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RESEARCH ARTICLE

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Alzheimer's disease biomarkers as predictors of trajectories of depression and apathy in cognitively normal individuals, mild cognitive impairment, and Alzheimer's disease dementia

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Objectives: To examine trajectories of depression and apathy over a 5-year follow-up period in (prodromal) Alzheimer's disease (AD), and to relate these trajectories to AD biomarkers.

Methods: The trajectories of depression and apathy (measured with the Neuropsychiatric Inventory or its questionnaire) were separately modeled using growth mixture models for two cohorts (National Alzheimer's Coordinating Center, NACC, n = 22 760 and Alzheimer's Disease Neuroimaging Initiative, ADNI, n = 1 733). The trajectories in ADNI were associated with baseline CSF AD biomarkers ($A\beta_{42}$, t-tau, and p-tau) using bias-corrected multinomial logistic regression.

Results: Multiple classes were identified, with the largest classes having no symptoms over time. Lower $A\beta_{42}$ and higher tau (ie, more AD pathology) was associated with increased probability of depression and apathy over time, compared to classes without symptoms. Lower $A\beta_{42}$ (but not tau) was associated with a steep increase of apathy, whereas higher tau (but not $A\beta_{42}$) was associated with a steep decrease of apathy.

Discussion: The trajectories of depression and apathy in individuals on the AD spectrum are associated with AD biomarkers.

KEYWORDS
Alzheimer's disease, apathy, cerebrospinal fluid biomarkers, depression, mild cognitive impairment, neurocognitive disorders

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the 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

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1 | INTRODUCTION

Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) occur in nearly all patients over the disease course, including its prodromal phases.[1,2] Unlike the deterioration seen for cognition and daily function, "affective" NPS such as depression and apathy do not necessarily progress in one direction over time but rather may persist, remit, or recur episodically.[3] Although depression and apathy frequently co-occur, they also exist separately and it has been argued that both should be considered as distinct conditions,[4] each with its own biological correlates[5] and course over time.

The neuropathological changes of AD are extracellular accumulation of amyloid-B peptides in plaques and the intracellular accumulation of hyperphosphorylated tau proteins in neurofibrillary tangles.[6,7] Cerebrospinal fluid (CSF) analytes such as amyloid-$\beta_{1\text{-}42}$ ($A\beta_{42}$), phosphorylated-tau (p-tau), and total tau (t-tau) are thought to reflect these changes by their association with the presence of beta-amyloid deposition, neurofibrillary tangles, and neuronal loss.[8] An increased understanding of the underlying biological mechanisms of depression and apathy in the context of AD can result in better recognition and treatment options. According to a recent systematic review, the association between CSF AD biomarkers and depression and apathy in mild cognitive impairment (MCI) and AD dementia has been examined in 16 and 3 studies, respectively.[9] Overall, no evidence was found that associated depression with amyloid, p-tau or t-tau. The authors hypothesized that this null-finding could be due to the grouping of heterogeneous phenotypes together. For apathy, the scarcity of studies and contrasting findings led to the recommendations for future research. In addition to the observed heterogeneity of study designs, settings, samples, and concept definitions, only few longitudinal studies were identified. That is, the association between baseline CSF biomarkers and depression[10] or apathy *over time*[11] was examined in *one* study each. Barca et al identified three distinct trajectories of depressive symptoms in a sample of persons with MCI and AD dementia.[10] Interestingly, the class with moderate and increasing depression scores had lower baseline CSF $A\beta_{42}$ levels (but not higher tau) compared to the class with stable low depression.[10] Donovan et al reported no association between CSF biomarkers and apathy over time, modeling a single growth trajectory.[11]

Key points

- Trajectories of depression and apathy across the AD spectrum were identified
- The largest classes identified had stable low symptoms over time
- The trajectories identified were then related to CSF AD biomarkers: more AD pathology was associated with increased probability of symptoms over time

The primary aim of the present study was to examine whether distinct trajectories of depression and apathy exist in individuals comprising the AD spectrum (ie, cognitively normal [CN], MCI, dementia) in two separate cohorts. The secondary aim was to investigate whether these trajectories are predicted differentially by baseline AD biomarkers.

2 | METHODS

2.1 | Sample

Both National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI) consist of referral/volunteer-based case series of individuals diagnosed as CN, MCI, or dementia at Alzheimer's Disease Centers across the United States. For NACC, data was used from Uniform Dataset (UDS) visits conducted between September 2005 and December 2018. For ADNI, data was used from visits conducted between September 2005 and January 2018. The initial studies for both NACC (UDS version 1) and ADNI (ADNI-1) have been extended throughout the years, resulting in various study-phases (NACC version 1, 2, and 3; ADNI-1, ADNI-go, and ADNI-2). A description of the study designs can be found elsewhere (NACC,[12,13]; ADNI (http://www.adni-info.org/). In NACC, individuals are followed up approximately yearly, whereas in ADNI half-yearly. Although the analyses with which the depression and

apathy trajectories were modeled (growth mixture modeling [GMM], see Section 2.5.1.) can handle missing values, data points after a 5-year follow-up were scarce. Therefore, for the present study, data up to 5 years were used.

For ADNI, the key eligibility criteria are as follows: individuals must be between 55- and 90-year old, the Hachinski Ischemic Score (indicator of vascular damage) must be less than or equal to 4, the Geriatric Depression Scale (GDS) must be less than 6, the cognitive impairment cannot be attributed to medication use, a current diagnosis of major depression or other psychiatric disorder. To ensure compatibility of the two cohorts, we retrospectively employed these criteria for NACC. Further, as ADNI was designed to examine AD specifically, etiologies other than AD dementia were excluded in NACC as well. In total, this resulted in the exclusion of 5 957 subjects. Baseline characteristics of the cohorts are shown in Table 1.

TABLE 1 Baseline demographic and clinical characteristics for participants enrolled in the in the National Alzheimer's Coordinating Center (NACC) or Alzheimer's Disease Neuroimaging Initiative (ADNI) and who were used in the trajectory analyses, excluding non-AD dementias

	NACC = 22 760	ADNI, n = 1 733
Diagnosis, N (%)		
Cognitively normal	13 778 (60.5)	521 (30.1)
Mild cognitive impairment	6289 (27.6)	874 (50.5)
AD dementia	2693 (11.8)	337 (19.5)
Age at baseline, M (SD)	72.9 (8.0)	73.8 (7.2)
Gender, female, N (%)	13 377 (58.8)	778 (44.9)
Education in years, M (SD)	15.5 (3.2)	15.9 (2.9)
Ethnicity, Caucasian, N (%)	4449 (19.6)	1601 (92.4)
MMSE, M (SD)	27.8 (2.6)	27.2 (2.7)
Follow-up visits, M (SD)	5.8 (4.0)	7.2 (3.1)
Follow-up time in months, M (SD)	28.9 (23.7)	37.3 (18.6)
Medical history[a]		
History of major depression, N (%)	4058 (18.1)	90 (35.4)
History of anxiety disorder, N (%)	NA	3 (0.6)
Medication use[a]		
Antidepressants, N (%)	4806 (21.2)	233 (25.5)
Other behavioral medication, N (%)	2646 (11.7)	48 (5.3)
Alzheimer medication[b], N (%)	3306 (14.6)	251 (27.5)
Affective symptoms[c]		
Depression present, N (%)	4130 (18.7)	367 (21.2)
Apathy present, N (%)	2391 (10.8)	272 (15.7)

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MMSE, Mini-Mental State Examination; NA, not available; NACC, National Alzheimer's Coordinating Centre.
[a]Information available for a subset of participants.
[b]Including cholinesterase inhibitors and memantine.
[c]According to the Neuropsychiatric Inventory.

2.2 | Clinical assessment

In both cohorts, a comparable standardized assessment took place at study entry. All participants underwent neurological, neuropsychological, and neuropsychiatric examination. This included recording of sociodemographic characteristics (gender, age, educational years, and race). Participants and a knowledgeable informant were asked about their medical and psychiatric history (recent/active or remote/inactive episodes of anxiety or depression), and whether they used prescription medications of interest here: (1) antidepressants, (2) other behavioral medications, such as antipsychotics/anxiolytics, sedative or hypnotic agents, or (3) FDA-approved "Alzheimer" medications. Global cognitive functioning was assessed in both cohorts on the Mini-Mental State Examination (MMSE[14]). These data were reviewed by a multidisciplinary team which made diagnoses of MCI based on the Petersen criteria.[15] For ADNI, diagnoses of dementia were based on DSM-IV-TR criteria. For NACC UDS versions 1 and 2, the diagnostic criteria for all-cause dementia were not specified. For UDS version 3, the NIA-AA criteria were used.[16] Etiological diagnoses of AD were established by NINCDS-ADRDA criteria[17] for NACC UDS versions 1 and 2 and ADNI, whereas NACC UDS version 3 utilized NIA-AA criteria.[16]

2.3 | Neuropsychiatric assessment

The Neuropsychiatric Inventory (NPI) is a widely used informant-based measure of neuropsychiatric symptoms (NPS) that follows positive screening responses up to characterize frequency, severity and caregiver burden in 12 domains of symptoms, including apathy and dysphoria (depression).[18] Typically, these frequency and severity ratings are multiplied to yield a total domain score. This "full-NPI" was utilized in ADNI phase II only; whereas in NACC, ADNI phase I, and ADNI GO, the NPI-questionnaire (NPI-Q) was used. The NPI-Q is a simplified version of the full questionnaire and unlike the full NPI, does not assess frequency of symptoms. In the present study, depression and apathy as outcome variables were therefore dichotomized at each visit as present (severity >0) or absent.

2.4 | Biomarker assessment (ADNI)

Baseline biomarker data from ADNI were considered in the present study. The CSF biomarker determination procedures have been

described in detail elsewhere (online at adni-info.org). To measure $A\beta_{42}$, t-tau and p-tau levels, the CSF biomarker aliquots of all available samples were recently re-analyzed using the Roche Elecsys electrochemiluminescence immunoassay, using the same reagent lot for each biomarker. To enhance the interpretation and comparison of the three pathologies (each with a different scale), the raw biomarker levels were converted into z-scores based on the means and SDs of the CN subjects. To facilitate comparison of the current results with other cohorts, we also report results for raw CSF scores in Table S1.

2.5 | Statistical analysis

All GMM analyses were done in Mplus, version 8.[19] Further analyses, such as descriptive analyses and plots, were done using R v. 3.5.1.[20] NACC was used to identify latent classes of trajectories. Next, we sought to validate the measurement model in ADNI (part I). Including ADNI trajectories also allowed us to examine whether these trajectories are predicted differentially by baseline AD biomarkers (part II).

Baseline values for demographic and clinical variables were summarized separately for NACC and ADNI (Table 1); for those with vs without follow-up measurements available (Tables S2-S4); for ADNI participants with vs without biomarker data available (Tables S2-S4); and per class (NACC-depression classes; NACC-apathy classes; ADNI-depression classes; ADNI-apathy classes, Tables S7-S10), and compared using analysis of variance and χ^2 tests.

2.5.1 | Part I: Symptom trajectories in NACC and ADNI

GMM was used to model subtypes of trajectories of the occurrence of depression or apathy over time, regardless of syndromal diagnosis or other clinical characteristics, for each cohort separately.[21] These models combine latent class analysis with growth curves, that is, they allow for the estimation of latent (unobserved) classes of individuals based on similarities on their affective symptom course. Model parameters of each growth trajectory (ie, intercept, linear slope, quadratic term) are allowed to vary across the latent classes.

Models with both linear and quadratic terms were fit with an increasing number of classes (up to 5). The optimal number of classes was chosen using the Lo-Mendell-Rubin likelihood ratio tests (LMR-LRT).[22,23] Model fit was assessed via comparison of observed and predicted trajectories. To fit a smooth curve to longitudinal dichotomous data (as depression and apathy were rated as absent/present), a LOESS-curve fitting method was used. This is a nonparametric method where least-squares regression is performed in localized subsets, resulting in a "running average" of zero's and ones.[24] The selection of the "correct" number of classes is central to our interpretation, which is known to be influenced by the method used to impose the random effects structure of the model. In addition to LMR-LRT, our decisions in model selection were based on parsimony, replicability, and clinical interpretability.

2.5.2 | Part II: Biomarker association with symptom trajectories in ADNI

Because NACC lacks standardized AD biomarker data, only ADNI baseline AD biomarkers were associated with symptom trajectories. After deciding upon number of classes for depression or apathy, probabilities of membership in each class were calculated for each participant, based on how well their trajectory matched the mean trajectories of each of the classes. These probabilities can then be used to assign individuals to a class, which in turn can be used as an outcome in logistic regression analyses. However, this method does not take uncertainty of assigned class membership into account. Therefore, the three-step method was used.[25,26] ADNI baseline biomarker levels were used as predictors.

3 | RESULTS

3.1 | Sample characteristics

Baseline characteristics of the two cohorts are in Table 1. NACC provided 20 724 participants with a mean follow-up of 29.5 months. At baseline, the prevalence of symptoms of depression and apathy were 17.4% and 9.3%, respectively. ADNI had 1733 eligible participants available with mean follow-up of 37.1 months. At baseline, the prevalence of depression and apathy were 21.2% and 15.7%. For NACC, the majority of participants falls within the CN diagnostic group, for ADNI this is the MCI group ($\chi^2_{(df)} = 1493_{(2)}$, $P < .0001$). As expected, biomarker levels differed significantly by diagnostic group, with CN having the highest $A\beta_{42}$ and lowest tau levels compared to MCI and AD participants.

For both cohorts, those with only one measurement available (ie, dropouts) had on average a lower MMSE score and were more often diagnosed with dementia. For NACC, dropouts took more often medication, and were more likely to have depression and apathy than those with follow-up measurements available (see Tables S2-S4). The subset of ADNI participants with biomarker data available (n = 1214) was younger, more educated, more often Caucasian, had higher MMSE scores, provided more follow-up data, and were less likely to take FDA-approved AD medications compared to those without biomarker data (Tables S2-S4).

3.2 | Part I: Symptom trajectories in NACC and ADNI

We independently repeated the modeling process to arrive at the best-fit model in NACC and thereafter in ADNI. Tables S5 and S6

provide a detailed overview of the processes of class enumeration and summarizes the series of model fit indices.

3.2.1 | Depression

For NACC, when fitting models with increasing number of classes, the 5-class model provided the best fit according to the LMR-LRT (4- vs 5-class model: 41.43, $P < .0001$). The best-fitting model included a quadratic term and no random effects. Figure 1 shows the fitted depression trajectories for each class, along with the (LOESS-curve smoothed) observed trajectories, where each individual is assigned to the class they most likely belong to. The majority of the sample (65.4%) would be expected to belong to class 5 with the absence of depression over time. Three classes had a relatively high probability of depression at baseline, and showed a small decrease (class 1, 14.0%), a steep decrease (class 4, 2.9%), and a small increase (class 3, 8.5%) of depression over time. One class started off with a low probability of depression, which increased over time (class 2, 9.2%).

For ADNI, when fitting models with increasing number of classes, the 2-class model provided the best fit according to the LMR-LRT (1- vs 2-class model: 20.39, $P < .05$; 3-class model did not converge). The best-fitting model included a quadratic term, random intercept and random slope. Figure 2 shows the fitted and observed trajectories for each class. A small majority of the sample (58%) would be expected to belong to a class with increasing probability of depression over time

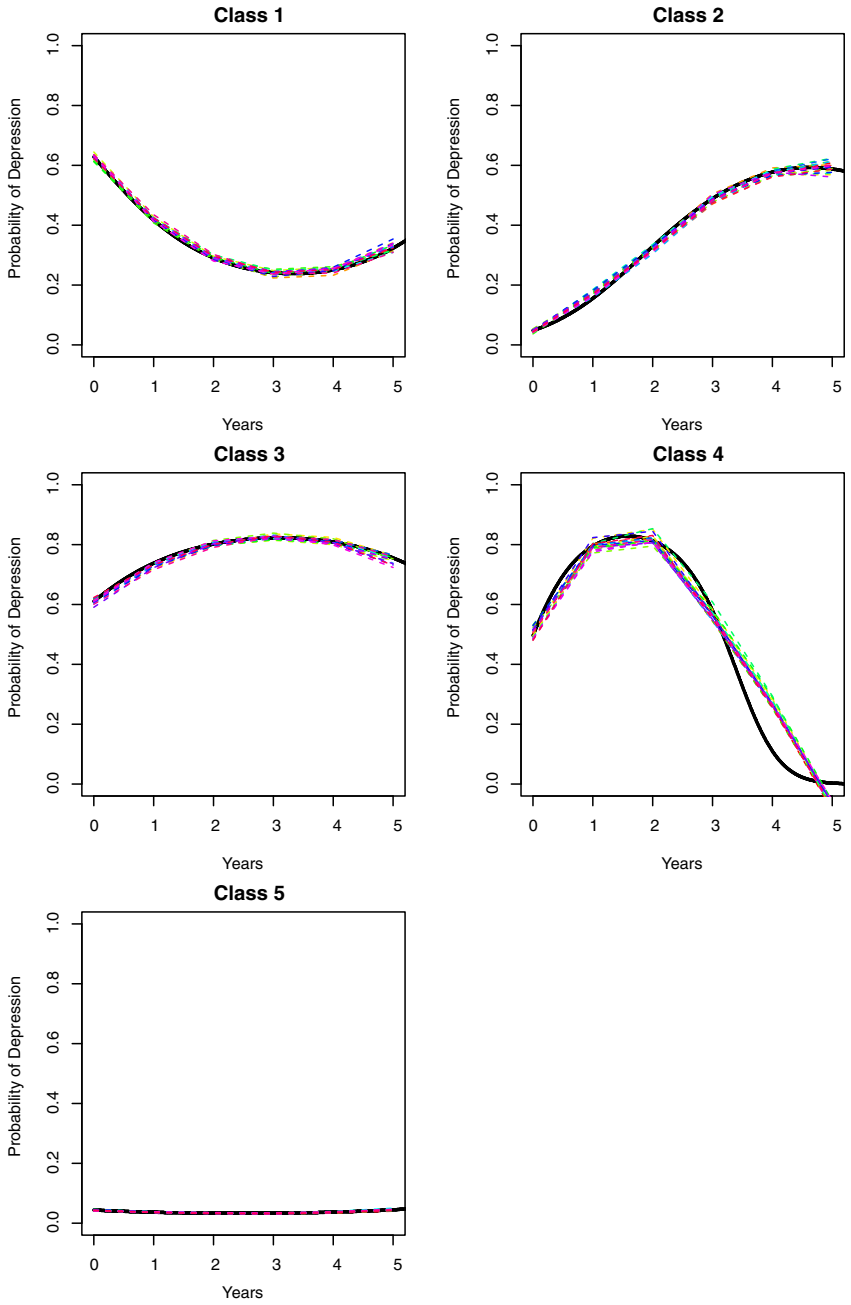

FIGURE 1 Depression, 5-class model without random effects, National Alzheimer's Coordinating Centre data. Class 1 = 14.0%, class 2 = 9.2%, class 3 = 8.5%, class 4 = 2.9%, class 5 = 65.4% [Colour figure can be viewed at wileyonlinelibrary.com]

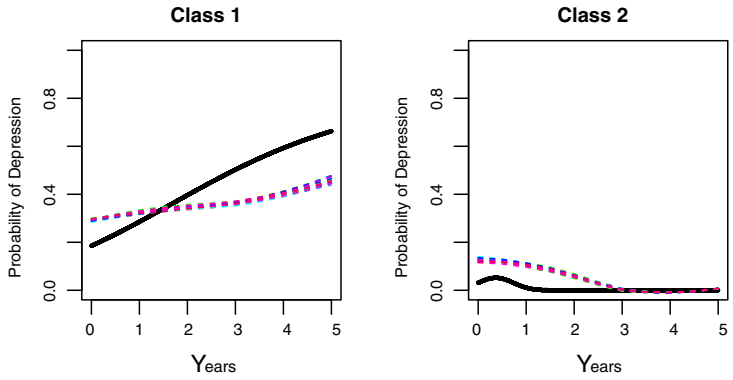

FIGURE 2 Depression, 2-class model with random intercept/random slope, Alzheimer's Disease Neuroimaging Initiative data. Class 1 = 58.2%, class 2 = 41.8% [Colour figure can be viewed at wileyonlinelibrary.com]

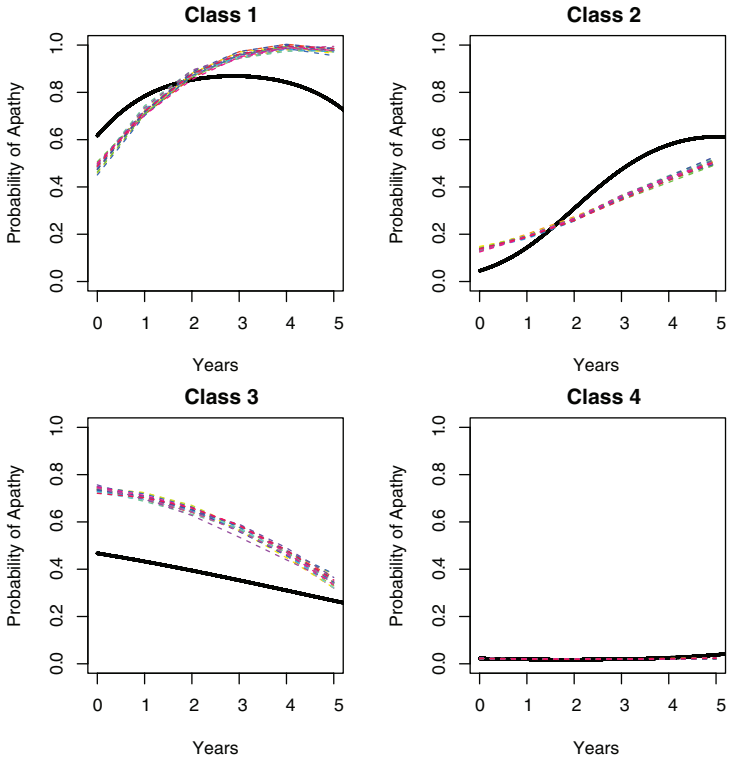

FIGURE 3 Apathy, 4-class model without random effects, National Alzheimer's Coordinating Centre data. Class 1 = 6.6%, class 2 = 9.4%, class 3 = 9.7%, class 4 = 74.3% [Colour figure can be viewed at wileyonlinelibrary.com]

(class 1). The other class showed constant low or no probability of depression (class 2, 42%).

3.2.2 | Apathy

For NACC, when fitting models with increasing number of classes, the 4-class model provided the best fit according to the LMR-LRT (3- vs 4-class model: 91.26, $P < .0001$, 4- *vs* 5-class model: 22.19, $P = .5$). The best-fitting model included a quadratic term and no random effects. Figure 3 shows the fitted and observed trajectories for each class. The majority of the sample (78.3%) would be expected to belong to class 4 with the absence of apathy over time. Two classes had a relatively high probability of apathy at baseline, and showed an increase (class 1, 6.6%) and decrease (class 3, 9.7%) of apathy over time. One class started off with a low probability of apathy, which increased over time (class 2, 9.4%).

For ADNI, when fitting models with increasing number of classes, the 4-class model provided the best fit according to the LMR-LRT (3- vs 4-class model: 8.46, $P = .05$; 5-class model did not converge). The best-fitting model included a quadratic term and random intercept only. Figure 4 shows the fitted and observed trajectories for each class. Three classes had a low or no probability of apathy at baseline, with either a steep increase (class 1, 14%), small increase (class 2, 47%), or stable low (class 4, 35%) over time. One class started off with a very high probability of apathy, which decreased steeply (class 3, 3%).

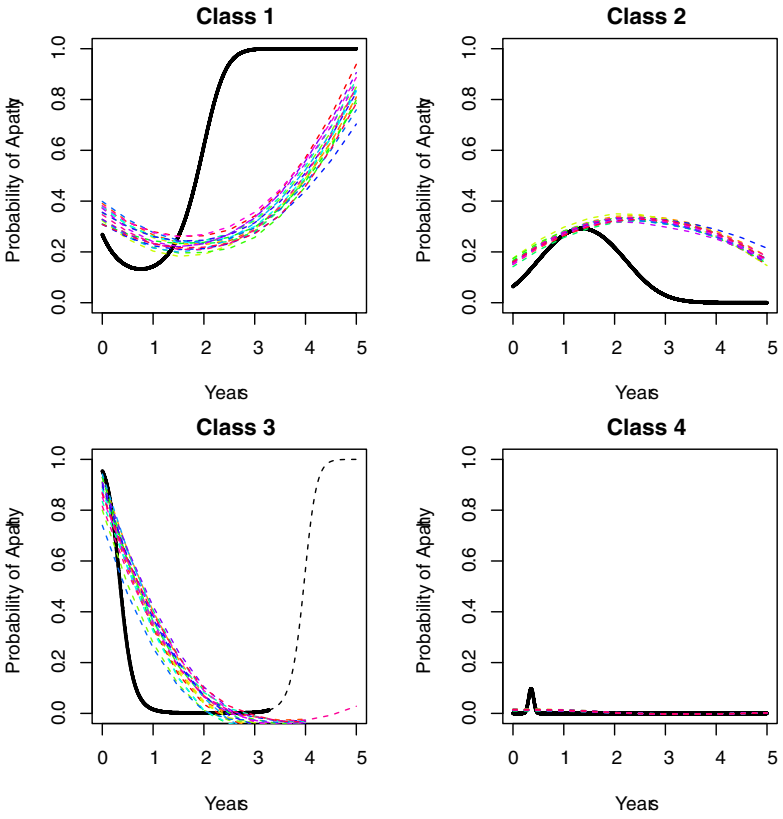

FIGURE 4 Apathy, 4-class model with random intercept only, Alzheimer's Disease Neuroimaging Initiative data. Class 1 = 14.2%, class 2 = 47.3%, class 3 = 3.4%, class 4 = 14.2%. *Note*. Fitted (black) and observed (colored) depression and apathy trajectories. The uncertainty of class membership—class membership is a latent unobserved variable, that is, not deterministic—was taken into account for the observed trajectories by multiple imputation of class membership (ie, considering class membership as pieces of missing information) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Part II: Biomarker association with symptom trajectories in ADNI

The association between baseline biomarkers and predicted class membership in ADNI was examined while adjusting for age and gender.

3.3.1 | Depression

In ADNI, more AD pathology (reflected in lower CSF $A\beta_{42}$ and higher t-tau and p-tau levels) was significantly associated with membership in the class with increasing probability of depression over time (class 1) compared to the class with stable low or no depression over time (class 2) (Table 2). For descriptive purposes, class 1 comprised relatively more dementia subjects, whereas class 2 relatively had more CN subjects. The classes were similar with regard to age, but class 1 had lower MMSE scores, greater use of psychotropic medications (antidepressants, other behavioral and AD medication), and had more pathology (ie, lower $A\beta_{42}$ and higher tau values) as compared to class 2 (see Table S7).

3.3.2 | Apathy

In ADNI, more AD pathology was associated with membership in the class with increasing probability of apathy over time (class 2); lower CSF $A\beta_{42}$ but not t-tau or p-tau levels were associated with membership in the class with a steep increase of apathy over time (class 1); and higher CSF tau and p-tau levels but not $A\beta_{42}$ were associated with membership in the class with a steep decrease of apathy over time (class 3), all compared to the class with low or no probability of apathy over time (class 4) (Table 2). For descriptive purposes, it is noteworthy that the class with low or no probability of apathy over time (class 4) contained less dementia subjects and had most normal $A\beta_{42}$, t-tau and p-tau scores (Table S9).

4 | DISCUSSION

The present study identified 5-year trajectories of depression and apathy in two separate, well-characterized cohorts, including CN individuals, as well as others with MCI or AD dementia. The largest proportion of individuals showed to have no symptoms of depression or apathy over time. Other trajectories were de novo increasing probabilities of symptoms over time, at baseline present and stable high symptoms over time, at baseline present and decreasing symptoms over time. More AD pathology was associated with membership in classes with increased probability of depression or apathy over time, compared to asymptomatic classes.

Typically, depression and apathy are modeled over time using a random effects model, generating one growth trajectory for the entire population, while it is reasonable to hypothesize that subsets of individuals with different trajectories exist, reflecting different underlying

TABLE 2 Multivariable effects of baseline biomarkers in the growth models for depression and apathy in ADNI

	Depression			Apathy		
	Class	N	OR (95% CI), *P* value	Class	N	OR (95% CI), *P* value
$A\beta_{42}$	1. Increasing depression	534	0.43 (0.31-0.60), *P* = .000	1. Steep increasing apathy	50	0.38 (0.16-0.91), *P* = .029
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	0.30 (0.17-0.52), *P* = .000
				3. Steep decreasing apathy	37	0.88 (0.16-3.24), *P* = .846
				4. Stable low apathy	716	Ref. class
t-tau	1. Increasing depression	534	2.08 (1.43-3.02), *P* = .000	1. Steep increasing apathy	50	1.45 (0.81-2.60), *P* = .214
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	1.98 (1.43-2.74), *P* = .000
				3. Steep decreasing apathy	37	2.31 (1.59-3.37), *P* = .000
				4. Stable low apathy	716	Ref. class
p-tau	1. Increasing depression	534	2.27 (1.54-3.33), *P* = .000	1. Steep increasing apathy	50	1.53 (0.90-2.60), *P* = .118
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	2.10 (1.46-3.03), *P* = .000
				3. Steep decreasing apathy	37	2.35 (1.57-3.52), *P* = .000
				4. Stable low apathy	716	Ref. class

Abbreviations: 95% CI = 95% confidence interval; ADNI, Alzheimer's Disease Neuroimaging Initiative; N, counts, based on modal (most likely) class assignment; OR, odds ratio.

Notes: The classes do not necessarily retain the original distribution from the measurement model because missingness of the biomarkers is not evenly distributed across classes. All models are corrected for age and sex. Depression, class 1 = 44.0%, class 2 = 56.0%. Apathy, class 1 = 4.1%, class 2 = 33.9%, class 3 = 3.1%, class 4 = 59.0%.

pathologies. Previous studies that examined trajectories of NPS, utilized NPI total score[27] or symptom clusters,[28] thereby possibly missing associations with specific NPI symptoms. Here, we report distinct trajectories specifically for depression and apathy. In both cohorts, for both symptoms, a large class was identified with stable low or no symptoms over time. For depression, we identified an additional four trajectories in NACC (three classes with relatively high probability of depression at baseline, two of which with either a steep or shallow decrease over time, one of which remained relatively stable over time; and a fourth class with low baseline probabilities and increasing depression over time) and one in ADNI (low probability at baseline and increasing over time). It is likely that these "extra" trajectories in NACC were captured in this single class with increasing probability of depression over time in ADNI, due to a smaller sample size. Indeed, when we repeated the analyses with a selected subset of NACC, resembling the ADNI diagnostic composition, also two classes were identified (Tables S5 and S6). The trajectories identified in ADNI are comparable to Holmes et al[29] who identified one stable trajectory with low depressive symptoms and another with consistent increasing depressive symptoms in CN. For apathy, in addition to the class with stable low or no symptoms over time, we identified two classes with relatively high probability of apathy at baseline (one decreasing, one increasing over time), and a third class with increasing probability of apathy over time in NACC; and two classes with low probabilities at baseline and increasing over time, and one high at baseline and decreasing over time in ADNI. To the best of our knowledge, this is the first study in AD literature examining trajectories of apathy.

Next, we related these trajectories to baseline biomarkers in ADNI. We found the presence of AD pathology to be related with *de novo* or (initially) rising symptoms of depression and apathy. This increase in symptomatology was associated with more $A\beta_{42}$ and tau pathology in the largest classes ($N_{\text{depression class 1}}$ = 534 and $N_{\text{apathy class 2}}$ = 411). For depression, these findings are in line with Barca et al who reported baseline CSF $A\beta_{42}$ levels to be associated with increasing depression over time[10] and Donovan et al who showed that higher Pittsburgh compound B positron emission tomography measures of cortical aggregate amyloid beta predicted an increase of self-report depressive symptoms over time.[30] For apathy, these findings contrast Donovan et al who reported no association with AD pathology, possibly because they assumed one growth trajectory for the entire population.[11] The two smaller classes for apathy, with steep increases and decreases, were, respectively, associated with $A\beta_{42}$ but not tau ($N_{\text{apathy class 1}}$ = 50) and tau but not $A\beta_{42}$ ($N_{\text{apathy class 3}}$ = 37) pathology. Possibly, different mechanisms underlie these more extreme symptom presentations, also reflected by the different types of subjects included in these classes: the class showing a steep increase of apathy over time (class 1) contains in general older MCI males, in comparison to the class with a steep decrease over time (class 3) which contains in general younger MCI and AD females, with lower MMSE scores and fewer follow-up measurements available. Class 3 might therefore reflect a "healthy survivor" effect, where those with apathy dropped out. On the other hand, this class might reflect misdiagnosis of AD, when in fact the individuals have a non-AD tauopathy such as frontal temporal lobe dementia, where NPS might take a different trajectory.

The major strength of our study is the use of well-characterized longitudinal data in two large samples, which allows modeling of the heterogeneity between subjects in growth trajectories and, additionally, to validate the growth models by comparing the results. NACC (with information on affective symptoms available for 22 760

participants) proved to be most suitable to model the symptom trajectories; whereas, ADNI had standardized baseline biomarker information available for 70% of the total sample. It is important to consider some methodological limitations. First, it was not possible to constrain the measurement model (ie, trajectory model) to be exactly the same in both cohorts. Modeling these complex random structures proved to be challenging because of the non-monotonic trajectories the affective symptoms take (ie, symptoms may increase and decrease at different points in time) and because of the dichotomous outcome (ie, we are modeling probabilities). Although repeating the analyses for the two cohorts separately and independent from each other allows for validation of the results within one study (indeed, we showed that the largest group of subjects has no symptoms of depression or apathy over time) it also highlights the complexity of comparing GMM results between cohorts that are different by design. For example, the unequal frequency of the cognitive statuses per cohort is reflected by the proportion of CN in the groups with stable low or no symptoms over time, which is larger in NACC compared to ADNI. Another caveat of using two different cohorts showed by the finding that in NACC (but not ADNI), those without follow-up had more often baseline symptoms of depression and apathy. As mentioned above, this might have resulted in a "healthy survivor" bias effect. Secondly, the NPI relies on caregiver report which may introduce bias in data collection, and has been validated in MCI and AD but not CN. Therefore, caregiver report may bias assessment of CN in unknown ways, potentially over- or under-reporting symptoms. However, considering the fact that the current sample is only mildly impaired, the burden (and therefore bias of over-reporting symptoms) of caregivers might be low. Third, because of sample size, the corrected three-step procedure did not allow consideration of comorbid NPS, use of psychotropic medications, or history of depression as covariates in addition to age and sex. This is important to acknowledge, given that we treated depression and apathy as separate symptoms, even though they were correlated at each timepoint ($r \approx 0.3$, $P < .001$). Therefore, this information was included in a descriptive way (see Tables S7-S10). This shows, for example, that subjects assigned to the classes with apathy also had more often symptoms of depression, and vice versa, compared to the classes without apathy or depression over time. Further, it shows that use of antidepressants is very common in all groups, and that in ADNI, history of depression was less common in class 1 (31.5%) compared to class 2 (41.8%). However, spouses or children might not be aware of such history, making this type of information less reliable. Fourth, the nature of the study sample (highly selective samples that consists memory clinic visitors, with add-on of highly educated, Caucasian volunteers that have low vascular burden) might have affected the external validity. Fifth, another source of bias might be introduced by the fact that, by design, the severity of NPS at screening were restricted (ie, via the exclusion of subjects with GDS score of 6 or more). Finally, the predictive value of AD pathology for symptoms of depression and apathy suggests that these symptoms are associated with the underlying pathology, confirming the view that they are a noncognitive symptom of the disease. However, we should be cautious with making cause-and-effect inferences as the possibility that the presence of these symptoms induces a biological cascade in the brain leading to AD pathology cannot be excluded. It is also possible that the observed relationships are indirect and are being mediated by, for example, participants' awareness of cognitive decline.

5 | FUTURE RESEARCH AND IMPLICATIONS

The current study is a first step in studying heterogeneity within and between persons with regard to progression of affective symptoms and their underlying etiology. The latter was defined as the association with AD pathology (CSF $A\beta_{42}$, t-tau and p-tau) but future research should consider biomarker assessment of other pathologies (eg, vascular components, neurotransmitter systems, or inflammation markers) and examine the influence of psychosocial factors. More advanced imaging data could provide more information on the relationship between affective symptoms and localization of amyloid and tau burden. Parallel-process GMMs could be utilized to investigate the interplay between trajectories of depression and apathy, or between cognition or biomarkers and individual symptoms. The fact that AD pathology was shown to be related with development of depression and apathy over time indicates that information on AD biomarkers could serve as a predictor for clinicians to be aware of the increased probability of affective symptomatology in the future. Further, biomarker information could be used to enrich cohorts for treatment and prevention trials of NPS. In addition, the findings show that there is considerable fluctuation of affective symptoms over time, suggesting that clinicians should monitor affect continuously over an extended period, even when affective symptoms are absent at any point in time.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the NACC database (funded by National Institute on Aging/National Institutes of Health) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) project. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.alz.washington.edu/WEB/researcher_home.html and http://adni.loni.usc.edu/ with their permission.

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SUPPORTING INFORMATION

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

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