Received: 4 March 2021 | Accepted: 21 March 2021

DOI: 10.1002/gps.5539

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Accelerated long-term forgetting in individuals with subjective cognitive decline and amyloid-β positivity

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Funding information

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Abstract

Objectives: We studied a sample of cognitively unimpaired individuals, with and without subjective cognitive decline (SCD), in order to investigate accelerated long-term forgetting (ALF) and to explore the relationships between objective and subjective cognitive performance and cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers.

Methods: Fifty-two individuals were included and SCD was quantified through the Subjective Cognitive Decline Questionnaire (SCD-Q), using its validated cutoff to classify participants as Low SCD-Q ($n = 21$) or High SCD-Q ($n = 31$). These groups were further subdivided according to the presence or absence of abnormal levels of CSF $A\beta_{42}$. Objective cognitive performance was assessed with the Ancient Farming Equipment Test (AFE-T), a new highly-demanding test that calls for acquisition and retention of novel object/name pairs and allows measuring ALF over a 6-month period.

Results: The High SCD-Q group showed a significantly higher free forgetting rate at 3 months compared to the Low SCD-Q (F [1,44] = 4.72; $p < 0.05$). When stratifying by amyloid status, High SCD-Q/Aβ+ showed a significantly lower performance than High SCD-Q/Aβ−on the final free and cued learning scores (F [1,27] = 6.44, $p < 0.05$ and F [1,27] = 7.51, $p < 0.05$, respectively), the 1-week free and cued recall (F [1,24] = 4.49; $p < 0.05$ and F [1,24] = 7.10; $p < 0.01$, respectively), the 1-week cued forgetting rate (F [1,24] = 5.13; $p < 0.05$), and the 3-month cued recall (F [1,24] = 4.27; $p < 0.05$). Linear regression analyses showed that higher SCD-Q scores were associated with higher forgetting rates on the AFE-T ($\beta = -0.212$; $p < 0.05$).

Conclusions: It is possible to detect ALF in individuals with high SCD ratings, appearing especially in those with abnormal CSF $A\beta_{42}$ levels. Both in research and the clinical field, there is an increasing need of using more demanding cognitive

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measures, such as the AFE-T, for identifying and tracking the earliest cognitive changes in these populations.

KEYWORDS
accelerated long-term forgetting, biomarkers, early detection, memory, subjective cognitive decline

Key Points

- We assessed accelerated long-term forgetting (ALF) in subjective cognitive decline (SCD)
- We found ALF over 3 months in individuals with high SCD ratings
- Individuals with high SCD ratings and abnormal Aβ42 levels displayed higher forgetting rates
- ALF might be a potential marker of subtle cognitive dysfunction in the AD continuum

1 | INTRODUCTION

Subjective cognitive decline (SCD), defined as a self-experienced impairment of cognitive abilities in otherwise cognitively unimpaired individuals, has been suggested to represent an early symptomatic manifestation in Alzheimer's disease (AD). The identification of subtle cognitive difficulties in cognitively unimpaired individuals within the AD continuum is critical for predicting progression towards later clinical stages. However, given that (by definition) individuals with SCD perform within the normal age-, gender-, and education-adjusted range on standardized cognitive tests, it seems mandatory to use more sensitive cognitive measures in order to detect the earliest changes in cognition in this population.

The preclinical stage of the Alzheimer's continuum is the earliest stage of AD and begins up to 15–20 years before the onset of an objective cognitive impairment. In this period, amyloid plaques and neurofibrillary tangles deposits begin to accumulate in the brain of asymptomatic individuals. The implementation of cerebrospinal fluid (CSF) biomarkers (e.g., $A\beta_{42}$ and p-tau) as indirect measures of these neuropathological processes allows the identification and study of this population. In recent studies, we have employed a new highly demanding cognitive test (the Ancient Farming Equipment Test; AFE-T) in order to study accelerated long-term forgetting (ALF) in cognitively unimpaired at-risk individuals.[1,2] The concept of ALF—defined as a loss of information over days or weeks despite normal acquisition—has recently emerged in the field of neurodegenerative diseases as a cognitive marker for the presymptomatic stages of AD.[3,4] To date, the AFE paradigm has been used to study acquisition of new words in groups of healthy adults[5,6] and in mild cognitive impairment (MCI) and AD patients.[7,8] The task engages the declarative memory system by requiring associative learning of previously unknown names and objects. Its comprehensive design allows the analysis of learning curves with free and cued recall measures, as well as free and cued long-term forgetting rates at one week, three months and six months. In a recent study, we employed the AFE-T to detect subtle cognitive difficulties in the preclinical stage of the Alzheimer's continuum. The AFE-T was found to be a promising tool for characterizing the cognitive profile of preclinical AD and sensitive enough to detect learning difficulties and ALF in this population.[2]

The concept of SCD includes two main features: (1) the self-experienced persistent decline of the cognitive function when compared with a previously normal status that is unrelated to an acute event and (2) the normal performance on standardized cognitive tests used for classifying MCI.[9] In the last years, several studies have suggested that SCD may represent an indicator of future cognitive decline,[10] particularly in cognitively unimpaired populations within the Alzheimer's continuum.[11,12] Also, it is important to note that SCD studies are significantly influenced by many factors such as the recruitment setting (i.e., epidemiological, memory clinic, research), the threshold used to determine cognitive normality, and/or the way of assessing and quantifying the cognitive concerns.[13] Regarding the latter, following the Subjective Cognitive Decline Initiative (SCD-I) guidelines[9] we recently developed and validated the Subjective Cognitive Decline Questionnaire (SCD-Q). The SCD-Q has emerged as a potential tool for measuring SCD. In contrast to the pre-existing questionnaires, the SCD-Q explores the perception of decline, as opposed to impairment, in a relatively short period of time (i.e., last 2 years), exploring the self-perceived performance in daily life activities that involve multiple cognitive domains. The questionnaire has been validated, showing high convergent validity, internal consistency, and discriminant power to distinguish between individuals with cognitive impairment and those without.[14] In a previous work, we employed the SCD-Q in cognitively unimpaired individuals within the Alzheimer's continuum, showing a correlation between SCD-Q scores and CSF AD biomarkers.[15] At the same time, our results have shown high specificity to the preclinical stage of the AD continuum of the SCD-Q items related with language and executive decline.[16] Finally, in a recent work, we explored the associations between gray matter volumes and the SCD-Q scores in a sample of cognitively healthy older adults. Those results suggested that the SCD-Q is related to incipient brain changes that may be due to preclinical AD.[17]

We explored ALF in cognitively unimpaired participants as a function of the SCD-Q scores. We also aimed to investigate the relationships between subjective and objective cognitive performance considering relevant factors such as AD CSF biomarker levels. We hypothesized that the AFE-T could be highly sensitive to detect possible subtle learning and retention difficulties that would otherwise go undetected by standard neuropsychological tests. We also expected to find more difficulties in individuals with higher SCD-Q scores and Aβ positivity.

2 | METHODS

2.1 | Participants

Fifty-two cognitively unimpaired individuals aged 50 or above were included. The participants were recruited from ongoing longitudinal projects at three Spanish memory centers: Hospital Clinic (n = 43) and Hospital de la Santa Creu i Sant Pau (n = 2) in Barcelona, and the CITA-Alzheimer Foundation (n = 7) in San Sebastian. The ethics committee of the Hospital Clinic of Barcelona approved the study, and all participants provided a signed, informed consent. All participants underwent a neuropsychological assessment, MRI and a lumbar puncture and had to meet the following inclusion criteria: (a) at least 3 years of formal education, (b) Mini-Mental State Examination (MMSE[18]; score > 24, and (c) scores within the normal range (cutoff 1.5 SD from normative mean[19]; in the total recall and delayed total recall scores from the Free and Cued Selective Reminding Test (FCSRT).[20] The following exclusion criteria were applied: (a) presence of any neurological diagnosis, (b) presence of a serious medical condition that could affect cognition, (c) diagnosis of a major psychiatric disorder including schizophrenia, major depression or substance abuse.

According to the SCD-Q cutoffs established by Rami et al.[14] the participants were classified as: (1) Low SCD-Q (n = 21): participants with a SCD-Q score < 7, or 2) High SCD-Q (n = 31): participants with a SCD-Q score ≥ 7. Following the NIA-AA recommendations,[21] the participants with high SCD-Q scores were further classified into: (1) Low SCD-Q with normal CSF $A\beta_{42}$ levels (Low SCD-Q/Aβ−; n = 15), (2) Low SCD-Q with Alzheimer's pathologic change (i.e., positive CSF $A\beta_{42}$ levels; Low SCD-Q/Aβ+; n = 6), (3) High SCD-Q with normal CSF $A\beta_{42}$ levels (High SCD-Q/Aβ−; n = 21) and (4) High SCD-Q with Alzheimer's pathologic change (High SCD-Q/Aβ+; n = 10).

2.2 | Determination of biological and AD CSF biomarkers

All participants underwent a lumbar puncture between 9 AM and 12 PM to collect 10 ml of CSF. The samples were centrifuged and stored in polypropylene tubes at −80°C within the first hour after extraction. CSF $A\beta_{42}$ levels, tau and p-tau were measured by enzyme-linked immunosorbent assay kits (Innogenetics). Cut-off values of abnormality for each AD CSF biomarker were defined according to previous work:[2] (a) Aβ42 ≤ 550 pg/ml, (b) tau≥400 pg/ml for participants between 50 and 70 years old, and ≥450 pg/ml for individuals older than 70 years, and (c) p-tau≥75 pg/ml. The AFE-T administrator and the participants were blind to CSF results.

2.3 | Apolipoprotein E analysis

Genomic DNA was extracted from peripheral blood of probands using the QIAamp DNAblood minikit (Qiagen AG). *APOE* genotyping was performed by polymerase chain reaction amplification and HhaI restriction enzyme digestion.

2.4 | Neuropsychological assessment

All participants were assessed both at the baseline and at the follow-up session with a comprehensive neuropsychological battery, administered by a trained neuropsychologist blind to the CSF results. The battery encompassed five cognitive domains. The memory domain included the free recall and delayed free recall scores from the FCSRT[20] and the constructional praxis recall subtest from the Consortium to Establish a Registry for Alzheimer' disease (CERAD) battery;[22] the language domain comprised of the Boston Naming Test[23] and a Category Fluency Task;[24] the praxis domain included the constructional praxis subtest from the CERAD battery;[22] the visual perception domain contained the Letters and Number Location subtests from the Visual Object and Space Perception (VOSP) battery;[25] the executive functions domain consisted of the Trail Making Test—Form A,[26] the Stroop Test,[27] the Symbol Digit Modalities Test,[28] and a Letter Fluency Task.[29] Global cognition was assessed with the MMSE.[18] Premorbid intelligence was measured through the Spanish Word Accentuation Test.[30]

2.5 | The Subjective Cognitive Decline Questionnaire

The SCD-Q is a self-administered, validated questionnaire that follows the SCD-I framework for research of SCD in preclinical AD.[9] It assesses perceived SCD by asking participants whether their present performance in daily tasks is now worse than two years ago. The questionnaire includes 24 items assessing perceived decline in instrumental activities of daily living that include memory, language, and executive tasks. Participants must answer if they believe to be performing these activities worse than roughly two years ago, in a Yes/No format (e.g., "I find it harder to remember doctor's appointments" or "I find it harder touse electronic devices"). The total score is computed from the 24 items (Yes = 1, No = 0), with higher scores indicating greater perceived cognitive decline. For more details, see Rami et al.[14] All participants in the study filled out the SCD-Q. The

average time lapse between the SCD-Q data collection and the AFE-T administration was 1.7 ± 0.3 months.

2.6 | The Ancient Farming Equipment Test

The AFE-T requests participants to learn a list of new-object/name pairs. The objects were 24 black-and-white images of non-familiar or unknown objects, taken from the picture pool of the Ancient Farming Equipment paradigm.[31] Each object was paired with a new-word (a non-existing word that follows the phonotactic rules of Spanish.[32] The object names consisted of 14 bisyllabic and 10 trisyllabic pseudowords. All stimuli were presented on a computer screen against a white background using the E-prime 2.0 version (Psychology Software Tools, Inc.).

2.6.1 | AFE-T administration procedure

Learning phase

The learning phase was administered in two initial learning sessions performed on two consecutive days. Each learning session included a total of seven runs and took approximately 45 min. Before starting, each of the 24 object/name pairs was displayed for 7 s with a 500 ms pause between the pairs. The participants were asked to read aloud the name of the object printed below, and to try to learn each object/name pair. After the presentation, the seven learning runs were performed. In each run, the participants were presented with the objects one at a time, and were asked to spontaneously say its name aloud. They were given a maximum of 7 s to recall the name of each object. After this, the correct name appeared below the object for 4 s, regardless of whether the participant had been able to produce the correct name or not. The following object was presented after 500 ms. The order of presentation in each run was randomized.

Learning indexes: free learning score and cued learning score

The performance (correct naming) during the last run of the second learning day was taken as a final learning index, providing the free learning score (FLS). Afterward, the *cued learning score* (CLS) was obtained. The CLS was based on the final cued learning run where, after each object appearance, the experimenter verbally provided the first syllable of the name (phonemic cue). For both scores, the range of scores was 0–24.

Forgetting measures at 1 week, 3 and 6 months

Each session took 10–15 min and began with a free recall run. Here, each trained object appeared on the screen in a randomized order, and the participant was asked to name it orally (free recall). When the participant could not provide the correct response, the experimenter provided the first syllable of the name (cued recall). Free and cued forgetting rates were also examined at 1 week, 3 and 6 months after the initial learning phase. Forgetting rates were defined as one minus the ratio between each delayed session score and the score obtained on the last learning run (for example, 1- [one-week free recall score/FLS], for 1-week free forgetting rate; and 1-[3-month cued recall score/CLS score], for 3-months cued forgetting rate), as in previous studies.[4,33] In this way, the forgetting rate represents the mean percentage of previously learned object/name items that were forgotten.

Forgetting slopes

In order to mathematically model the forgetting functions, we followed previous recommendations.[34–36] Forgetting curves are characterized by a curvilinear relation that shows a rapid initial decline of information followed by a slower and longer decay. Previous studies on forgetting have shown that power and logarithmic functions are the most accurate ones to describe forgetting curves. In the present sample, the logarithmic function ([y = a−b·ln [time]) provided a better fit than power function. Each data point (4-time data points) for each subject and condition (free and cued recall conditions) was fitted using a non-linear least-squares regression. Fit parameters were calculated based on the residual sum of squares and showing the proportion of data variance accounted for (R^2). The slope (parameter *b*) and intercept (parameter *a*) were computed separately for each subject and condition. The slope (b) captures the forgetting rate of encoded information while the intercept (*a*) represents the estimated initial level of performance (immediately after the last learning trial).

2.7 | Statistical analyses

Statistical analyses were performed using the SPSS (v. 22.0) package for Windows. An alpha value of $p < 0.05$ was considered to be significant for all the analyses. Demographics, biological and CSF data were compared using t-tests for independent samples or Chi-square analyses when appropriate.

Analyses of covariance (ANCOVA) controlling for age and years of education with post-hoc Bonferroni corrections were performed to explore possible cross-sectional learning and recall differences between the Low SCD-Q and High SCD-Q groups on the AFE-T. The analyzed learning indexes were FLS and CLS. Long-term free and cued recall scores and free and cued forgetting rates were also compared. Finally, group differences on the standard neuropsychological tests were also analyzed with ANCOVAs adjusted for age and education and with post-hoc Bonferroni corrections. The analyses were executed in order to (1) explore possible differences between the Low SCD-Q and High SCD-Q groups and (2) to further compare the Low SCD-Q and High SCD-Q participants' performance according to Aβ status (i.e., Low SCD-Q/Aβ− vs. Low SCD-Q/Aβ+ and High SCD-Q/Aβ− vs. High SCD-Q/Aβ+).

Pearson's bivariate correlations were calculated to assess overall associations between the AFE-T scores, AD CSF biomarker levels and the SCD-Q. To explore the relationships between the subjective and objective cognitive performance and relevant factors, linear regression models were set up. The analyses included the free (model 1) and cued (model 2) slopes from the AFE-T as the dependent variables

(slopes represents robust measures of long-term forgetting). Age, years of education, CSF $A\beta_{42}$, CSF p-tau and the SCD-Q score were included as independent variables.

3 | RESULTS

3.1 | Sample characteristics

Demographics, biological and CSF data for the whole sample and the Low SCD-Q and High SCD-Q groups are shown in Table 1. Age ranged between 53 and 80 years, and educational level ranged between 3 and 22 years. There were no significant differences in age (t [50] = 0.04; $p = 0.97$), years of education (t [50] = 0.71; $p = 0.48$) or premorbid intelligence (WAT; t [50] = 0.01; $p = 0.99$) between the Low SCD-Q and High SCD-Q groups. Gender distribution was also similar ($\chi^2 = 1.06$; $p = 0.38$) with women accounting for 57% of the Low SCD-Q group and 71% of the High SCD-Q group. Regarding the AD biomarkers, there were no significant differences between groups in CSF $A\beta_{42}$ (t [50] = −0.14; $p = 0.89$), CSF tau (t [50] = −0.98; $p = 0.33$) or CSF p-tau (t [50] = −1.15; $p = 0.25$). The Low SCD-Q and High SCD-Q groups did not differ on *APOE-ε4* allele frequency (19% vs. 16% of carriers, respectively; $\chi^2 = 0.12$; $p = 0.72$).

Regarding the cognitive testing results, there were no significant differences in global cognition, as assessed by the MMSE, between the Low SCD-Q and the High SCD-Q groups (28.8 ± 1.4 vs. 28.2 ± 1.5; t [50] = 1.21; $p = 0.23$). Nor was there a significant difference on verbal intelligence (24.8 ± 4.4 vs. 24.8 ± 4.1; t [47] = 0.01; $p = 0.99$). No single test of the standard neuropsychological battery showed significant differences between the groups, with p values ranging from 0.10 to 0.95 (see Table S1).

3.2 | AFE-T performance between low SCD-Q and high SCD-Q groups

3.2.1 | Free learning score and cued learning score

The Low SCD-Q group showed a FLS of 14.9 ± 6.7 on correctly named new-words, and the corresponding mean for the High SCD-Q group was 14.3 ± 7.0. Concerning CLS, the mean rate of correct responses for the Low SCD-Q group was 19.2 ± 5.1, and 19.0 ± 4.7 for the High SCD-Q group. ANCOVAs showed that these group differences were not statistically significant ([F {1,48} = 0.01; $p = 0.96$] and [F {1,48} = 0.07; $p = 0.93$], respectively). These comparisons on the FLS and CLS learning indexes between the High SCD-Q and Low SCD-Q groups are shown in Figure 1A and Table 2.

3.2.2 | Long-term recall and forgetting rates

Long-term memory performance between the High SCD-Q and Low SCD-Q groups is shown in Figure 1A (free and cued recall; slopes) and Figure 1B (free and cued forgetting rates), and in Table 2.

Forgetting rates at 1-week

For the one-week free recall session, the Low SCD-Q group had a forgetting rate of 0.28 ± 0.3 while the High SCD-Q group had a forgetting rate of 0.42 ± 0.2. This difference was not statistically significant (F [1,46] = 2.53; $p = 0.12$). When including the phonemic cue to facilitate naming, the forgetting rate decreased to 0.18 ± 0.1 in the Low SCD-Q and 0.22 ± 0.2 in the High SCD-Q group (F [1,46] = 0.71; $p = 0.40$).

TABLE 1 Demographics, biological data and CSF levels

Parameters	Total (N = 52)	Low SCD-Q (n = 21)	High SCD-Q (n = 31)	t	p
Demographics					
Gender (% women)	65.4%	57.1%	70.9%	1.06[a]	0.378
Age	67.2 ± 6.7	67.3 ± 6.4	67.2 ± 6.9	0.04	0.970
Years of education	11.0 ± 4.3	11.5 ± 4.4	10.6 ± 4.3	0.71	0.480
MMSE	28.5 ± 1.5	28.8 ± 1.4	28.2 ± 1.5	1.21	0.233
WAT	24.8 ± 4.2	24.8 ± 4.4	24.8 ± 4.1	0.01	0.999
Biological & CSF data					
APOE-ε4 (% positive)	17.3%	19.1%	16.1%	0.12[a]	0.724
$A\beta_{42}$	706.0 ± 268.9	699.5 ± 225.1	710.4 ± 298.6	−0.14	0.888
Tau	254.4 ± 105.5	236.8 ± 84.8	266.3 ± 117.4	−0.98	0.328
P-tau	53.3 ± 16.1	50.2 ± 14.4	55.4 ± 17.0	−1.15	0.254

Note: Data are presented as means ± standard deviation.

Abbreviations: APOE, Apolipoprotein E; $A\beta_{42}$, amyloid-beta isoform 42; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; P-tau, phosphorylated tau; Tau, total tau; WAT, Word Accentuation Test.

[a]Pearson Chi-Square.

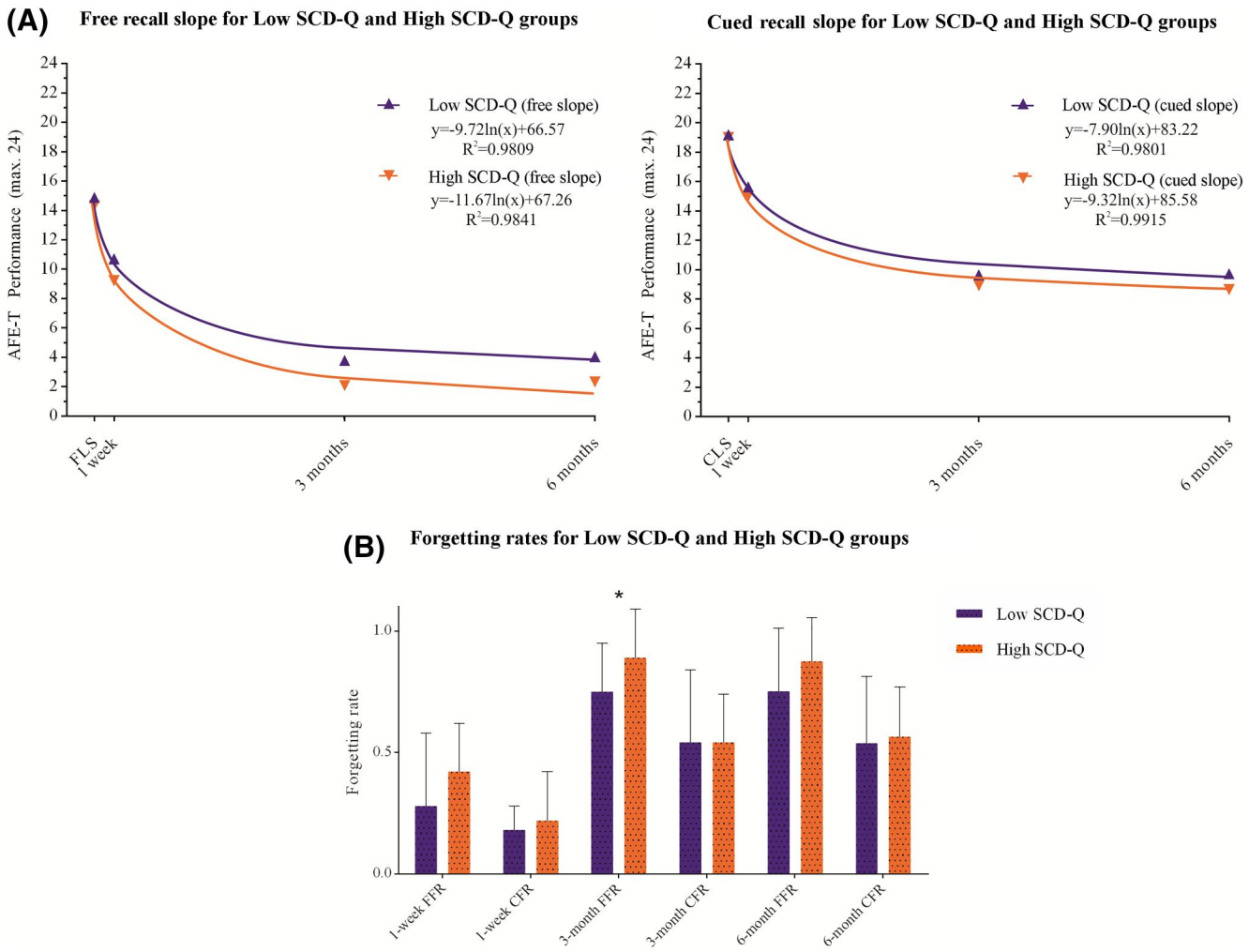

FIGURE 1 AFE-T performance in the Low SCD-Q and High SCD-Q groups. Abbreviations: AFE-T, Ancient Farming Equipment Test; CFR, cued forgetting rate; CLS, cued learning score; FFR, free forgetting rate; FLS, free learning score; SCD-Q, Subjective Cognitive Decline Questionnaire. *$p < 0.05$ [Colour figure can be viewed at wileyonlinelibrary.com]

Forgetting rates at 3 months

At three months, the Low SCD-Q group showed a forgetting rate of 0.75 ± 0.2 in the free recall, while the corresponding value for the High SCD-Q group was 0.89 ± 0.2. ANCOVA showed that this group difference was statistically significant (F [1,44] = 4.72; $p < 0.05$). When the cue was presented, both groups obtained the same forgetting rate (Low SCD-Q = 0.54 ± 0.3; High SCD-Q = 0.54 ± 0.2; F [1,44] = 0.01; $p = 0.93$).

Forgetting rates at 6 months

At six months, the Low SCD-Q group had a forgetting rate of 0.75 ± 0.3 while the High SCD-Q group had a forgetting rate of 0.87 ± 0.2 (F [1,42] = 3.26; $p = 0.08$). When including the phonemic cue, the forgetting rate decreased to 0.53 ± 0.3 in the Low SCD-Q group and 0.56 ± 0.2 in the High SCD-Q (F (1,42) = 0.07; $p = 0.78$). These differences were not statistically significant.

Forgetting slopes

Curves in Figure 1 represent the best-fitting function for each group (Low SCD-Q and High SCD-Q) and condition (free recall and cued recall). The fit of the logarithmic function to the group data was nearly perfect in both groups and conditions ($R^2 > 98\%$ of variance explained, in all cases). The function parameters for both groups are shown in Figure 1A.

3.3 | AFE-T performance in low SCD-Q and high SCD-Q according to Aβ status

3.3.1 | Free learning score and cued learning score

Within the Low SCD-Q group, the Low SCD-Q/Aβ+ subgroup obtained a significantly higher FLS when compared with the Low SCD-

TABLE 2 ANCOVA of learning indexes and long-term forgetting scores of the AFE-T between Low SCD-Q and High SCD-Q groups

Variables	Low SCD-Q (n = 21)	High SCD-Q (n = 31)	F	p
FLS	14.9 ± 6.7	14.3 ± 7.0	0.01	0.965
CLS	19.2 ± 5.1	19.0 ± 4.7	0.07	0.934
1-Week FR	11.2 ± 6.8	9.5 ± 6.7	0.678	0.415
1-Week CR	16.3 ± 5.2	15.4 ± 5.7	0.242	0.625
1-Week FFR	0.28 ± 0.3	0.42 ± 0.2	2.53	0.118
1-Week CFR	0.18 ± 0.1	0.22 ± 0.2	0.71	0.404
3-Month FR	3.8 ± 3.8	2.1 ± 3.9	1.92	0.172
3-Month CR	9.6 ± 5.9	9.1 ± 4.9	0.14	0.708
3-Month FFR	0.75 ± 0.2	0.89 ± 0.2	4.72	0.035*
3-Month CFR	0.54 ± 0.3	0.54 ± 0.2	0.01	0.929
6-Month FR	4.0 ± 4.3	2.3 ± 4.1	1.57	0.217
6-Month CR	9.7 ± 6.3	8.6 ± 5.0	0.26	0.610
6-Month FFR	0.75 ± 0.3	0.87 ± 0.2	3.26	0.078
6-Month CFR	0.53 ± 0.3	0.56 ± 0.2	0.07	0.786

Note: Data are presented as means ± standard deviation.

Abbreviations: CFR, cued forgetting rate; CLS, cued learning score; CR, cued recall; FFR, free forgetting rate; FLS, free learning score; FR, free recall; SCD-Q, Subjective Cognitive Decline Questionnaire.

*$p < 0.05$.

Q/Aβ− (17.3 ± 4.5 vs. 13.9 ± 7.3 points, respectively; F [1,17] = 5.97, $p < 0.05$). In the CLS, the mean for the Low SCD-Q/Aβ+ subgroup was 20.3 ± 3.0 points versus 18.7 ± 5.8 points for the Low SCD-Q/Aβ− (F [1,17] = 1.59, $p = 0.22$). Learning indexes of Low SCD-Q subgroups are shown in Figure 2A and in Table 3.

Within the High SCD-Q group, FLS was significantly lower for the High SCD-Q/Aβ+ subgroup compared to the High SCD-Q/Aβ− (8.7 ± 4.9 vs. 17.1 ± 6.2, respectively; F [1,27] = 6.44, $p < 0.05$). In the CLS, the mean for the High SCD-Q/Aβ+ subgroup was 15.1 ± 4.4, compared to 20.8 ± 3.6 points for the High SCD-Q/Aβ− subgroup. The ANCOVA showed that this group difference was also statistically significant (F [1,27] = 7.51, $p < 0.05$). Learning indexes are shown in Figure 3A and Table 3.

3.3.2 | Long-term recall and forgetting rates

Within the Low SCD-Q group, there were no differences between the Low SCD-Q/Aβ− and Low SCD-Q/Aβ+ subgroups in none of the long-term memory scores. Long-term recall and forgetting rates between Low SCD-Q subgroups are shown in Figures 2A and 2B, respectively; and in Table 3.

The High SCD-Q/Aβ+ subgroup displayed lower performance in all the long-term memory scores compared to the High SCD-Q/Aβ− subgroup. Significant differences between the High SCD-Q/Aβ− and High SCD-Q/Aβ+ subgroups were found in the one-week free recall (High SCD-Q/Aβ− = 11.4 ± 7.0 vs. High SCD-Q/Aβ+ = 4.6 ± 2.7; F [1,24] = 4.49; $p < 0.05$) and cued recall (High SCD-Q/Aβ− = 17.4 ± 5.0 vs. High SCD-Q/Aβ+ = 9.8 ± 4.3; F [1,24] = 7.10; $p < 0.01$), and in the 3-months cued recall (High SCD-Q/Aβ− = 10.6 ± 4.7 vs. High SCD-Q/Aβ+ = 5.2 ± 3.6; F [1,24] = 4.27; $p < 0.05$). Regarding the forgetting rates, the High SCD-Q/Aβ−subgroup's free forgetting rate at one week was 0.17 ± 0.1, whereas the High SCD-Q/Aβ+ obtained a forgetting rate of 0.35 ± 0.1. This difference was significant (F [1,24] = 5.13; $p < 0.05$). Long-term recall and forgetting rates are shown in Figures 3A and 3B, respectively; and in Table 3.

3.3.3 | Standard neuropsychological tests

Regarding the standard neuropsychological assessments, within the High SCD-Q group, there were no significant differences in any test of the neuropsychological battery between the Aβ−and Aβ+ subgroups (Table S2).

3.4 | Correlations between the AFE-T scores, AD CSF biomarkers and the SCD-Q

Significant correlations were found in the whole sample between CSF $A\beta_{42}$ and (1) the FLS ($r = 0.288$; $p < 0.05$), (2) the CLS ($r = 0.289$; $p < 0.05$), (3) the 1-week cued forgetting rate ($r = -0.465$; $p < 0.01$), and (4) the 3-month cued forgetting rate ($r = -0.328$; $p < 0.05$). A significant correlation was found between the 3-month free forgetting rate of the AFE-T and the SCD-Q ($r = 0.330$; $p < 0.05$).

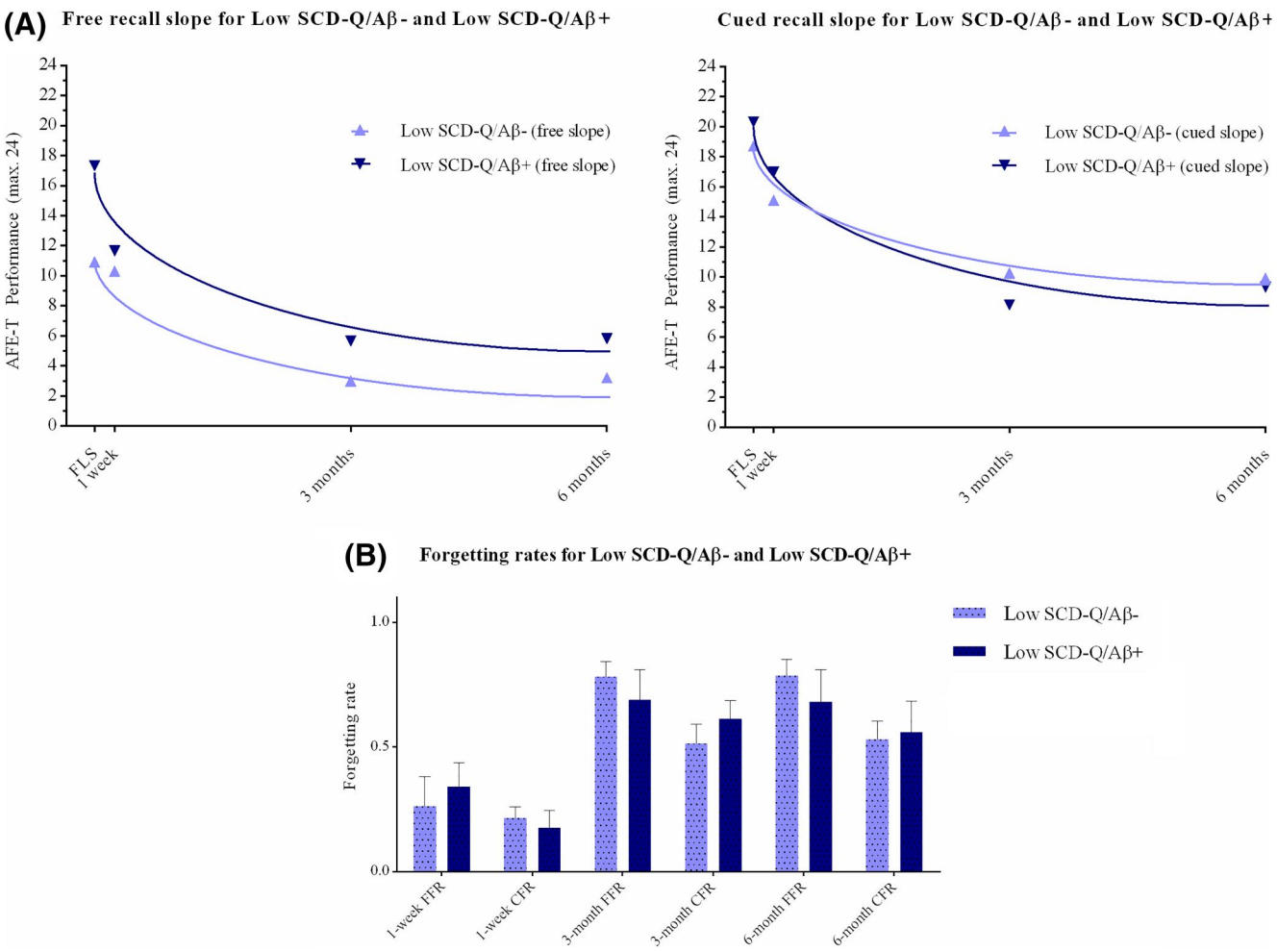

FIGURE 2 AFE-T performance in the Low SCD-Q group stratified by Aβ status. Abbreviations: AFE-T, Ancient Farming Equipment Test; CFR, cued forgetting rate; CLS, cued learning score; FFR, free forgetting rate; FLS, free learning score; SCD-Q, Subjective Cognitive Decline Questionnaire [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Models on the association between objective and subjective cognitive performance

Linear regression analyses were conducted to explore which variables were associated with the objective cognitive performance in the AFE-T. The models included the free recall slope (model 1) and the cued recall slope (model 2) as dependent variables. The AFE-T slopes were selected as dependent variables since they represent the most comprehensive measures of long-term forgetting across the whole time period covered by the test. Age, years of education, CSF $A\beta_{42}$, CSF p-tau and the SCD-Q were included as independent variables. While age, years of education, CSF $A\beta_{42}$ or CSF p-tau were not associated (all $p > 0.05$) with the free recall (model 1) and cued recall (model 2) slopes, the SCD-Q score was associated with the cued recall slope of the AFE-T ($\beta = -0.212$ [95% CI −0.406 to −0.018]; $p < 0.05$). Figure 4 shows the scatterplot on the association between the cued recall slope of the AFE-T and the SCD-Q score, indicating that higher scores in the SCD-Q were related to a faster decrease of information in long-term memory (higher forgetting).

4 | DISCUSSION

In this study, we examined learning and long-term recall in a well-characterized sample of cognitively unimpaired individuals by means of a new highly demanding associative memory test. The results revealed subtle objective memory difficulties in individuals with high SCD ratings, especially in those with abnormal CSF $A\beta_{42}$ levels. Our findings suggest an association between SCD ratings and objective memory performance.

Increasing evidence suggests that SCD might be the first manifestation in the AD continuum.[9,10,37] However, several cross-sectional studies have failed to show a significantly lower performance in cognitive tests in SCD samples compared to controls, demonstrating that the links between SCD and objective cognitive performance are difficult to find when standard neuropsychological tests are used.[38] This lack of significant association typically found between SCD and objective cognitive performance might be due to limitations in sensitivity of the standard neuropsychological tests.[39] To date, the use of more challenging measures has shown promising

TABLE 3 Demographics and ANCOVA of learning indexes and long-term forgetting scores of the AFE-T within the Low SCD-Q and High SCD-Q groups including Aβ status subgroups

	Low SCD-Q (n = 21)				High SCD-Q (n = 31)			
Variables	**Aβ− (*n* = 15)**	**Aβ+ (*n* = 6)**	***F***	***p***	**Aβ− (*n* = 21)**	**Aβ+ (n = 10)**	***F***	***p***
Demographics								
Gender (% women)	53.3%	66.6%	0.31[a]	0.577	66.6%	80%	0.58[a]	0.445
Age	65.9 ± 6.4	70.4 ± 5.7	−1.49[b]	0.152	65.0 ± 5.9	69.8 ± 6.6	−2.03[b]	0.052
Years of education	10.9 ± 4.5	13.0 ± 4.3	−0.96[b]	0.349	11.4 ± 4.4	9.1 ± 3.9	1.39[b]	0.174
MMSE	28.9 ± 1.5	28.5 ± 1.4	0.67[b]	0.546	28.5 ± 1.4	27.7 ± 1.7	1.47[b]	0.153
WAT	23.7 ± 4.7	27.6 ± 1.9	−1.97[b]	0.063	25.0 ± 4.3	24.5 ± 4.0	0.26[b]	0.797
AFE-T scores								
FLS	13.9 ± 7.3	17.3 ± 4.5	5.97	0.026*	17.1 ± 6.2	8.7 ± 4.9	6.44	0.017*
CLS	18.7 ± 5.8	20.3 ± 3.0	1.59	0.224	20.8 ± 3.6	15.1 ± 4.4	7.51	0.011*
1-week FR	11.1 ± 7.4	11.6 ± 5.9	0.79	0.385	11.4 ± 7.0	4.6 ± 2.7	4.49	0.044*
1-week CR	16.0 ± 5.4	17.0 ± 5.2	1.27	0.276	17.4 ± 5.0	9.8 ± 4.3	7.10	0.008**
1-week FFR	0.26 ± 0.4	0.34 ± 0.2	0.03	0.860	0.38 ± 0.2	0.53 ± 0.2	2.54	0.123
1-week CFR	0.19 ± 0.1	0.17 ± 0.2	0.86	0.366	0.17 ± 0.1	0.35 ± 0.1	5.13	0.032*
3-month FR	3.0 ± 2.8	5.6 ± 5.5	3.94	0.064	2.9 ± 4.4	0.3 ± 0.5	1.08	0.308
3-month CR	10.2 ± 6.4	8.1 ± 4.8	0.25	0.625	10.6 ± 4.7	5.2 ± 3.6	4.27	0.049*
3-month FFR	0.78 ± 0.2	0.69 ± 0.3	0.79	0.385	0.85 ± 0.2	0.96 ± 0.1	1.45	0.239
3-month CFR	0.51 ± 0.3	0.61 ± 0.2	0.20	0.659	0.48 ± 0.2	0.68 ± 0.2	2.76	0.110
6-month FR	3.2 ± 3.3	5.8 ± 5.9	2.87	0.111	2.9 ± 4.7	0.8 ± 1.1	0.29	0.595
6-month CR	9.9 ± 6.3	9.3 ± 6.8	0.71	0.413	9.9 ± 5.1	5.6 ± 3.4	0.97	0.334
6-month FFR	0.78 ± 0.2	0.68 ± 0.3	0.81	0.382	0.86 ± 0.2	0.91 ± 0.1	0.11	0.745
6-month CFR	0.53 ± 0.3	0.56 ± 0.3	0.45	0.511	0.53 ± 0.2	0.65 ± 0.2	0.25	0.621

Note: Data are presented as means ± standard deviation.

Abbreviations: Aβ, amyloid-beta; CFR, cued forgetting rate; CLS, cued learning score; CR, cued recall; FR, free recall; FFR, free forgetting rate; FLS, free learning score; MMSE, Mini-Mental State Examination; SCD-Q, Subjective Cognitive Decline Questionnaire; WAT, Word Accentuation Test.

[a]Pearson Chi-Square.

[b]Student's t-test.

*$p < 0.05$.

**$p < 0.01$.

results in cognitively unimpaired individuals, including preclinical AD,[40,41] presymptomatic mutation carriers of familial AD[42] and SCD[43] samples.

The usefulness of AFE-T for exploring memory function in the Alzheimer's continuum has been previously endorsed in several studies including preclinical AD,[2] MCI[8] and AD.[7] The present results show subtle memory difficulties by means of the AFE-T in individuals with high SCD ratings that were otherwise undetected by our comprehensive neuropsychological battery. Targeting memory function in SCD—especially by using more sensitive cognitive measures—is potentially relevant as subjective decline on memory capacities is thought to be more related to an increased risk of future cognitive decline.[44] At the same time, it is worth noting that most studies on SCD have concentrated on memory domain and there is scarce evidence[16,45] on subjective decline in other cognitive functions.

Another important point regarding the nature of AFE-T and its potential application in SCD concerns its neural correlates. Recently, the functional and structural brain correlates of the AFE-T have been identified in cognitively unimpaired individuals[6,46] as well as in patients.[8,47] These studies have suggested that performance on this task depends on specific brain regions that are typically affected in AD, such as the medial temporal lobe (MTL). In line with this, cross-sectional studies have shown incipient volume loss in these AD-related brain regions in individuals with SCD.[48–50]

When comparing AFE-T performances between individuals with low versus high SCD-Q scores, we found accelerated long-term forgetting (ALF) in those individuals with high SCD ratings. The concept of ALF, defined as a loss of information over days or weeks despite normal acquisition, has recently emerged in the neurodegenerative research field as a cognitive marker for the

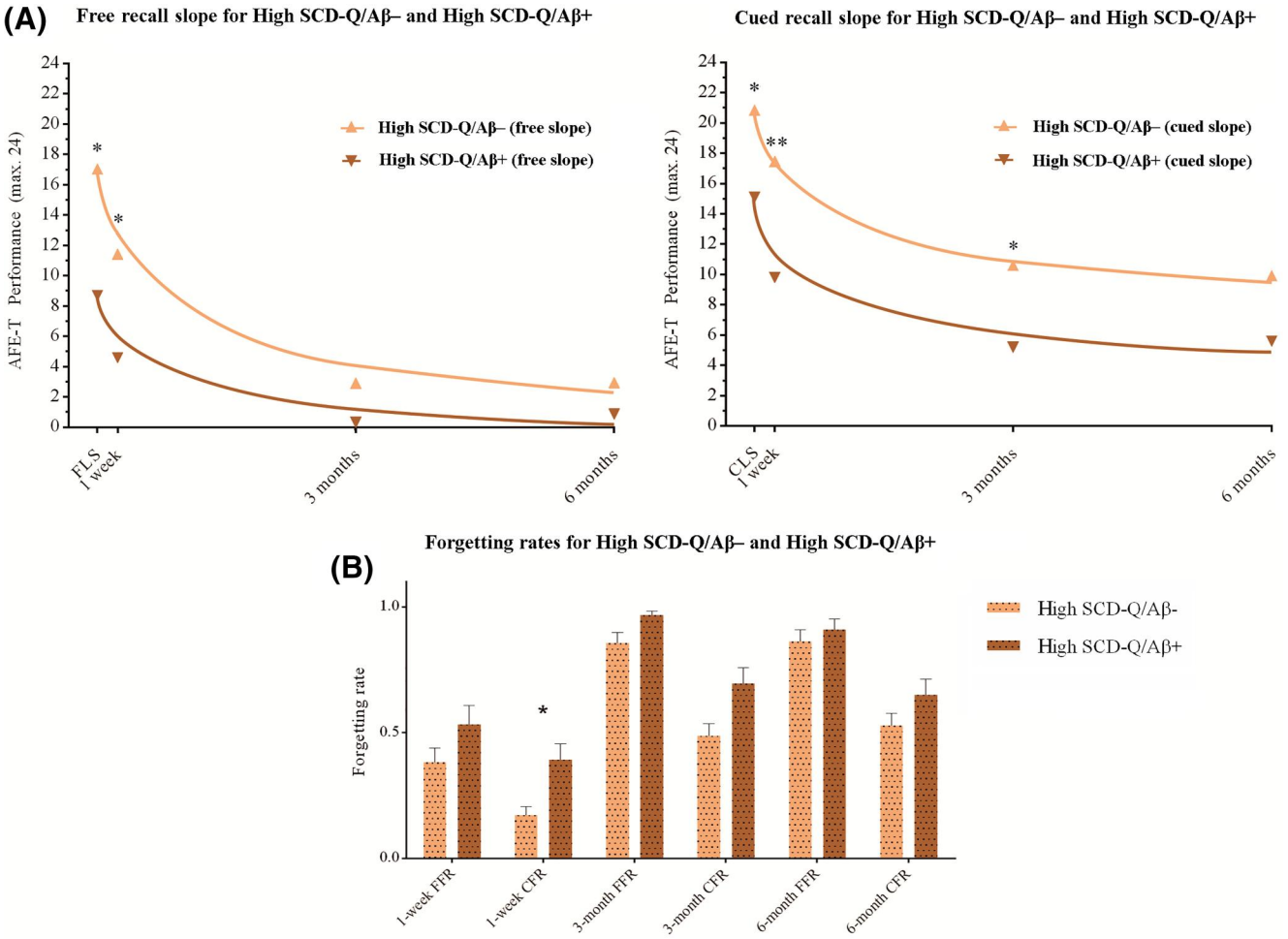

FIGURE 3 AFE-T performance in the High SCD-Q group stratified by Aβ status. Abbreviations: AFE-T, Ancient Farming Equipment Test; CFR, cued forgetting rate; CLS, cued learning score; FFR, free forgetting rate; FLS, free learning score; SCD-Q, Subjective Cognitive Decline Questionnaire. *$p < 0.05$ **$p < 0.01$ [Colour figure can be viewed at wileyonlinelibrary.com]

presymptomatic stages of AD.[3,4] A recent study on a cohort of autosomal dominant AD families revealed ALF at one week in pre-symptomatic mutation carriers.[4] In the same vein, Zimmermann & Butler[33] recently showed ALF in asymptomatic *APOE-ε4* carriers. Here, it is important to note that in addition to computing the forgetting rates—similar to those reported in these previous studies—we also modeled the participants' forgetting curves in order to obtain a comprehensive measure of information decay (i.e., the slopes). The modeled function provides an estimate of the intercept and the forgetting slope individually for each subject and allows to compute an overall forgetting measure for the whole period, instead of having multiple measures of forgetting rate calculated for each time-point. Our results suggest that ALF may be present in individuals with high SCD ratings and highlight the need of using more sensitive and specific cognitive measures when assessing cognitively unimpaired populations.

Interestingly, when stratifying by amyloid status (positive vs. negative), we observed significant differences in cognitive performance within the High SCD-Q group. Those individuals with abnormal $A\beta_{42}$ levels displayed poorer learning and long-term recall scores than those with normal CSF AD biomarkers. On the other hand, amyloid levels did not seem to influence cognitive performance in individuals without Low SCD-Q. These results are relevant since there are recent longitudinal studies showing that individuals with SCD and biomarker evidence of AD are at a higher risk of future decline.[12,51] At the same time, we found a relationship between the participants' amyloid-β levels and cognitive performance on the AFE-T. Also, our regression analyses pointed to cognitive complaints as relevant predictors of long-term memory performance, indicating that higher scores in the SCD-Q are associated with a faster decrease of information in long-term memory (higher forgetting, Figure 4). Our observations are in line with previous studies suggesting that cognitively unimpaired individuals with evidence of Aβ pathology and SCD undergo objective cognitive decline at a higher rate than individuals with either amyloidosis or SCD alone, and are at a higher risk of rapid cognitive decline.[11] Our findings suggest that individuals with SCD and amyloid-β positivity may be closer to develop the earliest cognitive manifestations in the AD continuum than individuals with only SCD.

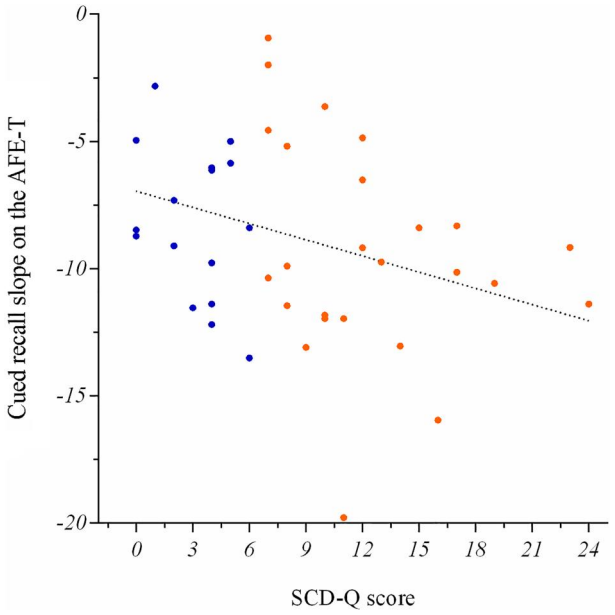

FIGURE 4 Scatterplot on the relationship between the cued recall slope and the SCD-Q score. Abbreviation: SCD-Q, Subjective Cognitive Decline Questionnaire. Key: Blue dots: Low SCD-Q participants; Orange dots: High SCD-Q participants [Colour figure can be viewed at wileyonlinelibrary.com]

Regarding the assessment of SCD, SCD-Q might be especially suited for the study of the earliest symptomatic manifestations in the AD continuum, as it was designed following the SCD-I framework for research of SCD in preclinical AD.[9] Previous studies have shown significantly higher SCD-Q scores in samples of preclinical AD individuals when compared to controls.[16,42] The SCD-Q distinguishes from the pre-existing SCD questionnaires in that it explores the perception of decline in a relatively short period of time, over an array of daily life activities that involve multiple cognitive domains, instead of being restricted to memory. These properties increase the likelihood of detecting SCD due to preclinical AD.[9] Taken together, our results suggest the use of more robust and sensitive measures to ensure an exhaustive evaluation of SCD when assessing cognitively unimpaired populations.

Our study has some limitations. First, the relatively small sample size could limit the power of the statistical analyses. Replication of the present results in independent and larger samples is therefore needed. Second, in this study we included both participants from memory clinic and research settings. This is an important consideration since it is well known that recruitment setting affects studies of SCD.[13,52] Furthermore, the way by which subjective and objective cognitive outcomes are assessed may also affect these studies. In this sense, it is important to note that the SCD-Q is a validated tool for measuring SCD. Also, regarding the objective assessment of participants' cognitive capacities, the comprehensive AFE-T protocol allowed for a thorough assessment of learning and long-term memory processes. However, validation of the present results is called for in future studies using different assessment methods. Finally, another important limitation concerns the cross-sectional nature of the study. Further assessment is needed to accurately follow up participants' trajectories of cognitive decline.

In sum, by using comprehensive measures for assessing subjective and objective cognition, we provide evidence for accelerated long-term forgetting in individuals with high SCD ratings, especially in those within the Alzheimer's continuum. The presence of significant associations between SCD ratings and AD biomarkers and objective cognitive performance, highlight the contribution of biological and cognitive markers (and their co-occurrence) as potential predictors of the earliest manifestations of Alzheimer's disease.

ACKNOWLEDGMENTS

This work has been supported by the Carlos III Health Institute (projects PI043610—AC14/00014 and PI19/00745 to LR), integrated in the State Plan of Scientific and Technical Research and Innovation, and co-financed by the European Regional Development Fund (ERDF) "Una manera de hacer Europa." ML was financially supported by the Academy of Finland (grant No. 323251). We thank all participants for their collaboration.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

The ethics committee of the Hospital Clinic of Barcelona approved the study, and all participants provided a signed, informed consent.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

How to cite this article: Tort-Merino A, Valech N, Laine M, et al. Accelerated long-term forgetting in individuals with subjective cognitive decline and amyloid-β positivity. *Int J Geriatr Psychiatry*. 2021;36:1037–1049. https://doi.org/10.1002/gps.5539