


## RESEARCH ARTICLE

# Adding cognition to AT(N) models improves prediction of cognitive and functional decline

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\*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). As such, investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

## Funding information

US Department of Veterans Affairs Clinical Sciences Research and Development Service; Institutional Development, Grant/Award Number: U54GM115677; National Institute of General Medical Sciences; National Institutes of Health

## Abstract

**Introduction:** This study sought to determine whether adding cognition to a model with Alzheimer's disease biomarkers based on the amyloid, tau, and neurodegeneration/neuronal injury—AT(N)—biomarker framework predicts rates of cognitive and functional decline in older adults without dementia.

**Methods:** The study included 465 participants who completed amyloid positron emission tomography, cerebrospinal fluid phosphorylated tau, structural magnetic resonance imaging, and serial neuropsychological testing. Using the AT(N) framework and a newly validated cognitive metric as the independent variables, we used linear mixed effects models to examine a 4-year rate of change in cognitive and functional measures.

**Results:** The inclusion of baseline cognitive status improved model fit in predicting rate of decline in outcomes above and beyond biomarker variables. Specifically, those with worse cognitive functioning at baseline had faster rates of memory and functional decline over a 4-year period, even when accounting for AT(N).

**Discussion:** Including a newly validated measure of baseline cognition may improve clinical prognosis in non-demented older adults beyond the use of AT(N) biomarkers alone.

## KEYWORDS

aging, Alzheimer's disease, AT(N), cognitive decline, dementia, functional decline

## 1 | INTRODUCTION

In 2018 the National Institute on Aging and Alzheimer's Association (NIA-AA) workgroup proposed a research framework for biologically

defining Alzheimer's disease (AD) using a biomarker-based classification scheme: amyloid, tau, and neurodegeneration/neuronal injury, or "AT(N)."<sup>1</sup> This research framework marked a shift from prior clinical symptom staging (e.g., preclinical, mild cognitive impairment [MCI],

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dementia) approaches that used AD biomarkers to support likely etiology (per the 2011 NIA-AA staging guidelines),<sup>2-4</sup> to a classification scheme based on biomarkers irrespective of clinical symptoms, citing evidence that AD pathologic changes may precede clinical symptoms/cognitive changes by decades.<sup>5</sup> Using this framework, results from a recent study<sup>6</sup> showed that the inclusion of amyloid positron emission tomography (PET), tau PET, and cortical thickness (N) resulted in a small but statistically significant improvement in prediction of memory decline in 480 non-demented older adults compared to a model with cardiovascular, metabolic, and apolipoprotein E (APOE) data only. One notable limitation of this study was the absence of baseline cognitive status in the analyses, thus potentially overestimating the incremental prognostic value of AT(N) biomarkers. Given recent evidence that subtle cognitive changes may be detectable during or prior to the preclinical stage of amyloid accumulation,<sup>7,8</sup> integrating cognitive test performance with the AT(N) research framework may add prognostic value above and beyond biomarkers alone.

The aim of the present study was to determine the incremental value of adding baseline cognition to the AT(N) framework in predicting longitudinal rates of cognitive and functional decline in non-demented older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

## 2 | METHODS

Data used in the preparation of this article were obtained from the 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 (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

### 2.1 | Participants

A detailed description of the enrollment criteria for ADNI has been previously described.<sup>9</sup> Briefly, participants met the following criteria at enrollment: (1) 55-90 years old, (2)  $\geq 6$  years of education or work-history equivalent, (3) Hachinski Ischemia Scale  $< 5$ , (4) Geriatric Depression Scale  $< 6$ , (5) adequate vision and hearing to perform neuropsychological tests, (6) generally good health and without history of significant head trauma or neurologic disease, (7) stable on permitted medications, (8) reliable study partner, and (9) fluent in either English or Spanish.

Our study included 465 older adults without dementia, defined as a Clinical Dementia Rating (CDR) global score  $< 1$ , who had baseline neuropsychological testing, structural MRI, florbetapir amyloid PET, and cerebrospinal fluid (CSF) data. Dependent variables measured longitudinally were ADNI Memory and Executive Functioning composite scores,<sup>10,11</sup> Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13), Functional Activities Questionnaire (FAQ), and CDR

### HIGHLIGHT

- A newly validated cognitive metric of predicted versus measured cognitive test scores (DELTA score) at baseline improved prediction of rates of memory decline beyond biomarker data in non-demented older adults over a 4-year period.
- DELTA also improved prediction of functional decline beyond biomarker data.
- Considering baseline cognitive function may improve cognitive and functional prognosis in non-demented older adults beyond biomarker data.

### RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using conventional (e.g., PubMed) sources and meeting abstracts and presentations. Previous research has demonstrated the application of the AT(N) framework proposed in 2018 by the National Institute on Aging-Alzheimer's Association. Building on this research we examined the contributions of cognition in the amyloid, tau, and neurodegeneration/neuronal injury (AT[N]) framework.
2. **Interpretation:** Our findings led to a greater understanding of how both baseline cognitive and biological markers can independently improve prognosis in older adults at risk of dementia.
3. **Future directions:** The findings demonstrate the utility of baseline cognition using a newly validated cognitive measure in improving prognosis in older adults at risk for dementia. This article proposes a framework for exploring these models in more demographically and clinically diverse samples.

Sum of Boxes (CDR-SB) for ADNI Baseline, Year 1, Year 2, Year 3, and Year 4. See Section 2.3 for further details on dependent variable measures.

## 2.2 | Independent variables

### 2.2.1 | Cognitive status

We used a newly validated measure of cognition referred to as the "DELTA" (Discrepancy-Based Evidence for Loss of Thinking Abilities) score. The score was derived from and validated within the ADNI sample.<sup>12</sup> The DELTA score provides a composite metric of the

discrepancy between predicted cognitive scores and measured cognitive scores in memory, executive function, and language domains.<sup>12</sup> Predicted scores were based on demographic factors (i.e., age, education, sex) and estimated premorbid intellect based on word-reading ability. Higher baseline DELTA scores (greater discrepancy) were associated with faster rate of worsening functional status, higher PET-amyloid beta ( $A\beta$ ) standardized uptake value ratio (SUVR), and higher CSF p-tau/CSF  $A\beta$ -42 ratio.<sup>12</sup> Scores range from 0 to 15 with higher scores suggesting greater evidence for cognitive decline.

#### *Structural T1-weighted MR imaging*

The details of ADNI MRI data acquisition and processing can be found on ADNI's website ([adni.loni.usc.edu](http://adni.loni.usc.edu)). Briefly, structural scans collected at baseline and follow-up visits were motion corrected, skull-stripped, segmented, and parcellated using FreeSurfer (version 5.1). FreeSurfer-derived hippocampal volume was included as the marker of neurodegeneration given its implication in early stages of AD (e.g., Braak stages I/II).<sup>13</sup> Normalized hippocampal volume was created by dividing absolute hippocampal volume by FreeSurfer-derived estimated total intracranial volume and then multiplying the resulting value by the intracranial volume mean of the sample.

#### *Florbetapir PET*

The 18F-florbetapir tracer was used to quantify cortical  $A\beta$  burden during PET imaging. The details of data acquisition and processing of ADNI florbetapir PET data are available on the ADNI website ([adni.loni.usc.edu](http://adni.loni.usc.edu)); also see supporting information for more detail.

#### *Cerebrospinal fluid*

CSF biomarkers of AD were measured using Elecsys immunoassays ([adni.loni.usc.edu](http://adni.loni.usc.edu)). Hyperphosphorylated tau (p-tau) was used as the biomarker for tau.

#### *Apolipoprotein E*

All participants had APOE  $\epsilon$ 4 genotyping data available. APOE  $\epsilon$ 4 carriers and non-carriers were determined based on the presence of at least one  $\epsilon$ 4 allele. Of the 465 participants overall, 189 (40.6%) were  $\epsilon$ 4 carriers.

## 2.3 | Dependent variables

### 2.3.1 | ADNI memory and executive composite scores

The ADNI memory composite (ADNI-MEM)<sup>10</sup> includes sum of z-scores from the following tests: Rey Auditory Verbal Learning Test (word list learning trials, recall, and recognition), memory scores from the modified the Alzheimer's Disease Assessment Scales (word list learning, recall and recognition), Mini-Mental State Examination (word recall), and Wechsler Memory Scale-Revised Logical Memory (immediate and delayed recall trials). Higher ADNI-MEM scores indicate better performances. The ADNI executive composite (ADNI-EF)<sup>11</sup> is composed of

Wechsler Adult Intelligence Scale Revised (WAIS-R) Digit Symbol Substitution and Digit Span Backwards subtests, Trail Making Tests A and B, Category Fluency, and Clock Drawing scores. Higher scores on this measure indicate better performances. For more details on the psychometric protocols for both the ADNI-MEM and ADNI-EF composite scores, see [adni.loni.usc.edu](http://adni.loni.usc.edu).

### 2.3.2 | ADAS-Cog-13

ADAS-Cog-13<sup>14</sup> is a version of the ADAS-Cog modified with the addition of a number cancellation task and a delayed free recall task. The ADAS-Cog-13 is scored from 0 to 85, with lower scores indicating better performance.

### 2.3.3 | Clinical Dementia Rating<sup>15</sup>

The CDR is another assessment of everyday function and is a semi-structured informant and patient interview. The CDR global score classifies the severity of the patient's impairment into one of five stages: 0 (normal), 0.5 (mildly impaired/MCI), 1 (mild dementia), 2 (moderate dementia), 3 (severe dementia), though only participants with a CDR Global Score of 0 or 0.5 were included at baseline. The CDR-SB provides a more granular score for patient functioning that ranges from 0 to 18, with low scores indicating better functional status.<sup>16</sup> CDR-SB ranges generally correspond with global score functional groups as 0 = "normal," 0.5–4.0 = MCI, and > 4.0 = "dementia."<sup>16</sup>

### 2.3.4 | Functional outcomes

The FAQ<sup>17</sup> is an informant-based measure of the study participant's everyday functioning scored from 0 to 30 with lower scores indicating less difficulty performing instrumental activities of daily living functioning.

## 2.4 | Statistical analyses

Linear mixed effects (LME) modeling was used to examine the 4-year longitudinal trajectories in five dependent variables (DVs): three of cognition (ADNI-MEM, ADNI-EF, ADAS-Cog-13) and two of everyday functioning (CDR-SB and FAQ). To account for overlap in the cognitive measures included in the DELTA score and the ADNI-MEM and ADNI-EF composites, we included the ADAS-Cog, CDR-SB, and FAQ as outcome measures; these three measures are independent of the measures included in the DELTA score and therefore ensure that circularity in the specific measures was not driving any observed findings related to the ADNI composite scores.

Our four independent variables (IVs) of interest are the three biomarkers (i.e., amyloid-PET, CSF p-tau, and hippocampal volume) and the DELTA score. Given recent evidence suggesting that dichotomizing

**TABLE 1** Baseline sample characteristics

	Mean (SD) or N	Median (IQR) or %	Range
Age	72.22 (6.87)	72.60 (67.75–77.05)	55–89
Education	16.28 (2.64)	16 (14–18)	9–20
Female	212	45.6%	–
MMSE	28.38 (1.60)	29 (28–30)	23–30
Modified Hachinski score	0.62 (0.72)	1.00 (0–1)	0–4
APOE $\epsilon$ 4 carrier	189	40.6%	–
Amyloid-PET SUVR	1.19 (0.22)	1.09 (1.01–1.34)	0.84–2.03
CSF p-tau (pg/mL)	25.13 (12.99)	21.32 (16.47–30.42)	8–92
Hippocampal volume	7230.85 (1118.44)	7382.00 (6600.35–8123.4–8)	4214.30–10281.77
DELTA score	1.62 (2.24)	0.00 (0–3)	0–12
Memory composite	0.59 (0.69)	0.53 (0.10–1.08)	–1.53–2.36
Executive composite	0.58 (0.88)	0.54 (–0.02–1.21)	–2.01–2.99
ADAS-Cog-13	13.02 (6.37)	12 (8–17)	1–38
CDR Global Score of 0.5	335	72.0%	–
CDR Sum of Boxes	1.05 (0.97)	1.00 (0–1.5)	0–4.5
Functional Activities Questionnaire	2.02 (3.43)	0.00 (0–3)	0–22

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DELTA, Discrepancy-Based Evidence for Loss of Thinking Abilities; IQR, interquartile range; MMSE, Mini-Mental State Examination; n, number; PET SUVR, positron emission tomography standardized uptake value ratio; SD, standard deviation.

AD biomarkers (i.e., positive vs. negative status) may result in loss of important prognostic information,<sup>18</sup> we treated the three biomarker variables as continuous measures. All models adjusted for baseline age, sex, education, and APOE  $\epsilon$ 4 carrier status. Variables were converted to sample-based z-scores prior to analyses so that the parameter estimates would be comparable. Given the possibility of both linear and quadratic (i.e., accelerated) declines over time, both Visit and Visit<sup>2</sup> were included as main effects. The model fit was improved when Visit<sup>2</sup> was included as a main effect, but not when included in the interaction terms, so interaction terms involving Visit<sup>2</sup> were omitted from the models. Intercept and slope were included as random effects and a first-order autoregressive (AR [1]) repeated covariance structure was used. Full information maximum likelihood was used to compare nested models and to allow all available data to be included.

First, separate models were run examining the interaction of time (Visit) with each of the three biological biomarkers (i.e., baseline amyloid-PET, CSF p-tau, and hippocampal volume) and cognition (DELTA score) to establish the independent contribution of each of these four IVs on the rate of change of the five DVs across the 4-year time frame. Next, the three biomarker  $\times$  Visit interactions were included in the model together. Then, the DELTA  $\times$  Visit interaction was added as a fourth interaction to the model to determine whether there is added utility of the DELTA score for predicting change in the five DVs, over and above the variance explained by baseline amyloid-PET SUVR, CSF p-tau, and hippocampal volume.

Secondary analyses of all five models were run without including the covariates (age, sex, education, and APOE status). The pattern of results did not change and had a minimal impact on beta values; how-

ever, because some of the covariates did have significant effects in the adjusted models, the results reported below are of the covariate-adjusted models.

## 2.5 | Data availability

ADNI data were retrieved from [adni.loni.usc.edu](http://adni.loni.usc.edu). Data are available to investigators in the scientific community who have been approved by the ADNI Data Sharing and Publications Committee and who agree to the terms of the ADNI Data Use Agreement for purposes of replicating procedures and results. Anonymized ADNI participant identification numbers used in this article are available by request from any qualified investigator.

## 3 | RESULTS

Baseline sample characteristics are included in Table 1. Participants had a mean age of 72 years and had a mean of 16 years of education. On average, participants had global cognition that was in the normal range and reported very few functional difficulties at baseline.

Differences in baseline sample characteristics (age, education, sex, modified Hachinski Ischemic score, APOE  $\epsilon$ 4 status, global CDR score) between participants who were missing (n = 189) or non-missing (n = 276) at the Year 4 follow-up visit were examined. Analyses revealed that only age differed between the missing (mean age = 73.14 years, standard deviation [SD] = 6.65) and non-missing groups (mean

**TABLE 2** Independent contributions of amyloid, p-tau, hippocampal volume, and DELTA on rate of change

	Memory Comp		Executive Comp		ADAS-Cog		CDR-SB		FAQ	
	$\beta$ (SE)	$\Delta$ -2LL	$\beta$ (SE)	$\Delta$ -2LL	$\beta$ (SE)	$\Delta$ -2LL	$\beta$ (SE)	$\Delta$ -2LL	$\beta$ (SE)	$\Delta$ -2LL
Amyloid x Visit	-0.123 (0.011)***	97.35	-0.116 (0.014)***	65.45	0.162 (0.016)***	93.16	0.222 (0.021)***	100.87	0.167 (0.017)***	91.49
CSF p-tau x Visit	-0.105 (0.012)***	68.78	-0.089 (0.014)***	38.01	0.149 (0.017)*	79.23	0.176 (0.022)***	59.74	0.164 (0.017)***	85.82
Hippocampal volume x Visit	0.101 (0.012)***	63.47	0.086 (0.014)***	35.60	-0.125 (0.016)***	54.41	-0.208 (0.021)***	90.11	-0.149 (0.017)***	74.70
DELTA x Visit	-0.119 (0.012)***	80.89	-0.074 (0.015)***	22.37	0.166 (0.017)*	89.93	0.249 (0.020)***	130.55	0.200 (0.017)***	131.96

\*\*\* $P < .001$ .  $\Delta$  -2LL is the change in -2 Log Likelihood for each model when the independent biomarker or DELTA x Visit interactions are added to the model relative to the initial model that adjusted for age, education, sex, APOE  $\epsilon$ 4 carrier status, Visit, Visit<sup>2</sup>, baseline amyloid-PET, CSF p-tau, Hippocampal volume, and DELTA scores.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; DELTA, Discrepancy-Based Evidence for Loss of Thinking Abilities; FAQ, Functional Activities Questionnaire.

age = 71.59 years, SD = 6.95;  $t[463] = 2.40$ ;  $P = 0.017$ ). Sample characteristics of participants who were present at Year 4 are included in Table S1 in supporting information. We also ran additional exploratory analyses to ensure that missing data at Year 4 were not largely responsible for the observed pattern of findings. These analyses are presented in the Results section in supporting information.

Adjusted LME models examined the independent contribution of each of the three baseline AD biomarkers and the baseline DELTA score on rate of change of the Memory Composite, Executive Functioning Composite, ADAS-Cog, CDR-SB, and FAQ. Table 2 shows the independent effect of each IV x Visit interaction on each outcome measure and change in model fit. When examined separately (i.e., the IV x Visit interaction terms were added separately to the models with covariates and main effects only), each interaction effect significantly predicted rate of decline in all five outcomes. Higher baseline DELTA score, higher amyloid-PET SUVR, higher CSF p-tau, and lower hippocampal volumes were associated with faster rates of cognitive and functional decline.

Next, we examined whether the DELTA x Visit interaction predicted rates of change after the amyloid x Visit, p-tau x Visit, and hippocampal volume x Visit interactions were already included in the model. These results are presented in the paragraphs that follow. Table 3 shows the estimates of the final models for all DVs after the DELTA x Visit interaction was included and Figure 1 shows the trajectories by DELTA score.

For the ADNI-MEM model the biomarker x Visit interactions were all significant such that higher amyloid ( $\beta = -0.065$ , 95% confidence interval [CI],  $-0.092$  to  $-0.038$ ,  $P < .001$ ,  $r = -.222$ ), higher p-tau ( $\beta = -0.042$ , 95% CI,  $-0.068$  to  $-0.016$ ,  $P = .002$ ,  $r = -.153$ ), and lower hippocampal volume ( $\beta = 0.055$ , 95% CI,  $0.032$  to  $0.078$ ,  $P < .001$ ,  $r = .226$ ) were all associated with faster rates of ADNI-MEM decline. The addition of the DELTA x Visit interaction to the model significantly improved model fit ( $\chi^2(1) = 28.09$ ,  $P < .001$ ) such that a higher DELTA score was associated with faster ADNI-MEM decline ( $\beta = -0.067$ , 95% CI,  $-0.092$  to  $-0.043$ ,  $P < .001$ ,  $r = -.244$ ).

For the ADNI-EF model, the biomarker x Visit interactions were all significant such that higher amyloid ( $\beta = -0.076$ , 95% CI,  $-0.109$

to  $-0.043$ ,  $P < .001$ ,  $r = -.215$ ), higher p-tau ( $\beta = -0.033$ , 95% CI,  $-0.065$  to  $-0.001$ ,  $P = .047$ ,  $r = -.099$ ), and lower hippocampal volume ( $\beta = 0.052$ , 95% CI,  $0.023$  to  $0.080$ ,  $P < .001$ ,  $r = .177$ ) were all associated with faster ADNI-EF decline. The addition of the DELTA x Visit interaction ( $\beta = -0.024$ , 95% CI,  $-0.054$  to  $0.007$ ,  $P = .132$ ,  $r = -.072$ ) did not significantly improve model fit ( $\chi^2(1) = 2.27$ ,  $P = .132$ ).

For the ADAS-Cog-13 model, the biomarker x Visit interactions were all significant such that higher amyloid ( $\beta = 0.076$ , 95% CI,  $0.040$  to  $0.112$ ,  $P < .001$ ,  $r = .196$ ), higher p-tau ( $\beta = 0.069$ , 95% CI,  $0.034$  to  $0.104$ ,  $P < .001$ ,  $r = .187$ ), and lower hippocampal volume ( $\beta = -0.062$ , 95% CI,  $-0.092$  to  $-0.031$ ,  $P < .001$ ,  $r = -.191$ ) were all associated with faster ADAS-Cog-13 decline (higher scores = more errors). The addition of the DELTA x Visit interaction significantly improved model fit ( $\chi^2(1) = 35.10$ ,  $P < .001$ ) such that higher DELTA scores were associated with faster ADAS-Cog-13 decline/more errors ( $\beta = 0.100$ , 95% CI,  $0.067$  to  $0.043$ ,  $P < .001$ ,  $r = .270$ ).

For the CDR-SB model, the biomarker x Visit interactions were all significant such that higher amyloid ( $\beta = 0.110$ , 95% CI,  $0.064$  to  $0.155$ ,  $P < .001$ ,  $r = .215$ ), higher p-tau ( $\beta = 0.049$ , 95% CI,  $0.005$  to  $0.094$ ,  $p = .030$ ,  $r = .101$ ), and lower hippocampal volume ( $\beta = -0.110$ , 95% CI,  $-0.149$  to  $-0.071$ ,  $P < .001$ ,  $r = -.256$ ) were all associated with a faster rate of functional decline (higher scores = more difficulty). The addition of the DELTA x Visit interaction significantly improved model fit ( $\chi^2(1) = 59.78$ ,  $P < .001$ ) such that higher DELTA scores were associated with faster functional decline/more difficulty ( $\beta = 0.162$ , 95% CI,  $0.122$  to  $0.202$ ,  $P < .001$ ,  $r = .346$ ).

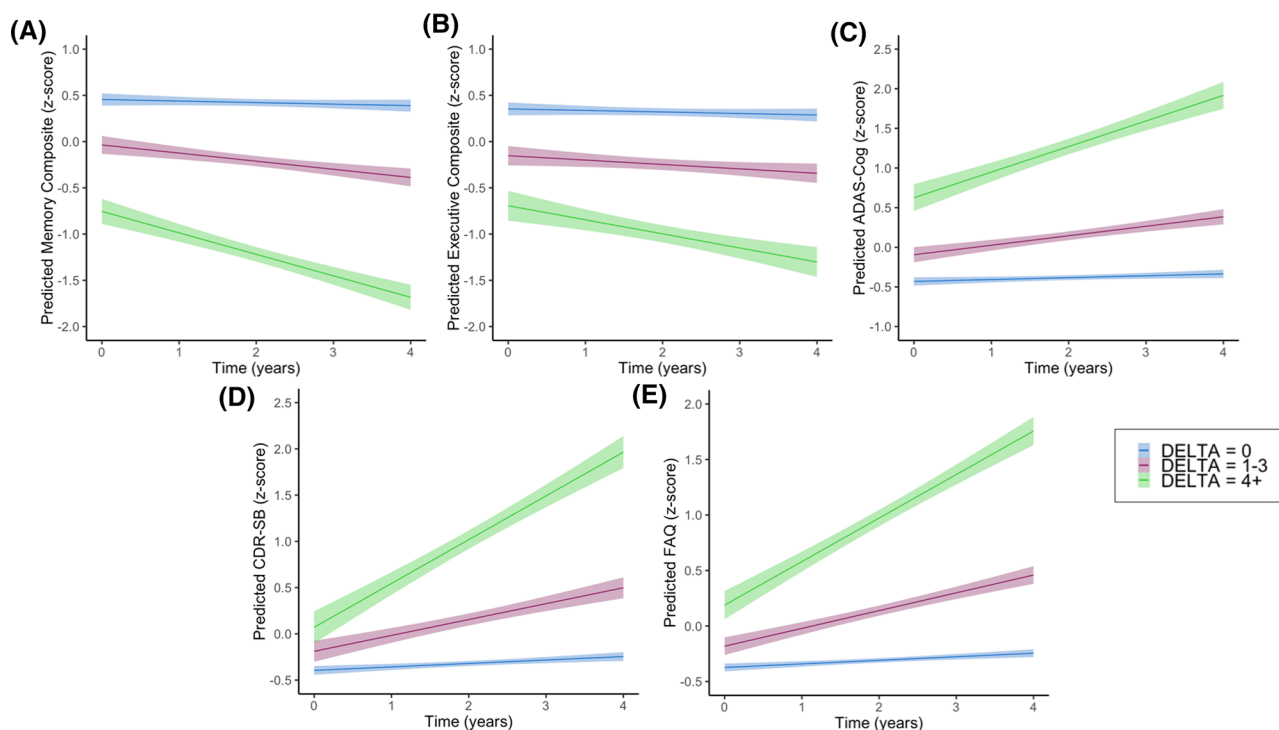
For the FAQ model, the biomarker x Visit interactions were all significant such that higher amyloid ( $\beta = 0.060$ , 95% CI,  $0.023$  to  $0.098$ ,  $P = .002$ ,  $r = .148$ ), higher p-tau ( $\beta = 0.079$ , 95% CI,  $0.042$  to  $0.115$ ,  $P < .001$ ,  $r = .196$ ), and lower hippocampal volume ( $\beta = -0.073$ , 95% CI,  $-0.105$  to  $-0.041$ ,  $P < .001$ ,  $r = -.214$ ) were all associated with faster functional decline (higher scores = more difficulty). The addition of the DELTA x Visit interaction significantly improved model fit ( $\chi^2(1) = 58.43$ ,  $P < .001$ ) such that higher DELTA scores were associated with faster functional decline/more difficulty ( $\beta = 0.133$ , 95% CI,  $0.100$  to  $0.166$ ,  $P < .001$ ,  $r = .348$ ).

**TABLE 3** Parameter estimates for AD biomarkers and DELTA scores and rates of change by longitudinal outcome

	Memory Comp $\beta$ (SE)	Executive Comp $\beta$ (SE)	ADAS-Cog $\beta$ (SE)	CDR-SB $\beta$ (SE)	FAQ $\beta$ (SE)
Intercept	-0.045 (0.029)	-0.072 (0.034) <sup>†</sup>	0.056 (0.029)	0.049 (0.030)	0.042 (0.031)
Age	-0.013 (0.033)	-0.184 (0.039) <sup>***</sup>	-0.040 (0.033)	-0.136 (0.034) <sup>***</sup>	-0.124 (0.035) <sup>***</sup>
Education	0.124 (0.030) <sup>***</sup>	0.117 (0.036) <sup>**</sup>	-0.056 (0.030)	-0.043 (0.032)	-0.021 (0.032)
Female	0.177 (0.030) <sup>***</sup>	0.018 (0.036)	-0.078 (0.030) <sup>†</sup>	-0.031 (0.032)	-0.051 (0.032)
APOE $\epsilon$ 4 carrier	-0.056 (0.033)	-0.019 (0.039)	0.028 (0.033)	0.041 (0.034)	0.034 (0.035)
Visit	0.063 (0.028) <sup>†</sup>	-0.016 (0.033)	-0.052 (0.035)	0.118 (0.035) <sup>**</sup>	0.198 (0.035) <sup>***</sup>
Visit <sup>2</sup>	-0.176 (0.028) <sup>***</sup>	-0.055 (0.034)	0.207 (0.036) <sup>***</sup>	0.101 (0.034) <sup>**</sup>	-0.012 (0.036)
Amyloid-PET	-0.175 (0.038) <sup>***</sup>	-0.205 (0.045) <sup>***</sup>	0.189 (0.038) <sup>***</sup>	0.208 (0.039) <sup>***</sup>	0.179 (0.041) <sup>***</sup>
CSF p-tau	-0.142 (0.035) <sup>***</sup>	-0.047 (0.042)	0.129 (0.034) <sup>***</sup>	0.089 (0.038) <sup>†</sup>	0.099 (0.038) <sup>†</sup>
HV	0.248 (0.034) <sup>***</sup>	0.103 (0.041) <sup>†</sup>	-0.264 (0.034) <sup>***</sup>	-0.255 (0.036) <sup>***</sup>	-0.250 (0.037) <sup>***</sup>
DELTA Score	-0.412 (0.033) <sup>***</sup>	-0.356 (0.039) <sup>***</sup>	0.447 (0.033) <sup>***</sup>	0.356 (0.034) <sup>***</sup>	0.338 (0.035) <sup>***</sup>
Amyloid $\times$ Visit	-0.065 (0.014) <sup>***</sup>	-0.076 (0.017) <sup>***</sup>	0.076 (0.018) <sup>***</sup>	0.110 (0.023) <sup>***</sup>	0.060 (0.019) <sup>**</sup>
p-tau $\times$ Visit	-0.042 (0.013) <sup>**</sup>	-0.033 (0.016) <sup>†</sup>	0.069 (0.017) <sup>***</sup>	0.049 (0.023) <sup>†</sup>	0.079 (0.019) <sup>***</sup>
HV $\times$ Visit	0.055 (0.012) <sup>***</sup>	0.052 (0.014) <sup>***</sup>	-0.061 (0.016) <sup>***</sup>	-0.110 (0.020) <sup>***</sup>	-0.073 (0.016) <sup>***</sup>
DELTA $\times$ Visit	-0.067 (0.013) <sup>***</sup>	-0.024 (0.016)	0.100 (0.017) <sup>***</sup>	0.162 (0.020) <sup>***</sup>	0.133 (0.017) <sup>***</sup>

\*\*\*  $P < .001$ ; \*\*  $P < .01$ ; <sup>†</sup>  $P < .05$ .

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; APOE, apolipoprotein E; CDR-SB, Clinical Dementia Rating-Sum of Boxes; DELTA, Discrepancy-Based Evidence for Loss of Thinking Abilities; FAQ, Functional Activities Questionnaire; HV, hippocampal volume; PET, positron emission tomography.



**FIGURE 1** Trajectories of cognitive and functional outcomes by DELTA score. The memory composite (A), executive composite (B), ADAS-Cog (C), CDR-SB (D), and FAQ (E) model predicted values displayed in z-score metric. The DELTA score categories shown in the figure of DELTA = 0 ( $n = 251$ ), DELTA = 1-3 ( $n = 133$ ), and DELTA = 4+ ( $n = 81$ ) were used for graphing purposes only. The continuous DELTA score was used in the models. Higher memory and executive composite scores are associated with better performance, while higher ADAS-Cog, CDR-SB, and FAQ scores are associated with worse functioning. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; DELTA, Discrepancy-Based Evidence for Loss of Thinking Abilities; FAQ, Functional Activities Questionnaire

## 4 | DISCUSSION

The current study investigated the value of incorporating cognition into models using the AT(N) research framework to predict rates of cognitive and functional decline among older adults without dementia. The results showed that amyloid-PET SUVR, CSF p-tau level, and hippocampal volume as continuous variables, as well as the DELTA score were each independently associated with rates of cognitive and functional decline after adjusting for demographic and genetic susceptibility variables. Importantly, we also found that baseline DELTA score improved these prognostic models above and beyond the AT(N) biomarkers for all cognitive and functional outcomes except for executive function. Our results showed that the incremental prognostic value of the DELTA score was greatest for functional status (i.e., CDR-SB and FAQ). This result highlights the value of comprehensive neuropsychological assessment for aiding patients, caregivers, and providers in making important prognostic and life-planning decisions.

We chose to focus on cognition and function because declines in these abilities are cardinal clinical features of most manifestations of AD. Our study addresses the limitation of the absence of cognition, in a previous study,<sup>19</sup> by incorporating a newly validated measure of cognition (DELTA) that we consider, based on previous findings,<sup>12</sup> to be a robust indicator of individuals "at risk" of cognitive decline. Moreover, cognitive evaluations are routinely performed in clinical settings in the context of memory complaints in older populations and so should be considered especially pertinent clinical data. The question of whether baseline cognitive status improves prediction of clinical decline over-and-above baseline biomarker status among individuals at risk of developing dementia due to presumed AD has not been well addressed. This may be due to a degree of consensus that AD biomarkers auger development of AD dementia decades before measurable cognitive decline occurs.<sup>3</sup> Recent studies<sup>7-8</sup> however, showed that subtle cognitive difficulties, objectively defined using neuropsychological measures, may emerge earlier than expected and be detectable during the stage of accelerated amyloid accumulation and prior to entorhinal cortex neurodegeneration. These findings and those of the present study highlight the prognostic importance of using sensitive neuropsychological measures to improve prediction of future memory and functional decline.

One challenge for researchers has been to develop cognitive metrics with greater sensitivity to early cognitive change and that can reliably discriminate between normal and early pathological cognitive aging.<sup>20</sup> An emerging approach is to validate cognitive assessments against biomarkers to increase confidence that evidence for cognitive changes reflects some meaningful biologic changes.<sup>21</sup> For example, the DELTA score incorporates several psychometric and interpretive principles (e.g., low score base rates, multiple test scores from different cognitive domains, key demographic and premorbid intellect factors) and core AD biomarkers were used to establish its validity.

While the increasing availability of acquiring biomarker information has rapidly accelerated neurodegenerative disease research, the acquisition of PET and CSF biomarkers is not feasible in many clinical settings given their extensive cost and burden to patients and

research participants. Blood-based biomarkers appear promising, particularly for detecting AD changes, but are still in development or not yet widely available.<sup>22,23</sup> This underscores the need for less expensive and more accessible measures that aid prognostic formulations. The current results highlight the prognostic value of cognitive metrics like the DELTA score, and future work should incorporate such cognitive composites with emerging blood-based biomarkers to fully optimize their translation from research to clinical settings. Furthermore, while these novel biomarkers will be critical for understanding underlying etiology and identifying treatment targets, any person-centered treatment approach ultimately needs to also consider cognition, which is more proximal to the clinical outcomes that ultimately impact people's lives.

### 4.1 | Limitations

There are several limitations to the current study. First, using NIA-AA recommended biomarkers as continuous variables limits direct comparison to other studies using a dichotomous classification scheme. Recently published research by Mattsson-Carlgen et al,<sup>18</sup> however, demonstrated that different operationalizations of AT(N) biomarkers (i.e., p-tau versus tau PET) resulted in divergent results and that dichotomization of biomarkers may result in loss of prognostic information compared to using data as continuous variables. Using these biomarkers on a continuous scale allows for more fine-tuned statistical modeling focused on exploring patterns of associations in older adults at risk for cognitive and functional decline.

Second, using a cognitive measure (i.e., the DELTA score) to predict cognitive outcomes (i.e., ADNI-MEM and ADNI-EF composite scores) raises the issue of shared variance/circularity and how this may superficially magnify associations because it has long been established that all cognitive abilities correlate with each other.<sup>24</sup> All models; however, were adjusted for baseline DELTA because our primary focus was on examining rates of decline rather than the main effect associations with outcomes. Additionally, a similar pattern of findings was revealed using conceptually distinct functional outcome measures (i.e., CDR-SB and FAQ), which further bolsters the robustness of the current study findings.

Third, we did not account or control for cerebrovascular pathology, which is common in older adults,<sup>25</sup> and early in AD.<sup>26</sup> Indices of cerebrovascular pathology, such as white matter hyperintensities, have been shown to negatively correlate with memory,<sup>26</sup> and executive functions.<sup>27-29</sup> Furthermore, the presence of cerebrovascular pathology may exacerbate or alter the presence of AD biomarkers,<sup>30</sup> although the interaction or synergistic effect of various age-related disease pathologies is not well understood. Notably, when we included the main effect of the modified Hachinski score as a crude measure of ischemia risk, as well as the Hachinski score by Visit interaction, in the models, the pattern of results remained the same, likely due to the relatively low variability of scores in this very healthy sample. Future studies should examine the potential role of cerebrovascular biomarkers (e.g., white matter hyperintensities) in addition to the AT(N) model

in understanding AD. The ADNI sample is predominantly White, highly educated, and has been screened to be very healthy at baseline, and is therefore not representative of the US population, significantly limiting the generalizability of these findings. Furthermore, as is common in longitudinal studies, not all participants contributed data to follow-up visits, which may reflect a survivor bias; however, exploratory analyses revealed that missing data did not significantly impact the association between the DELTA score and any of the outcome variables over time, with the exception of the FAQ score in which missing data had a small effect on this relationship. Future studies must extend and replicate these approaches in more diverse samples.

## 5 | CONCLUSION

Baseline cognition measured using a newly developed cognitive composite score (DELTA) improved prediction of longitudinal cognitive and functional changes above and beyond standard AD biomarkers. Integrating cognition with AT(N) biomarkers may improve clinical prognosis for non-demented older adults.

### CONFLICTS OF INTEREST

There are no conflicts of interest to report.

### AUTHOR CONTRIBUTIONS

Deirdre M. O'Shea, Breton Asken, Athene K.W. Lee, Jennifer D. Davis, Paul F. Malloy, Stephen P. Salloway, and Stephen Correia conceived the study. Kelsey R. Thomas conducted all the analyses and wrote up the interpretation of the results. Deirdre O'Shea, Breton Asken, and Stephen Correia contributed to the write-up of the study.

### FUNDING SOURCES

Dr. Thomas was supported by the US Department of Veterans Affairs Clinical Sciences Research and Development Service (Career Development Award-2 1IK2CX001865) and the Alzheimer's Association (AARF-17-528918).

Athene Lee is partially supported by Institutional Development Award Number U54GM115677 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds Advance Clinical and Translational Research (Advance-CTR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; NIH grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2- 0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen

Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California.

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## SUPPORTING INFORMATION

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

**How to cite this article:** O'Shea DM, Thomas KR, Asken B, et al. Adding cognition to AT(N) models improves prediction of cognitive and functional decline. *Alzheimer's Dement.* 2021;13:e12174. <https://doi.org/10.1002/dad2.12174>