aging*. 2006;21(4):774-789. doi:10.1037/0882-7974.21.4.774
5. Cooper DB, Lacritz LH, Weiner MF, Rosenberg RN, Cullum CM. Category fluency in mild cognitive impairment: reduced effect of practice in test-retest conditions. *Alzheimer Dis Assoc Disord*. 2004;18(3):120. doi:10.1097/01.wad.0000127442.15689.92
6. Duff K, Lyketsos CG, Beglinger LJ, et al. Practice effects predict cognitive outcome in amnestic mild cognitive impairment. *Am J Geriatr Psychiatry*. 2011;19(11):932-939. doi:10.1097/JGP.0b013e318209dd3a
7. Duff K, Atkinson TJ, Suhrie KR, Dalley BCA, Schaefer SY, Hammers DB. Short-term practice effects in mild cognitive impairment: evaluating different methods of change. *J Clin Exp Neuropsychol*. 2017;39(4):396-407. doi:10.1080/13803395.2016.1230596
8. Machulda MM, Pankratz VS, Christianson TJ, et al. Practice effects and longitudinal cognitive change in normal aging vs. incident mild cognitive impairment and dementia in the Mayo Clinic study of aging. *Clin Neuropsychol*. 2013;27(8):1247-1264. doi:10.1080/13854046.2013.836567
9. Zehnder AE, Bläsi S, Berres M, Spiegel R, Monsch AU. Lack of Practice Effects on Neuropsychological Tests as Early Cognitive Markers of Alzheimer Disease?. *Am J Alzheimer's Dis Dement*. 2007;22(5):416-426.
10. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. *Neuropsychology*. 2015;29(6):940-948. doi:https://doi.org/10.1037/neu0000208
11. Ihara R, Iwata A, Suzuki K, Ikeuchi T, Kuwano R, Iwatsubo T. Clinical and cognitive characteristics of preclinical Alzheimer's disease in the Japanese Alzheimer's Disease Neuroimaging Initiative cohort. *Alzheimers Dement Transl Res Clin Interv*. 2018;4:645-651. doi:10.1016/j.trci.2018.10.004
12. Machulda MM, Hagen CE, Wiste HJ, et al. Practice effects and longitudinal cognitive change in clinically normal older adults differ by Alzheimer imaging biomarker status. *Clin Neuropsychol*. 2017;31(1):99-117. doi:10.1080/13854046.2016.1241303
13. Oltra-Cucarella J, Sánchez-SanSegundo M, Ferrer-Cascales R. Predicting Alzheimer's disease with practice effects, *APOE* genotype, and brain metabolism. *Neurobiol Aging*. 2018;71:234-240. doi:10.1016/j.neurobiolaging.2018.08.004. Cognition or genetics?.
14. Samaroo A, Amariglio RE, Burnham S, et al. Diminished Learning Over Repeated Exposures (LORE) in preclinical Alzheimer's disease. *Alzheimers Dement Diagn Assess Dis Monit*. 2020;12(1):1-10. doi:10.1002/dad2.12132
15. Sánchez-Benavides G, Gispert JD, Fauria K, Molinuevo JL, Gramunt N. Modeling practice effects in healthy middle-aged participants of the Alzheimer and Families parent cohort. *Alzheimers Dement Diagn Assess Dis Monit*. 2016;4:149-158. doi:10.1016/j.dadm.2016.07.001
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
17. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414. doi:10.1212/wnl.43.11.2412-a
18. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *Journal of Gerontology*. 1982;37(3):323-329.
19. Grober E, Buschke H. Genuine Memory Deficits in Dementia. *Dev Neuropsychol—Dev NEUROPSYCHOL*. 1987;3:13-36. doi:10.1080/87565648709540361
20. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165. doi:10.1212/WNL.39.9.1159

21. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. Lea&Febiger; 2001. Accessed May 25, 2023. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft27208-000
22. Roth C. Boston Diagnostic Aphasia Examination. *Encyclopedia of Clinical Neuropsychology*. Pearson Canada Assessment Inc; 2011:428-430. doi:10.1007/978-0-387-79948-3_868
23. Warrington E, James M. In: St Edmunds B, ed. *Visual Object and Space Perception Battery (VOSP)*. Thames Valley Test Co; 1991.
24. Reitan R. *Neuropsychological Test Battery: Theory and Clinical Interpretation*. Neuropsychology Press; 1985.
25. Wechsler D. *Wechsler Adult Intelligence Scale: Fourth Edition (WAIS-IV)*. Pearson; 2008.
26. Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study. *Alzheimers Dement*. 2016;12(2):154-163. doi:10.1016/j.jalz.2015.08.003
27. Alcolea D, Clarimón J, Carmona-Iragui M, et al. The Sant Pau Initiative on Neurodegeneration (SPIN) cohort: a data set for biomarker discovery and validation in neurodegenerative disorders. *Alzheimers Dement*. 2019;5:597-609. doi:10.1016/j.trci.2019.09.005
28. Antonell A, Tort-Merino A, Ríos J, et al. axonal damage and inflammatory CSF biomarkers in neurodegenerative dementias. *Alzheimer's Dement*. 2019;16(2):262-272. doi:10.1016/j.jalz.2019.09.001
29. Illán-Gala I, Pegueroles J, Montal V, et al. Challenges associated with biomarker-based classification systems for Alzheimer's disease. *Alzheimer's Dement*. 2018;10:346-357. doi:10.1016/j.dadm.2018.03.004
30. Mattsson N, Andreasson U, Persson S, et al. CSF biomarker variability in the Alzheimer's Association quality control program. *Alzheimers Dement*. 2013;9(3):251-261. doi:10.1016/j.jalz.2013.01.010
31. Lim YY, Baker JE, Mills A, et al. Learning deficit in cognitively normal *APOE ε*4 carriers with LOW *β*-amyloid. *Alzheimers Dement Diagn Assess Dis Monit*. 2021;13(1):e12136. doi:10.1002/dad2.12136
32. Papp KV, Jutten RJ, Soberanes D, et al. Early detection of amyloid-related changes in memory among cognitively unimpaired older adults with daily digital testing. *Ann Neurol*. 2024;95(3):507-517. doi:10.1002/ana.26833
33. Young CB, Mormino EC, Poston KL, et al. Computerized cognitive practice effects in relation to amyloid and tau in preclinical Alzheimer's disease: results from a multi-site cohort. *Alzheimers Dement*. 2023;15(1):e12414. doi:10.1002/dad2.12414. Published 2023 Mar 20.
34. Jutten RJ, Rentz DM, Fu JF, et al. Monthly at-home computerized cognitive testing to detect diminished practice effects in preclinical Alzheimer's disease. *Front Aging Neurosci*. 2022;13:800126. doi:10.3389/fnagi.2021.800126. Published 2022 Jan 13.
35. Eliassen IV, Kirsebom BE, Fladby T, et al. Regression-based cognitive change norms applied in biochemically defined predementia Alzheimer's disease. *Neuropsychology*. 2023;37(1):32-43. doi:10.1037/neu0000853
36. Galvin JE, Powlishta KK, Wilkins K, et al. Predictors of preclinical Alzheimer disease and dementia: a clinicopathologic study. *Arch Neurol*. 2005;62(5):758-765. doi:10.1001/archneur.62.5.758
37. Jutten RJ, Grandoit E, Foldi NS, et al. Lower practice effects as a marker of cognitive performance and dementia risk: a literature review. *Alzheimers Dement Diagn Assess Dis Monit*. 2020;12(1):e12055. doi:10.1002/dad2.12055
38. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog Neurobiol*. 2014;117:20-40. doi:10.1016/j.pneurobio.2014.02.004
39. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013;29(4):737-752. doi:10.1016/j.cger.2013.07.002
40. Mormino EC, Betensky RA, Hedden T, et al. Synergistic effect of *β*-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurol*. 2014;71(11):1379-1385. doi:10.1001/jamaneurol.2014.2031
41. Soldan A, Pettigrew C, Cai Q, et al. Hypothetical preclinical Alzheimer disease groups and longitudinal cognitive change. *JAMA Neurol*. 2016;73(6):698-705. doi:10.1001/jamaneurol.2016.0194
42. Papp KV, Amariglio RE, Mormino EC, et al. Free and cued memory in relation to biomarker-defined abnormalities in clinically normal older adults and those at risk for Alzheimer's disease. *Neuropsychologia*. 2015;73:169-175. doi:10.1016/j.neuropsychologia.2015.04.034
43. Tort-Merino A, Valech N, Peñaloza C, et al. Early detection of learning difficulties when confronted with novel information in preclinical Alzheimer's disease stage 1. *J Alzheimers Dis*. 2017;58(3):855-870. doi:https://doi.org
44. Rubio-Guerra S, Sánchez-Saudinós MB, Sala I, et al. Added value of neuropsychological norms derived from amyloid-negative cognitively normal adults. In preparation.
45. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128. doi:10.1016/S1474-4422(09)70299-6
46. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70(11):960-969. doi:10.1097/NEN.0b013e318232a379
47. Ehrenberg AJ, Suemoto CK, EP FrançaResende, et al. Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis*. 2018;66(1):115-126. doi:10.3233/JAD-180688
48. Falgàs N, Peña-González M, Val-Guardiola A, et al. Locus coeruleus integrity and neuropsychiatric symptoms in a cohort of early- and late-onset Alzheimer's disease. *Alzheimers Dement*. 2024;20(9):6351-6364. doi:10.1002/alz.14131
49. Jacobs HIL, Riphagen JM, Ramakers IHGB, Verhey FRJ. Alzheimer's disease pathology: pathways between central norepinephrine activity, memory, and neuropsychiatric symptoms. *Mol Psychiatry*. 2021;26(3):897-906. doi:10.1038/s41380-019-0437-x
50. Jacobs HIL, Becker JA, Kwong K, et al. Waning locus coeruleus integrity precedes cortical tau accrual in preclinical autosomal dominant Alzheimer's disease. *Alzheimers Dement*. 2023;19(1):169-180. doi:10.1002/alz.12656
51. Prokopiou PC, Engels-Domínguez N, Schultz AP, et al. Association of novelty-related locus coeruleus function with entorhinal tau deposition and memory decline in preclinical Alzheimer disease. *Neurology*. 2023;101(12):e1206-e1217. doi:10.1212/WNL.0000000000207646
52. Pahl J, Prokopiou PC, Bueichekú E, et al. Locus coeruleus integrity and left frontoparietal connectivity provide resilience against attentional decline in preclinical Alzheimer's disease. *Alzheimers Res Ther*. 2024;16(1):119. doi:10.1186/s13195-024-01485-w
53. Jutten RJ, Papp KV, Hendrix S, et al. Why a clinical trial is as good as its outcome measure: a framework for the selection and use of cognitive outcome measures for clinical trials of Alzheimer's disease. *Alzheimers Dement*. 2023;19(2):708-720. doi:10.1002/alz.12773
54. Duff K, Hammers DB, Dalley BCA, et al. Short-term practice effects and amyloid deposition: providing information above and beyond baseline cognition. *J Prev Alzheimers Dis*. 2017;4(2):87-92. doi:10.14283/jpad.2017.9
55. Aschenbrenner AJ, Hassenstab J, Wang G, et al. Avoid or embrace? Practice effects in Alzheimer's disease prevention trials. *Front Aging Neurosci*. 2022;14(June):1-11. doi:10.3389/fnagi.2022.883131
56. Asperholm M, Högman N, Rafi J, Herlitz A. What did you do yesterday? A meta-analysis of sex differences in episodic memory. *Psychol Bull*. 2019;145(8):785-821. doi:10.1037/bul0000197
57. Brugulat-Serrat A, Cañas-Martínez A, Canals-Gispert L, et al. Enhancing the sensitivity of memory tests: reference data for the free and cued selective reminding test and the logical memory task from cognitively healthy subjects with normal Alzheimer's disease cerebrospinal

fluid biomarker levels. *J Alzheimers Dis*. 2021;84(1):119-128. doi:10.3233/JAD-210640

58. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. *Clin Neuropsychol*. 2012;26(4):543-570. doi:10.1080/13854046.2012.680913

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