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RESEARCH ARTICLE

Self- and study partner–reported cognitive decline in older adults without dementia: The role of α-synuclein and amyloid biomarkers in the Alzheimer's Disease Neuroimaging Initiative

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Abstract

INTRODUCTION: Subjective cognitive decline (SCD) may be an early marker of Alzheimer's disease (AD) pathology. Until recently, it was impossible to measure biomarkers specific for α-synuclein pathology; therefore, its association with subjective reports of cognitive decline is unknown.

METHODS: Alzheimer's Disease Neuroimaging Initiative participants without dementia ($n = 918$) were classified as positive or negative for amyloid beta (Aβ+ or Aβ−) and α-synuclein (α-syn+ or α-syn−) biomarkers. Self- and study partner–reported cognitive decline was measured with the Everyday Cognition (ECog) questionnaire.

RESULTS: Per self-report, Aβ+/α-syn+ had the greatest cognitive decline. Aβ−/α-syn+ did not differ from Aβ−/α-syn− across ECog scores. Study partner–reported results had a similar pattern, but Aβ+/α-syn− and Aβ+/α-syn+ did not differ across ECog scores. Mild cognitive impairment classification moderated the study partner–reported memory score.

DISCUSSION: While α-syn+ alone did not increase subjective reports of cognitive decline, Aβ+/α-syn+ had the most self- and study partner–rated cognitive decline. Therefore, the presence of multiple pathologies was associated with greater SCD.

KEYWORDS
α-synuclein, Alzheimer's Disease Neuroimaging Initiative, amyloid beta, Everyday Cognition, Lewy body pathology, seed amplification assay, subjective cognitive decline

Highlights

- Cerebrospinal fluid α-synuclein (α-syn) seed amplification assay was used to determine α-syn positivity.
- Amyloid beta (Aβ)−/α-syn−, Aβ−/α-syn+, Aβ+/α-syn−, and Aβ+/α-syn+ biomarker groups were created.
- Aβ+/α-syn+ had greater subjective cognitive decline (SCD) than the other biomarker groups.
- Aβ−/α-syn+ did not differ from Aβ−/α-syn− across self- or study–partner reported SCD scores.
- Study partner–reported subjective memory results were largely driven by participants with mild cognitive impairment.

1 | BACKGROUND

Lewy body pathology, which is primarily found in dementia with Lewy bodies (DLB) and Parkinson's disease (PD), results from the intraneuronal aggregation of misfolded α-synuclein.[1] Clinical studies suggest that DLB comprises 4.2% of dementias diagnosed in community-based studies and 7.5% in clinic-based studies.[2] However, until recently, it has been difficult to ascertain the prevalence of Lewy body pathology in individuals without dementia, as well as examine the effects of Lewy body pathology both independently and in combination with amyloid beta (Aβ) pathology because there has not been a reliable biomarker for misfolded α-synuclein. Recent studies, however, have now shown the cerebrospinal fluid (CSF) α-synuclein seed amplification assay (SAA) accurately predicts Lewy body pathology, including in individuals with co-occurring Alzheimer's disease (AD) and at any disease stage (pre-clinical, mild cognitive impairment [MCI], dementia).[3–6]

In participants from the BioFINDER study with MCI or dementia, 23% were Lewy body positive (of whom 48% had AD pathology).[7] The pattern of cognitive performance showed that Lewy body pathology was most associated with attention/executive and visuospatial functioning and was also associated with cognitive decline across domains, independent of AD pathology. Furthermore, within cognitively unimpaired (CU) older adults from the BioFINDER study, 8% were α-synuclein SAA positive and 26% were Aβ positive, but 13% of those were also positive for co-occurring α-synuclein SAA.[8] Notably, in this study, α-synuclein SAA was independently associated with cross-sectional and longitudinal cognitive declines in CU participants. Despite associations with objective cognition, the associations of α-synuclein and α-synuclein plus Aβ biomarkers with self- and informant-rated subjective cognitive decline (SCD) in CU and MCI participants is unknown.

SCD has garnered significant attention over the past decade as a potential tool to identify individuals at risk for dementia.[9] SCD is defined as a self-experienced decline in cognition relative to previous cognitive functioning that is not due to an acute event, psychiatric symptoms, medical disorder, medication, or substance use.[9] Importantly, this cognitive marker has the potential to be an extremely simple and cost-effective way to identify people at risk for future AD-related declines relative to many biomarker methods. While several factors can complicate the utility of SCD (e.g., clinic vs. community-based cohorts, mood symptoms, health factors)[10–13] several studies have demonstrated associations between SCD and cognitive decline[14–17] and Aβ pathology.[18,19] The current study uses the Everyday Cognition (ECog) questionnaire to measure participant (i.e., self)- and study partner–reported cognitive decline.[20] This measure has been widely used to capture subjective change (i.e., relative to 10 years ago) on complex cognitive and everyday tasks.

Although participant- and study partner–reported cognitive decline and the associations with AD biomarkers have been thoroughly examined, very little is known about SCD in individuals with Lewy body pathology. One study that examined the rate of progression to AD and non-AD (DLB, vascular, fronto-temporal) dementia found that approximately one-third of incident dementia participants with SCD had non-AD dementia.[10] Within PD, SCD in CU individuals has been shown to be associated with objective cognitive decline.[21] However, there are no studies examining the associations of α-synuclein biomarker positivity and the pattern of subjective decline on complex cognitive and everyday functioning tasks in CU and MCI older adults. Taken together, the goal of this study was to examine the severity of participant- and study partner–reported cognitive decline across amyloid and α-synuclein biomarker-defined groups and then determine the extent to which cognitive classification (CU or MCI) moderates this association. We hypothesized that participant- and study partner–reported cognitive decline would be the highest in the group that is positive for both amyloid and α-synuclein biomarkers and that the results would largely be driven by MCI participants.

2 | METHODS

2.1 | The Alzheimer's Disease Neuroimaging Initiative dataset

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private

partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.2 | Participants

Enrollment criteria for ADNI have been previously described in detail.[22] ADNI was approved by the institutional review boards at each of the participating institutions. Written informed consent was obtained from all participants or authorized representatives at each site. The current study included 918 participants without dementia. The time point used in the study was the last available visit in which the participant had a lumbar puncture as this is the visit when the CSF α-synuclein SAA data are available. Data were downloaded on March 4, 2024; ADNI roster ID (RID) numbers from the de-identified study data are included in the online supplement in supporting information. Participants were included if they also had relevant covariate, SCD, and CSF Aβ42 data available at the same visit.

2.3 | Participant- and study partner–reported cognitive decline

SCD was measured using the participant-report (PT) and study partner-report (SP) of the ECog questionnaire.[20] The ECog is a 39-item measure in which the PT and SP separately rate the participant's ability to perform cognitively demanding everyday tasks *relative to 10 years ago* as 1 = better or no change, 2 = questionable/occasionally worse, 3 = consistently a little worse, or 4 = consistently much worse. Items in which "don't know" was selected were coded as missing. The everyday tasks are divided into six cognitive domains: memory (eight items), language (nine items), visuospatial (seven items), planning (five items), organization (six items), and divided attention (four items). The mean of all 39 items created the total score, which was the primary outcome, and mean of each cognitive domain created the individual domain scores. Higher scores are associated with more subjective cognitive and complex everyday functioning decline.

2.4 | CSF biomarkers

Participants were classified as positive and negative for α-synuclein (α-syn+, α-syn−) using a CSF synuclein SAA carried out in the Amprion Clinical Laboratory (CLIA ID No. 05D2209417; CAP No. 8168002). Additional details of SAA have been described elsewhere.[6] The most recent CSF visit for ADNI participants was used to select the sample that was processed using SAA, which detects misfolded α-synuclein aggregates.[5] A positive SAA result indicates that α-synuclein aggregates were detected and are either consistent with seeds seen in PD and Lewy body dementia (Type 1) or with seeds seen in multiple system atrophy (Type 2). An indeterminate result indicates that a determination cannot be made after a sample is tested twice. A negative result reflects the absence of α-synuclein aggregates. Given the low number of participants positive for Type 2 seeds ($n = 4$) and indeterminate results ($n = 3$), this study only included participants positive for Type 1 seeds or who were determined to be α-syn−.

CSF amyloid was measured using the Elecsys Aβ42 immunoassay.[23] Aβ42 values ≥ 980 pg/mL were characterized as Aβ negative (Aβ−), while those < 980 pg/mL were considered Aβ positive (Aβ+).[6,24] CSF Aβ42 was used to maximize the overlap of participants with both an amyloid marker and SAA data. Using the CSF α-synuclein and Aβ42 data, four biomarker groups were created: Aβ−/α-syn− ($n = 435$), Aβ−/α-syn+ ($n = 80$), Aβ+/α-syn− ($n = 329$), and Aβ+/α-syn+ ($n = 74$).

2.5 | Cognitive classification

Both ADNI CU and participants classified as MCI, but not those classified as dementia,[22] were included in this study. MCI status was determined using the Jak/Bondi comprehensive neuropsychological approach, which has been previously described and widely applied within ADNI as an MCI classification approach that does not require the use of subjective report of cognitive decline[25–28] and may reduce

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed, Google Scholar). While several papers have used the α-synuclein seed amplification assay specifically in Parkinson's disease, there are now recent publications describing this assay in larger aging/Alzheimer's disease cohorts as well as its association with cognitive test scores and neuropathology.
2. **Interpretation**: Our findings are the first to examine the role of α-synuclein and amyloid co-pathologies on self- and study partner–reported subjective cognitive decline (SCD) in older adults without dementia. While α-synuclein alone did not elevate SCD, positivity on both α-synuclein and amyloid biomarkers led to increased SCD ratings.
3. **Future directions**: This study is an important step in understanding the role of co-pathologies and the associations with subjective cognition. Future work is needed to explore the extent to which the first biomarker to emerge (α-synuclein or amyloid) impacts the trajectory and domain-specific pattern of subjective and objective cognitive decline.

false-positive MCI diagnoses.[26] Briefly, participants were classified as MCI if they: (1) performed > 1 standard deviation (SD) below the age-/education-/sex-adjusted mean on two neuropsychological measures within the same cognitive domain (memory, language, or attention/executive functioning) *or* (2) performed > 1 SD below the demographically adjusted mean on at least one measure across all three cognitive domains that were sampled. Six neuropsychological scores were used and included two memory measures: Rey Auditory Verbal Learning Test (AVLT) delayed free recall and AVLT recognition (hits minus false positives); two language measures: either 30-item Boston Naming Test (BNT) or the Multilingual Naming Test (MiNT) and Animal Fluency; and two attention/executive function measures: Trail Making Test (TMT), Part A and Part B. The neuropsychological age-/education-/sex-adjusted *z* scores were based on regression coefficients derived from a sample of ADNI's CU participants who remained cognitively normal throughout their participation in ADNI (i.e., "robust" controls; $N = 525$).[27–29] Regressions to determine demographic adjustment were completed at baseline, 12 month, and 24+ month visits to account for differential exposure to the measures. Participants who did not meet the neuropsychological criteria for MCI were considered CU.

2.6 | Additional descriptive and covariate variables

Demographic data included participant age, sex, years of education, race, and ethnicity. Apolipoprotein E (*APOE*) ε4 carrier status is defined as the presence of at least one ε4 allele. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS) score. ADNI only included participants with a baseline GDS score < 6, so there was a somewhat restricted range of depressive symptoms, though participants were not excluded if their GDS score increased to ≥ 6 after the baseline visit. Because there is an item on the GDS focused on memory concerns, we included the GDS minus this item so as not to overlap with the SCD outcome. The Montreal Cognitive Assessment (MoCA) was used to characterize global cognition. The Clinical Dementia Rating (CDR) global score and sum of boxes (higher scores indicate more functional difficulties) were used to characterize functioning. Aβ PET using either florbetapir ($n = 709$) or florbetaben ($n = 138$) ligands was used to characterize a large subset of the sample ($n = 847$; 92%). The details of data acquisition and processing of ADNI florbetapir PET and florbetaben PET data are available at adni.loni.usc.edu. A summary standardized uptake value ratio (SUVR) was calculated by dividing the mean uptake across four AD-vulnerable cortical regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) by whole cerebellar (white and gray matter) uptake. SUVR to Centiloid transformations were then used to put both ligands on a common metric.[30] Pulse pressure (systolic minus diastolic blood pressure), a proxy for arterial stiffening,[31] was used as a measure of vascular risk to describe the sample. The visit that was used for these variables was the same visit in which the CSF α-synuclein SAA data were available.

2.7 | Statistical analyses

Unadjusted analyses of variance, Kruskall–Wallis tests, or chi-squared tests were used to examine differences in demographic and clinical data by biomarker group (i.e., Aβ/α-syn). Next, general linear models, adjusting for age, education, sex, race/ethnicity, *APOE* ε4+, and cognitive classification (CU or MCI), examined biomarker group differences in participant-reported ECog (ECog-PT) and study partner–reported ECog (ECog-SP) total and ECog cognitive domain scores. Sensitivity analyses examined the biomarker group associations with the ECog-PT and ECog-SP total score while including depressive symptoms as an additional covariate to determine whether depressive symptoms may be contributing to the experience of SCD. Secondary analyses examined cognitive group as a moderator of the association between biomarker group and ECog scores. Consistent with recent work in ADNI that also included the CSF synuclein SAA, an alpha = 0.05 was used for all analyses.[4]

3 | RESULTS

3.1 | Characteristics of the biomarker groups

Across the sample, participants had a mean age of 73.68 years and mean education of 16.47 years, were 51.7% women, 89.4% non-Hispanic White individuals, and 37.6% *APOE* ε4 carriers; 586 (63.8%) participants were classified as CU and 332 (36.2%) were classified as MCI. Demographic and clinical characteristics of the participants by Aβ/α-syn biomarker group are shown in Table 1. Briefly, the Aβ−/α-syn− group was the youngest and performed the best on the MoCA. The Aβ−/α-syn− and Aβ−/α-syn+ groups generally had lower rates of MCI classification, better functioning on the CDR, lower rates of *APOE* ε4 carriers, and biomarkers that are indicative of little-to-no AD pathology relative to the Aβ+/α-syn− and Aβ+/α-syn+ groups. There were no significant group differences by race/ethnicity, sex/gender, education, pulse pressure, or depressive symptoms.

3.2 | Biomarker group differences in participant-reported cognitive decline

For participant-reported ECog (ECog-PT) ratings, when adjusting for age, education, sex, race/ethnicity, *APOE* ε4+, and cognitive classification (CU or MCI), the Aβ+/α-syn+ group generally reported the highest (i.e., worst) cognitive decline across all ECog-PT scores and significantly differed from the other three groups on the total, language, and organization scores (Figure 1). Table 2 shows the parameter estimates for the ECog-PT total score model. On the memory, visuospatial, and planning scores, the Aβ+/α-syn+ group reported greater cognitive decline than the Aβ−/α-syn− and Aβ−/α-syn+ groups, but did not significantly differ from the Aβ+/α-syn− group. The Aβ−/α-syn− and Aβ−/α-syn+ groups did not differ across any of the ECog-PT scores, while the Aβ−/α-

TABLE 1 Baseline demographic, clinical, and biomarker characteristics of the biomarker groups.

	Aβ−/α-syn− (*n* = 435)	Aβ−/α-syn+ (*n* = 80)	Aβ+/α-syn− (*n* = 329)	Aβ+/α-syn+ (*n* = 74)	*p*
Age	72.27 (7.60)[a,b,c]	75.76 (6.56)[d]	74.56 (7.42)[d]	75.88 (7.53)[d]	<0.001
Education	16.45 (2.48)	16.60 (2.68)	16.47 (2.45)	16.53 (2.85)	0.962
Female, %	55.9%	45.0%	49.2%	45.9%	0.101
Race					0.920
American Indian/Alaska Native, %	0.2%	0.0%	0.3%	0.0%	
Asian, %	1.6%	2.5%	0.9%	0.0%	
Black/African American, %	3.7%	5.0%	4.9%	2.7%	
Hawaiian/Other Pacific Islander, %	0.2%	0.0%	0.3%	0.0%	
White, %	93.3%	91.3%	90.9%	95.9%	
More than one race, %	0.9%	1.3%	2.1%	1.4%	
Unknown	0.0%	0.0%	0.6%	0.0%	
Hispanic/Latino, %	3.2%	3.8%	4.0%	2.7%	0.901
MoCA	25.56 (2.71)[a,b,c]	24.56 (2.83)[a,d]	24.20 (3.26)[a,d]	23.08 (2.94)[b,c,d]	<0.001
MCI, %	26.2%%[a,b]	26.3%%[a,b]	45.9%[a,c,d]	62.2%[b,c,d]	<0.001
CDR Global of 0, %	57.1%[a,b]	58.8%[a,b]	37.3%[c,d]	30.1%[c,d]	<0.001
CDR–Sum of Boxes	0.59 (0.87)[a,b]	0.66 (0.94)[a,b]	1.03 (1.13)[c,d]	1.25 (1.22)[c,d]	<0.001
APOE ε4 carrier, %	22.5%[a,b]	13.8%[a,b]	57.1%[c,d]	64.9%[c,d]	<0.001
Amyloid PET Centiloids (*n* = 847)	8.00 (19.13)[a,b]	11.02 (26.11)[a,b]	59.29 (41.38)[c,d]	65.08 (41.39)[c,d]	<0.001
CSF Aβ42 pg/mL	1625.56 (512.88)[a,b]	1703.21 (637.49)[a,b]	681.79 (167.27)[c,d]	623.14 (192.55)[c,d]	<0.001
CSF p-tau pg/mL	20.66 (8.73)[a,b]	22.20 (10.13)[a,b]	27.45 (14.88)[c,d]	30.92 (15.44)[c,d]	<0.001
Pulse pressure	59.18 (14.71)	62.18 (13.95)	59.81(15.51)	63.27 (17.62)	0.096
GDS score (minus subjective memory item)	1.14 (1.54)	1.01 (1.35)	1.12 (1.46)	1.45 (1.55)	0.219

Note: Data are summarized as mean (standard deviation) or %.
Abbreviations: Aβ, amyloid beta; α-syn, α-synuclein; *APOE*, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PET, positron emission tomography; p-tau, phosphorylated tau.
[a]Significantly different than Aβ+/α-syn+ ($p < 0.05$).
[b]Significantly different than Aβ+/α-syn−.
[c]Significantly different than Aβ−/α-syn+.
[d]Significantly different than Aβ−/α-syn−.

syn− group had significantly lower scores on the total, memory, and visuospatial scores compared to the Aβ+/α-syn− group. The Aβ−/α-syn+ and Aβ+/α-syn− groups differed on the memory and visuospatial scores such that the Aβ+/α-syn− group reported more decline. None of the groups significantly differed on ECog-PT divided attention. In a sensitivity analysis that included the GDS score (minus the subjective memory question) as a covariate in the ECog-PT total score model, the general pattern of results did not change, though the significant difference between the Aβ+/α-syn− and Aβ+/α-syn+ group was slightly attenuated ($P = 0.106$).

3.3 | Biomarker group differences in study partner–reported cognitive decline

For study partner–reported ECog (ECog-SP) ratings, when adjusting for age, education, sex, race/ethnicity, *APOE* ε4+, and cognitive classification (CU or MCI), the study partners of the Aβ+/α-syn+ group generally reported the highest cognitive decline across biomarker groups, but did not significantly differ from the Aβ+/α-syn− group on any of the ECog-SP scores (Figure 2). On ECog-SP total, memory, language, and planning scores, the study partners of the Aβ+/α-syn+ group reported significantly greater cognitive decline relative to the Aβ−/α-syn− and Aβ−/α-syn+ groups, but not the Aβ+/α-syn− group. Table 3 shows the parameter estimates for the ECog-SP total score. The Aβ−/α-syn− and Aβ−/α-syn+ groups did not differ across any of the ECog-SP scores, while the Aβ−/α-syn− group had less study partner–reported cognitive decline on total, memory, language, visuospatial, planning, and divided attention scores compared to the Aβ+/α-syn− group. The Aβ−/α-syn+ and Aβ+/α-syn− groups did not significantly differ across any of the ECog-SP scores, though there was a general pattern of the Aβ+/α-syn− group having more study partner-reported cognitive decline. None of the groups statistically differed on ECog-SP organization. In a sensitivity analysis that included the GDS score (minus the subjective memory question) as a covariate in the ECog-SP total score model, the general pattern of results did

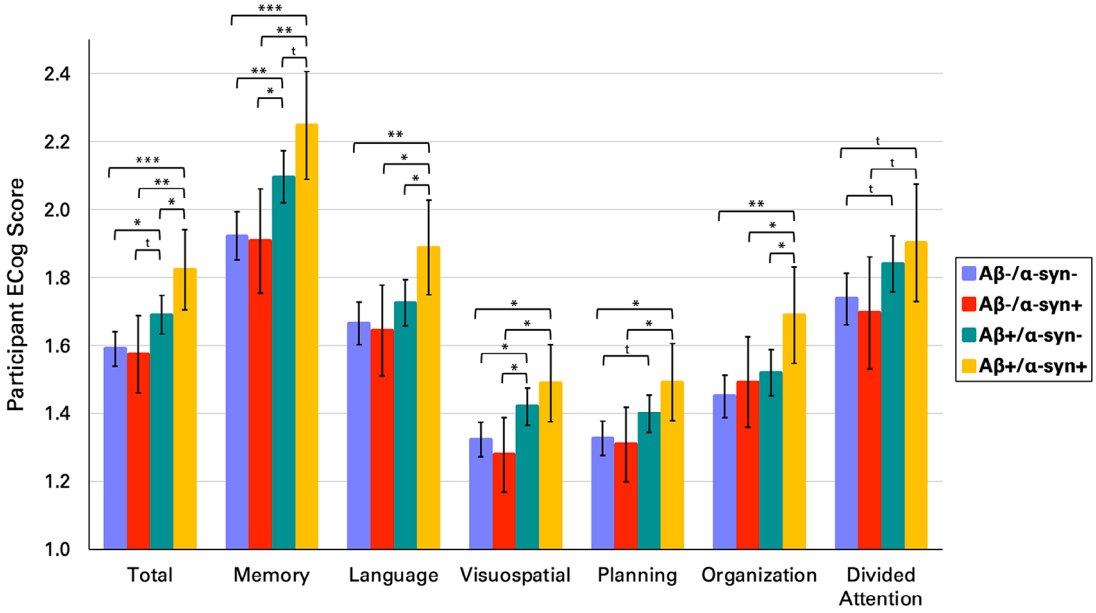

FIGURE 1 Estimated marginal means of participant-reported ECog scores by biomarker group. Error bars = 95% confidence interval. $^{t}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Aβ, amyloid beta; α-syn, α-synuclein; ECog, Everyday Cognition questionnaire.

TABLE 2 Parameter estimates for participant-reported ECog (ECog-PT) total score.

	Estimate	SE	*t*	η_p^2	*p*
Intercept	1.989	0.224	8.563	0.080	<0.001
Age	0.000	0.002	−0.153	0.000	0.878
Education	−0.009	0.007	−1.292	0.002	0.197
Female	0.023	0.034	0.677	0.001	0.499
Non-Hispanic white	0.107	0.055	1.960	0.004	0.050
MCI	0.201	0.036	5.834	0.036	<0.001
APOE ε4 carrier	0.002	0.038	0.058	0.000	0.954
Aβ−/α-syn−	−0.232	0.067	−3.441	0.013	<0.001
Aβ−/α-syn+	−0.248	0.084	−2.935	0.009	0.003
Aβ+/α-syn−	−0.132	0.065	−2.024	0.004	0.043
Aβ+/α-syn+ (ref)	–	–	–	–	–

Abbreviations: Aβ, amyloid beta; α-syn, α-synuclein; *APOE*, apolipoprotein E; ECog, Everyday Cognition questionnaire; MCI, mild cognitive impairment; SE, standard error.

not change, though the significant difference between the Aβ−/α-syn+ and Aβ+/α-syn+ group was slightly attenuated ($p = 0.059$).

3.4 | Impact of cognitive classification on the associations between biomarker group and participant- and study partner–reported cognitive decline

Next, we examined cognitive classification (CU or MCI) as a moderator between the associations of the biomarker group and ECog scores. For ECog-PT scores, cognitive classification was not a significant moderator of the association between the Aβ/α-syn biomarker group and any of the ECog-PT scores (all *p*s > 0.05).

For ECog-SP scores, cognitive classification was a significant moderator for the association between the Aβ/α-syn biomarker group and the ECog-SP memory score ($p = 0.025$). Specifically, within CU participants, ECog-SP memory scores did not differ across Aβ/α-syn biomarker groups ($p = 0.354$). However, within participants classified as MCI, there was a significant effect of the biomarker group ($p = 0.005$), suggesting that the MCI group drove the associations of the ECog-SP memory score and Aβ/α-syn biomarker group (Figure 3). Cognitive classification was not a significant moderator for any of the other ECog-SP scores (*p*s > 0.05).

4 | DISCUSSION

For both the ECog-PT and ECog-SP scores, there was a consistent pattern such that the Aβ+/α-syn+ had the greatest reported cognitive decline, followed by the Aβ+/α-syn− group, and then the Aβ−/α-syn+ and Aβ−/α-syn− groups. In general, the Aβ−/α-syn+ group did not differ from the Aβ−/α-syn− group. MCI classification did not moderate the associations for the ECog-PT scores and only moderated the association for the memory ECog-SP score.

For participant-reported cognitive decline, even after adjusting for cognitive classification, the ECog-PT total score was higher in the Aβ+/α-syn+ than in the other three groups. The Aβ+/α-syn− group significantly differed from the Aβ−/α-syn− group on the ECog-PT total and memory subscales (as well as visuospatial), which is consistent with prior work showing that subjective memory concerns are associated with Aβ in older adults without MCI or dementia.[14,18] We hypothesized

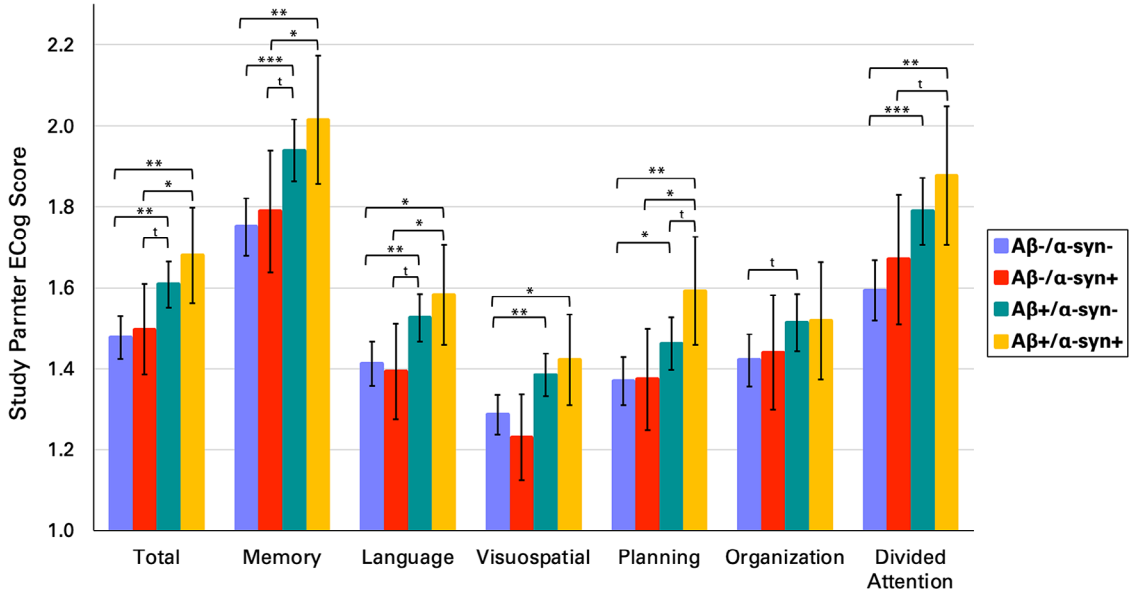

FIGURE 2 Estimated marginal means of study partner–reported ECog scores by biomarker group. Error bars = 95% confidence interval. $^{t}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Aβ, amyloid beta; α-syn, α-synuclein; ECog, Everyday Cognition questionnaire.

TABLE 3 Parameter estimates for study partner–reported ECog (ECog-SP) total score.

	Estimate	SE	*t*	η_p^2	*p*
Intercept	1.964	0.244	8.769	0.080	<0.001
Age	0.001	0.002	0.427	0.000	0.669
Education	−0.023	0.007	−3.474	0.013	<0.001
Female	0.117	0.034	3.413	0.013	<0.001
Non-Hispanic white	0.174	0.055	3.173	0.011	0.002
MCI	0.397	0.036	10.986	0.120	<0.001
APOE ε4 carrier	0.033	0.038	0.385	0.001	0.385
Aβ−/α-syn−	−0.204	0.067	−3.023	0.010	0.002
Aβ−/α-syn+	−0.183	0.084	−2.184	0.005	0.029
Aβ+/α-syn−	−0.108	0.065	−1.108	0.001	0.268
Aβ+/α-syn+ (ref)	–	–	–	–	–

Abbreviations: Aβ, amyloid beta; α-syn, α-synuclein; *APOE*, apolipoprotein E; ECog, Everyday Cognition questionnaire; MCI, mild cognitive impairment; SE, standard error.

that α-syn+ participants would report a greater decline in visuospatial and executive functions (e.g., planning, organization, divided attention) as these domains tend to change earlier in DLB/PD than in AD on objective neuropsychological measures.[32] This hypothesis was not consistent with the results for the Aβ−/α-syn+ biomarker group, and while the Aβ+/α-syn+ group did report the greatest visuospatial, planning, and organization difficulty, it only significantly differed from the Aβ+/α-syn− group on the total and organization score. Given the low sensitivity of α-synuclein SAA to detect amygdala predominant and transitional Lewy body pathology[6] in addition to the ADNI sample being selected for participants at risk for AD (e.g., amnestic MCI, those with subjective memory concerns) and not individuals at risk for DLB, it is possible that the power to detect effects of α-syn+ contributions to specific domains such as visuospatial and executive functioning is limited.

The ECog-PT total score results were slightly attenuated when depressive symptoms were included in the model such that the Aβ+/α-syn+ group still differed from the Aβ−/α-syn− and Aβ−/α-syn+ groups, but no longer statistically differed from the Aβ+/α-syn− group ($p = 0.106$). Consistent with some previous work showing that depressive symptoms can impact SCD,[11,33] this attenuated pattern suggests that even the restricted range of depressive symptoms of participants in ADNI may have a small impact on subjective report of cognitive decline. There are important nuances to consider about these depressive symptom results as neuropsychiatric symptoms may be prodromal symptoms related to AD and related dementias neuropathology.[34,35] Specifically, while depressive symptoms have been shown to be related to progression to AD dementia,[36] there is not consistent evidence that depressive symptoms are associated with amyloid pathology.[37,38] On the other hand, depressive symptoms are thought to be a more prominent feature of Lewy body pathology[39,40] and may be present at earlier stages in DLB and PD than in AD processes.[41] Thus, while the ECog-PT total score results are slightly attenuated for the comparison of Aβ+/α-syn− and Aβ+/α-syn+ groups with inclusion of depressive symptoms (mostly very mild symptoms) as a covariate, it may be possible that AD pathology, and, to a greater extent, Lewy body pathology, are impacting both subjective experience of cognitive decline and depressive symptoms. Notably, given that most participants in this study endorsed 0 to 3 depressive symptoms, further work is needed to understand the relationship of depressive symptoms, α-synuclein, and cognitive decline in a sample in which the results would generalize more broadly.

The overall pattern of results for the ECog-SP scores was very similar to those for the ECog-PT described above; however, there was not a statistically significant difference between the Aβ+/α-syn− and

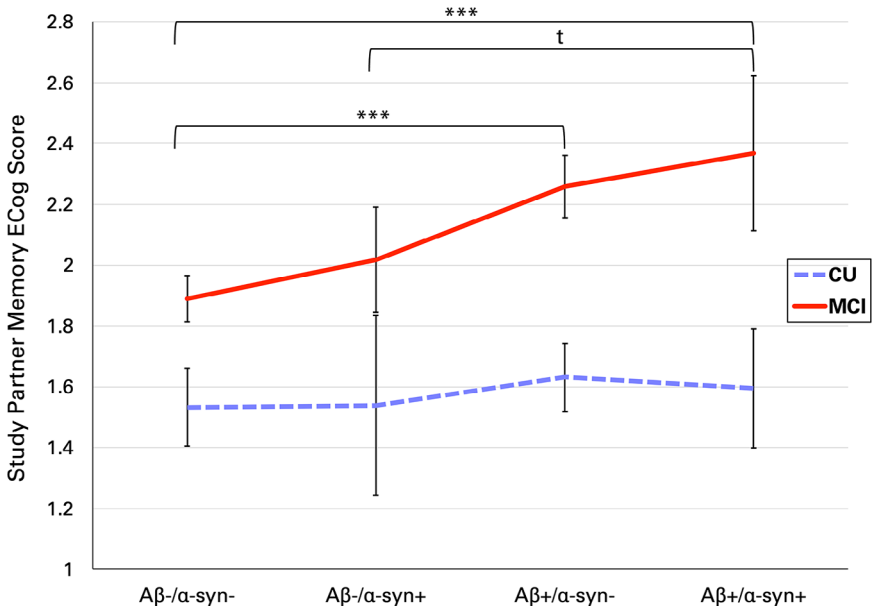

FIGURE 3 Moderating effect of cognitive group on estimated marginal means of study partner–reported ECog memory score by biomarker group. Error bars = 95% confidence interval. ***$p < 0.001$; $^{t}p < 0.1$. Aβ, amyloid beta; α-syn, α-synuclein; CU, cognitively unimpaired; ECog, Everyday Cognition questionnaire; MCI, mild cognitive impairment.

Aβ+/α-syn+ on the ECog-SP total score or any of the domain-specific subscales. This pattern of results was minimally impacted when depressive symptoms were adjusted for in the ECog-SP total score model, though the significant difference between the Aβ−/α-syn+ and Aβ+/α-syn+ group was attenuated ($p = 0.059$). For context, prior work has identified a study partner–reported ECog total score cutoff of 1.81 to best distinguish CU from impaired older adults with MCI/dementia and a cutoff of 1.32 to best distinguish CU older adults from MCI specifically.[42]

When cognitive classification was examined as a moderator of the association between the biomarker group and ECog-SP scores, the memory score differences were driven by the MCI group. This is consistent with prior work suggesting that informant reports on the ECog may be more consistent with objective cognition and AD biomarkers than self-report once someone reaches the MCI stage,[43,44] possibly due to the start of anosognosia.[45] Notably, prior work shows that amnestic MCI participants in particular begin to underreport their cognitive difficulties relative to their study partner,[45,46] which is in line with only the study partner–reported memory domain difficulties being moderated by MCI classification. Further, it is also possible that a study partner simply cannot observe very subtle cognitive changes in CU individuals because the participant is not yet making mistakes in their everyday life, even when the participant feels like everyday tasks are more effortful or difficult. Of note, the use of the comprehensive neuropsychological approach to classifying MCI[25–27] uses only objective cognitive measures and does not rely on subjective cognitive concerns in the classification of MCI, which avoids any potential circularity that might occur using MCI criteria that require a subjective cognitive concern.

When examining the role of amyloid on participant and study partner–reported ECog declines, we see that the Aβ+/α-syn+ had the greatest reported cognitive decline, followed by Aβ+/α-syn−. While the Aβ+/α-syn+ had slightly worse Aβ burden measured using the continuous CSF Aβ42 levels and amyloid PET in a large subset of participants ($n = 847$), these levels of Aβ did not significantly differ between Aβ+/α-syn+ and Aβ+/α-syn− groups (despite the Aβ+/α-syn+ being slightly older), suggesting that a non-significant higher amyloid level is likely not driving the greater report of cognitive decline in the Aβ+/α-syn+ group, particularly for self-reported cognitive decline. Rather, there may be a synergistic effect between Aβ and α-synuclein resulting in greater SCD, though the exact mechanisms are unclear. Prior work has suggested that Aβ and α-synuclein may interact to reduce protein clearance, activate inflammatory processes, increase tau phosphorylation, and/or directly enhance α-synuclein aggregation.[47] Given that a continuous measure of α-synuclein is not available with the synuclein SAA and there is no biomarker that yet reflects the burden of α-synuclein pathology in the brain, we cannot determine whether the Aβ−/α-syn+ and Aβ+/α-syn+ have different burdens or stages of α-synuclein brain pathology.

These SAA data in the context of the rich information available in ADNI are unique, though this SAA measure is likely to become used more widely in both research and clinical settings in coming years, particularly as skin biopsy and other even less invasive sampling approaches such as plasma α-synuclein SAAs continue to develop.[48] ADNI data provide many strengths including the multidomain nature of the ECog measure to get at cognitive domains beyond the usual memory concern questions, which could be important in the context of non-amnestic/non-AD or co-occurring pathologies. As shown in Figures 1 and 2, the memory subscale had higher self- and study partner–reported cognitive declines relative to other domains, which is consistent with memory concerns being the most common in other studies.[49] Unlike many SCD measures, the ECog allows for the measurement of declines in memory and non-memory cognitive domains, and these different ECog domain scores have been shown to be differentially related to biomarkers such as amyloid and tau.[50] The use of the ECog allows for a nuanced examination of the severity of self- and study partner–reported declines on cognitive and everyday tasks,

rather than providing a dichotomous classification of the presence or absence of SCD.

Limitations of the study include the cross-sectional CSF SAA data, the exclusion of individuals with prominent DLB features (e.g., notable psychiatric symptoms) from ADNI as well as the limited diversity of race/ethnicity in the available ADNI cohorts. Future longitudinal studies will investigate the extent to which the first pathology (Aβ or α-synuclein) impacts the subjective and subtle objective cognition profiles of older adults in the preclinical phase of their disease process. Further, the ADNI-4 cohort data collection is underway,[51] so it will be very important to examine how Aβ and α-synuclein co-pathologies relate to self- and study partner–reported cognitive declines across race/ethnicity groups in coming years.

The Aβ−/α-syn+ group had SCD levels more consistent with the Aβ−/α-syn− than the other single pathology group (Aβ+/α-syn−). This information provides important insights because neither self-report nor study partner report of everyday cognitive decline seem to be particularly useful at capturing α-synuclein pathology in the prodromal stages of DLB/PD when elevated Aβ is not also present. Thus, if SCD is used clinically to recommend biomarker testing,[52] early Lewy body disease might be missed. On the other hand, if an individual who does not yet meet criteria for dementia (or someone close to them) is reporting cognitive decline, use of α-synuclein SAA in addition to typical AD biomarkers could be useful when it comes to clinical decision making. For example, if someone has slightly elevated amyloid, but is also α-syn+ and has a neuropsychological profile or other features that may be more consistent with DLB (e.g., rapid eye movement sleep behavior disorder), it may alter whether AD is considered the primary pathology driving the cognitive difficulties and whether an amyloid-reducing medication should be considered. Taken together, the results highlight the notable benefit of measuring AD and Lewy body co-pathologies and show the importance of measuring co-pathologies to understand the etiology of self- and study partner–reported cognitive declines.

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CONFLICT OF INTEREST STATEMENT

Dr. Galasko is a consultant for Biogen, Eisai, Fujirebio, General Electric Healthcare, and Artery Therapeutics. Other authors report no disclosures. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

All data used in this manuscript are available to the public at the ADNI data repository at the Laboratory of Neuroimaging (http://adni.loni.usc.edu). Derived data are available from the authors upon request.

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SUPPORTING INFORMATION

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