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Development of Apathy, Anxiety, and Depression in Cognitively Unimpaired Older Adults: Effects of Alzheimer's Disease Pathology and Cognitive Decline

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ABSTRACT

BACKGROUND: The impact of Alzheimer's disease (AD) pathology and cognitive deficits on longitudinal neuropsychiatric symptoms is unclear, especially in early disease stages.

METHODS: Cognitively unimpaired older adults ($N = 356$) enrolled in the prospective Swedish BioFINDER study were examined. Neuropsychiatric assessments encompassed the Apathy Evaluation Scale and the Hospital Anxiety and Depression Scale, performed biennially (together with tests of global cognition) for up to 8 years. Biomarkers were measured in cerebrospinal fluid or plasma at baseline. Magnetic resonance imaging quantified white matter lesions. We used linear mixed-effect models to test associations between baseline AD biomarkers (for amyloid-β [Aβ], tau, and neurodegeneration) and white matter lesions with longitudinal neuropsychiatric symptoms (apathy, anxiety, and depressive symptoms). We also tested associations between changes in cognition and changes in neuropsychiatric symptoms. Finally, we tested if change in cognition mediated the effects of different brain pathologies on neuropsychiatric symptoms.

RESULTS: Aβ pathology at baseline was associated with increasing levels of apathy ($\beta = -0.284$, $p = .005$) and anxiety ($\beta = -0.060$, $p = .011$) longitudinally. More rapid decline of cognition over time was related to increasing levels of apathy. The effects of baseline Aβ pathology on longitudinal apathy were partly mediated by changes in cognitive performance (proportion mediated 23%).

CONCLUSIONS: Aβ pathology may drive the development of both apathy and anxiety in very early stages of AD, largely independent of cognitive change. The effect of Aβ on apathy is only partially conveyed by worse cognition. Together, these findings highlight certain neuropsychiatric symptoms as early manifestations of AD.

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Key hallmarks of Alzheimer's disease (AD) include cerebral amyloid-β (Aβ) plaques, neurofibrillary tangles of hyperphosphorylated tau, and neurodegeneration, as well as clinical manifestations including both cognitive deficits and neuropsychiatric symptoms (NPSs) (e.g., apathy, depression, and anxiety) (1,2). According to the National Institute on Aging and Alzheimer's Association criteria, AD is defined as a neurobiological construct related to core AD pathologies, where its clinical progression is staged according to the level of cognitive deterioration (2). This view is supported by a robust relationship between AD pathology and future cognitive decline (1). Although the criteria do not highlight NPSs, it is known that the frequency and severity of NPSs increase with worsening cognition (3,4). This suggests that NPSs and cognitive deficits can develop in parallel and that NPSs may constitute early manifestations of AD (5). In support, cross-sectional studies in early disease stages have shown associations between AD pathology and NPSs (6–10). Other studies demonstrate NPSs as predictors of future cognitive decline and dementia already in preclinical AD (6,11,12). Moreover, anxiety and Aβ are reported to interact, resulting in accelerated cognitive decline (6,13). In line, the novel concept of mild behavioral impairment emphasizes that NPSs can develop before, in concert with, or somewhat after mild cognitive impairment (MCI) due to neurodegenerative disease (14). However, only a few studies have tested effects of both neuropathology and cognition on the development of NPSs (8). Therefore, the exact temporal and causal relationships between pathology, cognition, and NPSs in AD remain unclear. Here, we investigated how biomarkers of AD pathology, white matter lesions (WMLs), and cognitive deficits potentially drive the development of apathy, anxiety, and depressive symptoms in cognitively unimpaired (CU) older adults. We also tested if cognitive change mediates the effect of brain pathologies on longitudinal NPSs.

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METHODS AND MATERIALS

Study Sample

CU participants (n = 359) in the prospective Swedish BioFINDER study (Clinical Trial No. NCT01208675) were recruited. However, only participants with at least one NPS rating during the biennial follow-up of up to 8 years were included (N = 356). Of note, not all had completed the 6- and 8-year visits at the time of data extraction. In short, the CU participants were eligible for inclusion in the BioFINDER study if they 1) were ≥60 years old, 2) had a Mini-Mental State Examination (MMSE) score of 28 to 30 at the screening visit (allowed MMSE 27–30 at the baseline visit), 3) were not in need of a Swedish interpreter, 4) had absence of cognitive symptoms, and 5) did not fulfill criteria of MCI or dementia. Details on design are provided in the Supplement and reported previously (6). Additional information is found at http://www.biofinder.se.

Standard Protocols, Registrations, and Patient Consents

The Regional Ethical Review Board in Lund, Sweden, approved the study. All participants gave their written informed consent.

Clinical Assessments

Clinical assessments were administered biennially for up to 8 years.

Apathy was assessed by the Swedish Apathy Evaluation Scale, self-rated (AES-S) and informant-rated (AES-I) (15). AES is a well-studied tool consisting of 18 items rated at a 4-point scale (not at all, slightly, somewhat, or a lot) (15). Higher scores indicate a higher level of apathy (range, 18–72).

The self-rated Hospital Anxiety and Depression Scale (HADS) assessed levels of depression (HADS-D) and anxiety (HADS-A). HADS has preferable psychometric properties, and higher scores indicate more distress (range, 0–21) (16).

Global cognition was measured using the MMSE (17) and a modified Preclinical Alzheimer's Cognitive Composite (mPACC5) (18). The color/form task in A Quick Test (AQT-CF) (19,20) assessed executive functioning and was further used in the mPACC5 composite [the executive test has also previously varied in different PACC5 publications (21–23)], as well as used separately in a post hoc analysis (outlined below). A more detailed description of AQT-CF and the computation of mPACC5 is provided in the Supplement.

AES was incorporated in the BioFINDER study after study start. Hence, some participants lacked AES at baseline or the 2-year follow-up. Given an administrative error at year 2, HADS was not distributed to some participants at this visit. The number of available assessments at each visit are presented in Figures S1 and S2.

Fluid Biomarkers

Cerebrospinal fluid (CSF) and blood samples were collected close in time after the baseline NPS examination (mean = 1.4 [SD = 0.1] mo) and handled according to structured preanalytic protocols (24,25). Levels of CSF $A\beta_{42}$, $A\beta_{40}$, and neurofilament light (NfL) were measured on an Elecsys platform according to the manufacturer's instructions (Roche Diagnostics International Ltd.) (25,26). CSF $A\beta_{42}$, and $A\beta_{40}$ were combined into a CSF $A\beta_{42}/A\beta_{40}$ ratio, with high specificity for AD-related amyloidopathy (27). CSF NfL was used as a marker for cortical and subcortical axonal degeneration (28). Plasma phosphorylated tau (P-tau217) was analyzed, as previously described in detail (25), using immunoassay on a Mesoscale Discovery platform developed by Lilly Research Laboratories. There were missing data at baseline (CSF $A\beta_{42}/A\beta_{40}$, n = 33; CSF NfL, n = 35; plasma P-tau217, n = 36).

Magnetic Imaging Acquisition and Processing

High-resolution T1-weighted and T2-weighted FLAIR images were acquired on a Siemens Tim Trio 3T MR scanner (Siemens Medical Solutions) (mean = 0.6 [SD = 0.1] mo from baseline). WML volumes were generated by an automated segmentation process, using the lesion prediction algorithm in the LST toolbox (http://www.statistical modelling.de/lst.html) for SPM (29). Eleven subjects lacked magnetic resonance imaging data.

Statistical Analyses

First, individual change per year (slope) for the cognitive measures MMSE, mPACC5, and AQT-CF were calculated using individual univariate linear regression models with cognitive scores as dependent variables and time as an independent variable.

Second, we tested associations between longitudinal NPSs (as dependent variables) and different predictors in primary linear mixed-effect (LME) models. Baseline measures of continuous CSF $A\beta_{42}/A\beta_{40}$, plasma P-tau217, CSF NfL, and WML volumes, individually, were entered as zero-centered predictors interacting with time (biomarker × time). In similar LME models, baseline values or slopes of MMSE or mPACC5 (extracted from linear regression in the first step of the analyses) were used as predictors interacting with time (cognition × time). All models included age, sex, and education as covariates, as well as random slopes and intercepts. The number of participants and NPS observations per model are presented in Table S1. We report on the interacting effects; main effects are provided in Tables S2 and S3. To reduce the risk of type I error, Bonferroni corrections were made sectionwise for each dependent variable in each table (in total: 32 models, 64 p values, 4 p values per correction).

We also conducted sensitivity analyses where the primary models were refitted when removing participants with only one NPS measure. Given missing AES data at baseline, we also reran the apathy models when including only the 2-year to 8-year follow-up data. A survival bias analysis was further conducted using logistic regressions, where missingness of data at the 2-, 4-, or 6-year visit were predicted by neuropathology (one model per biomarker and visit). Age, sex, and education constituted covariates. Here, false discovery rate correction adjusted for multiple comparisons. Additional sensitivity analyses were conducted in which antidepressants at any visit (dichotomous variable) was added as a covariate to the primary models.

In post hoc analyses, associations between longitudinal apathy and baseline executive function or executive slopes (assessed by AQT-CF) were examined using similar models as in the primary LME analyses.

Third, we conducted mediation analyses to test if the cognitive slopes for MMSE or mPACC5 over time mediated the effects of neuropathology on longitudinal NPSs. Analyses were restricted to models in which longitudinal NPSs had significant associations with both neuropathology and global cognitive decline also after Bonferroni correction. A bootstrap procedure (n = 1000 iterations) calculated 95% confidence interval [CI] for the mediated effects. A detailed description of the model setups is provided in the Supplement. The number of participants and NPS observations for each mediation analysis are also presented in Table S4.

For all statistical tests, a significance threshold of $p < .05$ (two-sided) was used. Regression model assumptions were assessed by evaluating normality and homoscedasticity of residuals with probability plots and plots of residuals versus fitted values. Statistical analyses were performed using R version 3.6.1 with the packages "lme4," "lmerTest," "visdat," and "ggeffects" and IBM SPSS Statistics version 25 (IBM Corp.).

RESULTS

Demographics and Clinical Characteristics

Demographics and clinical characteristics are presented in Table 1. Mean age was 73.8 (SD = 5.1) years, 9.8% of the participants used antidepressants at any visit, and 28.5% were *APOE* ε4 carriers.

Effects of Pathology on Longitudinal NPSs

First, we tested associations between individual baseline biomarkers interacting with time and longitudinal NPS scores (Table 2). Longitudinal increase in AES-I was greater in participants with lower (i.e., more abnormal) CSF $A\beta_{42}/A\beta_{40}$ ($\beta = -0.284$, $p = .005$) or higher (i.e., more abnormal) plasma P-tau217 ($\beta = -0.253$, $p = .015$). Lower CSF $A\beta_{42}/A\beta_{40}$ ($\beta = -0.060$, $p = .011$) or higher (i.e., more abnormal) CSF NfL ($\beta = 0.054$, $p = .024$) were also associated with higher longitudinal HADS-A scores. A high (i.e., more abnormal) WML volume ($\beta = 0.136$, $p = .016$) was associated with increased longitudinal AES-S scores. Only the effect of CSF $A\beta_{42}/A\beta_{40}$ over time on AES-I and HADS-A remained significant after correction for multiple comparisons. Figure 1 demonstrates these associations for Aβ-negative versus Aβ-positive individuals and displays that those with the highest level of pathology show the steepest increases in NPS scores. None of the pathologies was associated with longitudinal HADS-D.

Effects of Cognition and Cognitive Slopes on Longitudinal NPSs

Next, we tested associations between baseline cognition or cognitive slopes over time and longitudinal NPS scores (Table 3). Over time, there was an effect on longitudinal AES-S by baseline mPACC5 ($\beta = -0.126$, $p = .033$), but this did not hold for Bonferroni correction.

As shown in Figure 2, there were also associations between longitudinal NPSs and cognitive slopes. Both steeper MMSE (AES-S: $\beta = -0.179$, $p = .007$; AES-I: $\beta = -0.500$, $p < .001$) and mPACC5 slopes interacting with time (AES-S: $\beta = -0.227$, $p < .001$; AES-I: $\beta = -0.467$, $p < .001$) displayed associations with longitudinal change (higher levels) in AES-S and AES-I. These findings remained significant after correction for multiple comparisons. Participants with steeper mPACC5 slopes had higher HADS-A scores over time ($\beta = -0.065$, $p = .023$), but this did not remain significant after Bonferroni correction (Figure 3).

The post hoc analyses demonstrated increasing effects over time by both reduced baseline executive function ($\beta = 0.166$, $p = .004$) and executive slopes ($\beta = 0.163$, $p = .036$) on longitudinal AES-S but not AES-I (Table S5).

Sensitivity Analyses

As a sensitivity analysis, the primary LME analyses were rerun on a restricted sample, removing participants with NPS data for only one visit (n removed: AES-S = 36, AES-I = 111, HADS-A = 53, and HADS-D = 53). Effects and p values were found to be similar to the primary analyses (Table S6), with the exceptions that WML volumes were now associated with change in AES-I and that the association between MMSE slope and longitudinal AES-S was lost.

Rerunning the primary apathy models including only 2-year to 8-year data also gave results consistent with the primary models (Table S7). Corroborating this, our survival bias analysis in general did not find associations between pathology and missing follow-up data (Table S8). The exceptions were that plasma P-tau217 strongly predicted the presence of missing AES-S data at the 2-year follow-up (odds ratio = 41.4, 95% CI = 6.0–286.4, p-adj = .002) and that CSF NfL predicted missing AES-I data at the 4-year visit (odds ratio = 1.003, 95% CI = 1.000–1.007, p-adj = .048).

We further controlled the primary models for the use of antidepressants at any visit, which did not change the results (Table S9).

Cognition as a Mediator of Pathology on NPSs

Finally, we tested whether some associations between neuropathology and longitudinal NPSs were statistically mediated via cognitive slopes. The association between baseline CSF $A\beta_{42}/A\beta_{40}$ interacting with time and longitudinal AES-I was partly mediated by mPACC5 slopes with 23% mediation (Figure 3A). The effect of CSF $A\beta_{42}/A\beta_{40}$ over time on longitudinal AES-I remained significant also after controlling for mPACC5 slopes, indicating a remaining statistically direct effect of Aβ independent from cognitive change. A similar result was obtained using MMSE (Figure 3B).

DISCUSSION

This study explored associations between longitudinal NPSs and AD-related pathologies, WMLs, and cognition in CU individuals. Our main finding was that Aβ exerted a weak to moderate effect over time on the trajectories of apathy and anxiety, and this was mainly independent from cognition. Longitudinal anxiety and cognitive decline associated merely on a trend level, and cognitive change only partially mediated the effect of Aβ on longitudinal apathy.

Associations Between Aβ and Longitudinal NPSs

Scores on repeated measures of informant-rated apathy increased in participants with signs of Aβ pathology at study

Table 1. Demographics and Clinical Characteristics (*N* = 356)

Characteristics	Value	Range
Demographics		
Sex, female, *n* (%)	212 (59.6%)	–
Age, years, mean (SD)	73.8 (5.1)	65.0 to 88.4
Educational level, years, mean (SD)	12.5 (3.7)	6 to 30
Use of antidepressants at any visit, *n* (%)	35 (9.8%)	–
Pathology Measurements at Baseline		
APOE ε4 carrier status, *n* (%)	100 (28.5%)	–
CSF $A\beta_{42}/A\beta_{40}$ quota, mean (SD)	0.080 (0.025)	0.022 to 0.133
Plasma P-tau217, mean (SD)	0.152 (0.177)	0.003 to 0.824
CSF NfL, mean (SD)	145.1 (86.3)	41.5 to 860.5
WML volume, median (IQR)	5.7 (12.4)	0.0 to 117.5
Clinical Assessments at Baseline		
mPACC5, *z* score, median (IQR)	0.10 (0.68)	−2.76 to 1.40
MMSE, median (IQR)	29 (2)	27 to 30
Longitudinal Clinical Assessments		
mPACC5, *z* score, mean change/year (SD)	−0.07 (0.2)	−1.1 to 0.4
MMSE, mean change/year (SD)	−0.2 (0.4)	−2.4 to 1.0
AES-S, median (IQR)		
Follow-up 0 years	28 (7)	18 to 43
Follow-up 2 years	27 (7)	18 to 53
Follow-up 4 years	28 (10)	18 to 53
Follow-up 6 years	28 (10)	18 to 55
Follow-up 8 years	27 (11)	18 to 53
AES-I, median (IQR)		
Follow-up 0 years	27 (11)	18 to 63
Follow-up 2 years	26 (10)	18 to 54
Follow-up 4 years	27 (12)	18 to 61
Follow-up 6 years	26 (10)	18 to 62
Follow-up 8 years	26 (10)	18 to 62
HADS-A, median (IQR)		
Follow-up 0 years	1 (4)	0 to 14
Follow-up 2 years	2 (5)	0 to 16
Follow-up 4 years	1 (4)	0 to 14
Follow-up 6 years	2 (4)	0 to 14
Follow-up 8 years	2 (5)	0 to 16
HADS-D, median (IQR)		
Follow-up 0 years	1 (3)	0 to 11
Follow-up 2 years	1 (3)	0 to 11
Follow-up 4 years	1 (3)	0 to 10
Follow-up 6 years	1 (4)	0 to 15
Follow-up 8 years	2 (4)	0 to 12

Demographic and clinical characteristics of the 356 cognitively unimpaired older adults. If not specified, results presented in the table are generated from data at study start (baseline). Continuous normally distributed variables are presented with mean and SD, while non-normally distributed data are presented with median and IQR. mPACC5 data (*z* scores) were generated as a composite of the neuropsychological tests MMSE, Animal Fluency, The Alzheimer Disease Assessment Scale–Cognitive Subscale–Delayed Memory Recall Test as well as A Quick Test—Color/Form.

Aβ, amyloid-β; AES-I, Apathy Evaluation Scale–Informant-Rated Version; AES-S, Apathy Evaluation Scale−Self-Rated Version; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; CU, cognitively unimpaired; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; IQR, interquartile range; MMSE, Mini-Mental State Examination; mPACC5, modified Preclinical Alzheimer's Cognitive Composite; NfL, neurofilament light, P-tau, phosphorylated tau; WML, white matter lesion.

start. This finding conforms with most cross-sectional studies (6,30–32) but also points to the direction of the relationship, where Aβ to some extent could be accountable for the subsequent development of apathy. We are aware of a similar study on CU individuals from the Harvard Aging Brain Study, which did not find an association between Aβ interacting with time and the development of apathy-anhedonia cluster items derived from the self-rated Geriatric Depression Scale (GDS)

Table 2. Associations Between Baseline Biomarkers of Pathology Over Time and Longitudinal NPSs

	AES-S Longitudinal				AES-I Longitudinal				HADS-A Longitudinal				HADS-D Longitudinal			
Biomarkers	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2
Biomarker of Amyloid Pathology																
CSF $A\beta_{42}/A\beta40$ × time	−0.075	.194	.776	0.070	−0.284	.005[a,b]	.020	0.119	−0.060	.011[a,b]	.044	0.078	−0.010	.569	1.000	0.026
Biomarker of Tau Pathology																
Plasma P-tau217 × time	0.033	.586	1.000	0.045	0.253	.015[a]	.060	0.094	0.032	.185	.540	0.065	0.026	.135	.540	0.023
Biomarker of Neurodegeneration																
CSF NfL × time	0.090	.152	.608	0.056	−0.007	.944	1.000	0.101	0.054	.024[a]	.096	0.075	−0.001	.943	1.000	0.028
Biomarker of Vascular Pathology																
WML volume × time	0.136	.016[a]	.064	0.075	0.182	.052	.208	0.091	−0.012	.609	1.000	0.068	−0.029	.113	.452	0.040

Linear mixed-effect models to investigate the effects of different biomarkers for neuropathology over time (pathology × time interaction) on the development of NPSs in CU participants. Longitudinal NPS measures of apathy, anxiety, and depressive symptoms were entered as the dependent variable in separate models. Biomarker measures at baseline were one by one entered as fixed effects interacting with time (biomarker × time). Fixed effects were zero centered. All models were corrected for age, sex, and education and included random slopes and intercepts. Main effects are reported in Table S2. The significance threshold was set at $p < .050$. Bonferroni corrections were run sectionwise for each dependent variable. Overall, 35 participants lacked CSF data for $A\beta_{42}/A\beta_{40}$ and NfL, 36 participants lacked data for plasma P-tau217, and 11 participants lacked WML volume data.

Aβ, amyloid-β; AES-I, Apathy Evaluation Scale–Informant-Rated Version; AES-S, Apathy Evaluation Scale–Self-Rated Version; CSF, cerebrospinal fluid; CU, cognitively unimpaired; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale−Depression; mR^2, marginal *R*-squared; NfL, neurofilament light; NPSs, neuropsychiatric symptoms; *p*-adj, *p* value corrected for multiple comparisons; P-tau, phosphorylated tau; WML, white matter lesion.

[a]Significant *p* value.

[b]*p* Value significant after correction for multiple comparisons by the Bonferroni method.

(33). This does not agree with our findings on informant-rated apathy but is well in line with our self-rated findings, which were not affected by Aβ over time. Therefore, the discrepancy between our studies could reflect the critical challenges in rater source selection (as further discussed in Differences Between AES-S and AES-I in Their Relation to Neuropathology).

The same Harvard Aging Brain Study instead displays associations between Aβ interacting with time and the development of self-rated anxiety-concentration cluster item scores. In addition to earlier cross-sectional findings on nondemented samples (6,9,10,13,32,34), this aligns with our results where an effect over time by Aβ on longitudinal self-rated anxiety was found. In contrast, longitudinal data from the PREVENT-AD cohort on CU individuals at increased risk of AD (due to a family history of sporadic AD) displayed a lack of such an association (32). Instead, they displayed a cross-sectional association between Aβ and some latent behavioral factors, including, e.g., neuroticism, anxiety, and apathy (the latter two informant-rated). Potentially, the disagreement in longitudinal results is best explained by the somewhat shorter follow-up in the PREVENT-AD study, where participants on a group level might not have had time to progress in their anxiousness. Nevertheless, their cross-sectional finding implies the useful sensitivity of informant ratings even in early AD.

The relationship between Aβ and depressive manifestations has remained unsettled (35). This study supports several previous studies that have reported a lack of such a relationship (6,34,36–39). However, other studies have displayed an

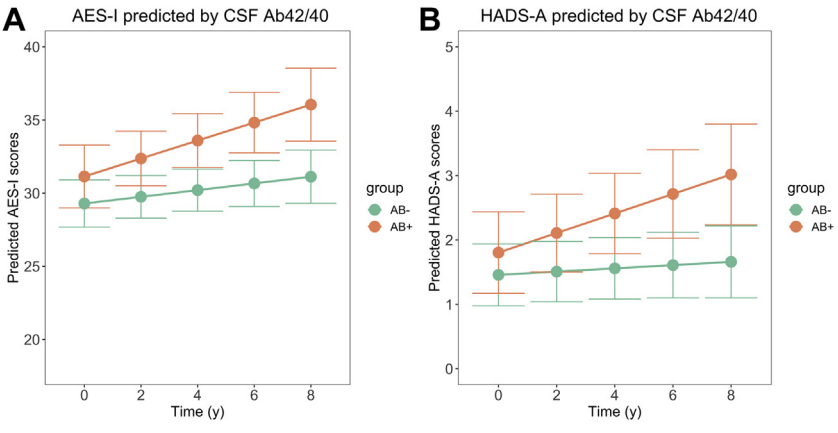

Figure 1. Linear mixed-effect models displaying effects of pathology at baseline over time on the development of neuropsychiatric symptoms. Plots of estimated marginal means and 95% confidence interval of the means obtained from linear mixed-effect models displaying significant effects (also after adjustment for multiple comparisons) by pathology over time on the longitudinal measures of neuropsychiatric symptoms found in Table 1. Longitudinal measures of informant-rated apathy **(A)** (274 participants) and self-rated anxiety **(B)** (321 participants) were separately entered as the dependent variable. Interaction terms between time and amyloid-β $(A\beta)_{42}/A\beta_{40}$ ratio were entered as a zero-centered fixed effect. Models were corrected for age, sex, and education and included random slopes and intercepts. Participants were grouped according to a cerebrospinal fluid (CSF) $A\beta_{42}/A\beta_{40}$ cut point of 0.066 obtained by mixture modeling. Models initially displaying significant effects, but notwithstanding adjustment for multiple comparisons, are found in the Supplement. AES-I, Apathy Evaluation Scale–Informant-Rated Version; HADS-A, Hospital Anxiety and Depression Scale–Anxiety.

Table 3. Associations Between Cognition Over Time and Longitudinal NPSs

	AES-S Longitudinal				AES-I Longitudinal				HADS-A Longitudinal				HADS-D Longitudinal			
Cognitive Function Tests	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2	β	*p* Value	*p*-adj	mR^2
MMSE × Time	−0.094	.111	.444	0.053	0.027	.781	1.000	0.070	−0.031	.196	.784	0.065	−0.002	.897	1.000	0.024
MMSE Slope × Time	−0.179	.007[a,b]	.028	0.078	−0.500	<.001[a,b]	<.001	0.172	−0.041	.138	.552	0.073	−0.016	.425	1.000	0.035
mPACC5 × Time	−0.126	.033[a]	.132	0.065	−0.066	.487	1.000	0.104	0.018	.441	.100	0.077	0.004	.824	1.000	0.034
mPACC5 Slope × Time	−0.227	<.001[a,b]	.003	0.086	−0.467	<.001[a,b]	<.001	0.190	−0.065	.023[a]	.092	0.079	−0.040	.059	.236	0.037

Linear mixed-effect models to investigate effects of cognition over time (cognition by time interaction) on the development of NPSs in CU participants. Longitudinal NPS measures of apathy, anxiety, and depressive symptoms were entered as the dependent variable in separate models. Cognitive measures at baseline, as well as cognitive slopes, were one by one entered as fixed effects interacting with time (cognition × time). Fixed effects were zero centered. Individual change per year (slope) in MMSE and mPACC5 score were generated using individual linear regression models in which longitudinal MMSE and mPACC5 were predicted by time. All models were corrected for age, sex, and education and included random slopes and intercepts. Main effects are reported in Table S3. The significance threshold was set at $p < .050$. Bonferroni corrections were run sectionwise for each dependent variable.

AES-I, Apathy Evaluation Scale–Informant-Rated Version; AES-S, Apathy Evaluation Scale−Self-Rated Version; CU, cognitively unimpaired; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; MMSE, Mini-Mental State Examination; mPACC5, modified Preclinical Alzheimer's Cognitive Composite; mR^2, marginal *R*-squared; NPSs, neuropsychiatric symptoms; *p*-adj, *p* value corrected for multiple comparisons; P-tau, phosphorylated tau.

[a]Significant *p* value.

[b]*p* Value significant after correction for multiple comparisons by the Bonferroni method.

association (33,40–44). There are many possible reasons for these divergent findings. One is that the definition of depression or the assessment of its severity varies considerably. Many subsyndromal depression studies that report a relationship have assessed depressive symptoms using the GDS. In the Harvard Aging Brain Study, the authors displayed steeper rates of total GDS scores over time for participants with higher levels of Aβ deposition (33). However, according to their subanalysis, in which the three item clusters of the GDS scale (dysphoria, anxiety-concentration, and apathy-anhedonia) were analyzed, the average dysphoria item cluster score was shown lower than the other item clusters. Moreover, change in dysphoria was not linked to Aβ. Similar findings on the GDS are reported from the Australian Imaging Biomarkers and Lifestyle Study (38). Together, these studies suggest that GDS total scores primarily reflect on anxiety or apathy rather than dysphoria. Because dysphoria could be argued central in the concept of major depression, this questions the validity of the GDS in samples where apathy and anxiety are prevalent, as in older adults at risk of neurodegenerative disease (3).

Associations Between Tau, Neurodegeneration, WMLs, and Longitudinal NPSs

We further report associations between longitudinal informant-rated apathy and baseline plasma P-tau217 interacting with time and longitudinal anxiety and baseline CSF NfL interacting with time. Although this suggests links between tau or neurodegeneration and the trajectories of some NPSs, these findings did not hold for Bonferroni correction and are only suggestive findings. As for Aβ, the literature on tau and neurodegeneration in relation to NPSs in CU individuals displays both mixed results and methodologies (7,8,32,34,40,45,46). In favor of an association, we earlier demonstrated cross-sectional associations between tau and mild behavioral impairment among CU Aβ-positive individuals (partly overlapping with this sample) (7). However, future longitudinal studies are needed to determine the role of these pathologies in the development of NPSs.

We also demonstrate WMLs to be initially associated with longitudinal self-rated apathy (informant-rated was near the significance threshold). Yet, this association did not hold for correction for multiple comparisons. This was unexpected given that cross-sectional studies consistently have demonstrated strong associations between apathy and WMLs already in preclinical stages (6,47). However, another longitudinal study on apathy could also not report an effect of WMLs over time (48).

Differences Between AES-S and AES-I in Their Relation to Neuropathology

Our results diverge regarding self- and informant-rated apathy. For instance, AES-I, but not AES-S, was related to baseline Aβ. We have also previously reported diverging results for these rater sources in relation to Aβ (6). In the earlier study, using a mixed sample of CU individuals and individuals with MCI, the median scores for AES-I and AES-S among CU participants were similar. But in participants with MCI, the median for AES-S was less increased compared with AES-I. This suggests that participants with MCI tend to underreport, resulting in less steep slopes for AES-S than AES-I as participants progress from CU to MCI. This further agrees with a study comparing the repeated measures for the different versions in CU individuals and individuals with MCI (49). Hypothetically, individuals with AD could underreport NPSs due to lost insight in a similar fashion because this loss has been reported to affect assessments of memory complaints (50).

Association Between Cognition and Longitudinal NPSs

The connection between NPSs and cognition is emphasized by findings showing that the worse the cognitive status is in a sample, the higher is the frequency and severity of NPSs (4,51). Several reports have also shown that certain NPSs

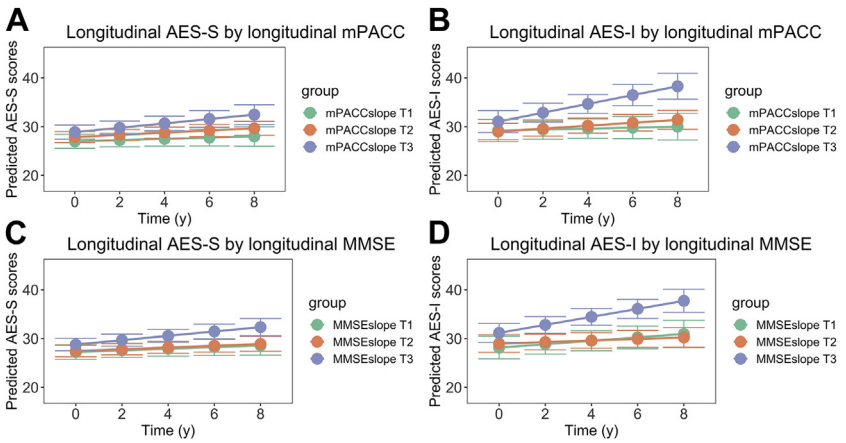

Figure 2. Linear mixed-effect models displaying effects on longitudinal neuropsychiatric measures by longitudinal cognition. Plots of estimated marginal means and 95% confidence interval of the means demonstrating significant effects (also after adjustment for multiple comparisons) on longitudinal measures of neuropsychiatric symptoms by longitudinal cognition in Table 1. In linear mixed-effect models, longitudinal neuropsychiatric symptom measures of apathy (longitudinal Apathy Evaluation Scale–Self-Rated Version [AES-S] by longitudinal modified Preclinical Alzheimer Cognitive Composite [mPACC5] [*n* = 333], longitudinal AES-S by longitudinal Mini-Mental State Examination [MMSE] [*n* = 333], longitudinal Apathy Evaluation Scale–Informant-Rated Version [AES-I] by longitudinal mPACC5 [*n* = 300], longitudinal AES-I by longitudinal MMSE [*n* = 300]) were, respectively, entered as the dependent variable. Interaction terms between time and mPACC5 slopes (change per year) **(A, B)** or MMSE slopes **(C, D)** were entered as fixed effects in separate models. Participants are grouped according to tertile of the fixed effect variable (T1, T2, T3 [the higher figure, the more cognitive deficits]). All models were corrected for age, sex, and education and included random slopes and intercepts.

constitute risk markers for more rapid cognitive decline or conversion to dementia (6,11,12). For instance, in an earlier study, we demonstrated that apathy and anxiety predicted cognitive decline in CU individuals and individuals with MCI (6).

Yet, only few studies have addressed the impact of cognition on longitudinal NPSs. In a longitudinal study on CU individuals by the AIBL Research Group, neither cognitive test performance nor retrospective informant ratings of cognitive change exerted effects over time on apathy (48). Here, conversely, we show a strong statistical effect by longitudinal cognitive test performance on longitudinal apathy. However, similar to the prior study, no effect over time by baseline cognitive test performance was found. Perhaps cognitive tests at baseline are not affected to such an extent that associations with longitudinal NPSs can be detected, or the tests are not sensitive enough to capture more subtle deficits. Given that baseline NPSs seem to predict future cognitive decline (6,13), and not vice versa, this highlights the potential clinical utility of early monitoring of NPSs as prognostic markers for disease progression. However, these findings partly rest upon studies using mixed samples of CU individuals and individuals with MCI, which limits the interpretation (6,13).

We found stronger associations between apathy and cognitive slopes than with pathology. Maybe this is explained by resilience factors against both cognitive deficits and NPSs. Hence, those who develop clinical symptoms due to pathology show both cognitive deficits and NPSs. Hypothetically, this could inflate the statistical relationship.

We further show that elevated trajectories of anxiety are associated with mPACC5 slopes, but this association did not survive Bonferroni correction. Hence, longitudinal anxiety

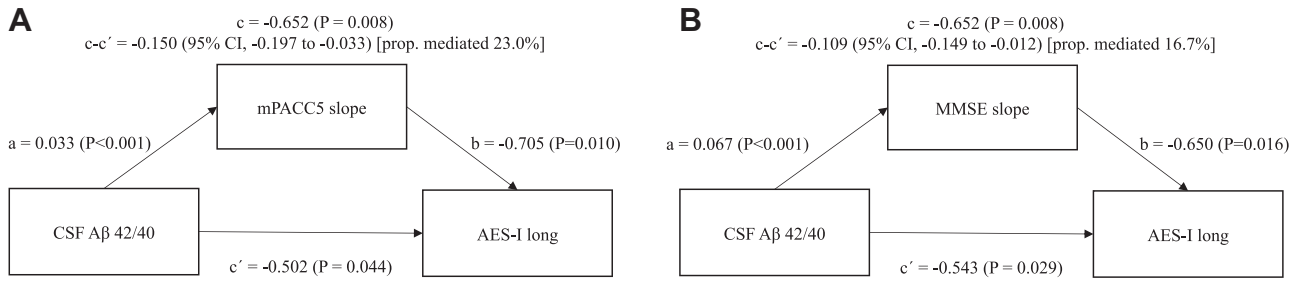

Figure 3. Cognition measured with modified Preclinical Alzheimer Cognition Composite (mPACC5) as a statistical mediator of the relationship between neuropathology and longitudinal neuropsychiatric symptoms. Mediation analyses of the relationship between neuropathology, cognition, and longitudinal neuropsychiatric symptoms in initially cognitively unimpaired participants. Only regression models in the primary analyses (Tables 2 and 3) displaying significant Apathy Evaluation Scale–Informant-Rated Version [AES-I] associations between measures of longitudinal neuropsychiatric symptoms, baseline neuropathology (cerebrospinal fluid [CSF] amyloid-β [Aβ]$_{42}$/Aβ$_{40}$), and cognitive slopes (mPACC5 and Mini-Mental State Examination [MMSE]) were used. The direct effect (*c*) of baseline CSF Aβ$_{42}$/Aβ$_{40}$ on the development of AES-I was obtained using linear mixed-effect models. The mediated effect of cognitive slopes, measured with mPACC5 **(A)** or MMSE **(B)** is designated *c*–*c*′. The remaining effect of baseline CSF Aβ$_{42}$/Aβ$_{40}$ on longitudinal AES-I is designated *c*′. The direct effect of baseline CSF Aβ$_{42}$/Aβ$_{40}$ on the mediator mPACC5 or MMSE is designated *a* and was obtained using linear regression modeling. The direct effect of the mediator mPACC5/MMSE on the development of AES-I is designated *b*. Models were corrected for age, sex, and education. All fixed and random effects, as well as covariates, were zero centered. Linear mixed-effect models included random slopes and intercepts. Confidence intervals (CIs) for mediation effects were obtained using bootstrapping with 1000 iterations. prop., proportion.

seems less related to cognitive decline compared with apathy. Individuals who debut with cognitive deficits could likely become anxious over its functional impact or worry over having a progressive neurocognitive disorder. However, anxiety does not inevitably accelerate owing to progressive cognitive deterioration. Instead, the anxiety or its increase over time due to cognitive change could remain stable, as indicated in Figure S4.

The Mediating Effects of Cognitive Decline for AD Pathology on Longitudinal NPSs

The association between Aβ and longitudinal apathy was only partly (23%) mediated by cognitive slopes. This indicates that Aβ mainly conveys its effect on apathy development through direct mechanisms somewhat independent from cognitive decline. In AD, Aβ is known to accumulate early in the parietal and frontal cortices with effects on neuronal connectivity in the default mode network and the frontoparietal control network (52). Even if these networks serve several purposes, the default mode network is considered important for cognitive task performance, while the frontoparietal control network predominately relates to goal-related behavior (53). In support, apathy has been shown to be associated with interrupted connectivity in the frontoparietal control network but not in any other network (53). Aligning with our finding that longitudinal anxiety is associated with Aβ but merely on a trend level with cognitive change, certain NPSs and cognitive decline could hypothetically share common anatomical locations of neuropathology but arise from dysfunction in separate functional brain networks.

Yet, our findings also support an indirect less prominent pathway to apathy, where Aβ may act through cognitive decline. The mechanism behind this mediation needs further exploration. However, diagnostic criteria for apathy emphasize change in goal-directed cognitive activities as an essential part of the construct (54), and associations between apathy and executive functioning have been reported (55,56). Even so, our post hoc analyses only support a role of executive dysfunction in the development of self-rated, but not informant-rated, apathy. Hence, if these associations arise due to an overlap in the theoretical frameworks of these manifestations (e.g., the ability to take initiative or complete tasks) (54,56) or if they are given by a shared common functional network disruption needs further exploration. Perhaps the divergency between the ratings is attributed to the self-rated version's potential to register the internal experience of a reduced executive function or goal-directed cognition, whereas the informant-rated version is limited to observations of external goal-directed behavior.

All in all, with previous studies demonstrating a strong association between Aβ positivity and future cognitive decline (57), our findings strengthen the proposed idea that cognitive deficits and NPSs can develop independent of, yet parallel to, each other, given a common underlying neuropathology. However, they also seem to reinforce one another, even if only to a limited extent (5).

Limitations and Strengths

The strength of this study is its well-characterized sample and its repeated measures of both NPSs and cognition. However, there are limitations. First, there are missing NPS data. However, LME models are known to be advantageous in dealing with missing values, and our sensitivity and survival bias analyses argue against such a strong effect. Second, the NPS data rest on assessments, not clinical diagnoses, and major psychiatric illness at baseline constituted an exclusion criterion. This limits the generalizability toward CU individuals with only subsyndromal NPSs or good mental health. Third, findings are not controlled for a history of psychiatric illness, although we did control for antidepressants during study follow-up (data on other psychopharmacologic treatments were not available). Fourth, tau and neurodegeneration are believed to develop somewhat later than Aβ in AD. As expected, levels of P-tau217 and NfL in this study on CU individuals are therefore low, which may reduce the power to detect very early associations between tau or neurodegeneration with longitudinal NPSs. Fifth, the corrections for multiple comparisons increase the risk of type II error. Nonetheless, we do display associations between NPSs, Aβ, and cognition, and uncorrected *p* values are also provided. Finally, neuropathologies other than those studied here could have contributed to the evolution of NPSs.

Conclusions

Early Aβ pathology may be a significant driver behind the development of both apathy and anxiety in CU older adults. The association between Aβ pathology and longitudinal apathy is only partly conveyed by cognitive decline; hence, Aβ pathology may influence apathy directly and somewhat independent of cognitive changes.

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ClinicalTrials.gov: The Swedish BioFINDER Study; https://clinicaltrials.gov/ct2/show/NCT01208675?term=NCT01208675&draw=2&rank=1; NCT01208675.

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REFERENCES

1. Hansson O (2021): Biomarkers for neurodegenerative diseases. Nat Med 27:954–963.
2. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, *et al.* (2018): NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14:535–562.
3. Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, *et al.* (2016): The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis [published correction appears in J Affect Disord 2016; 206:8]. J Affect Disord 190:264–271.
4. Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJH, Pankratz VS, *et al.* (2008): Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. Arch Gen Psychiatry 65:1193–1198.
5. Geda YE, Krell-Roesch J, Sambuchi N, Michel BF (2017): Neuropsychiatric symptoms and neuroimaging biomarkers in Alzheimer disease: "Which is the cart and which is the horse?". Am J Geriatr Psychiatry 25:694–696.
6. Johansson M, Stomrud E, Lindberg O, Westman E, Johansson PM, van Westen D, *et al.* (2020): Apathy and anxiety are early markers of Alzheimer's disease. Neurobiol Aging 85:74–82.
7. Johansson M, Stomrud E, Insel PS, Leuzy A, Johansson PM, Smith R, *et al.* (2021): Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. Transl Psychiatry 11:76.
8. Ng KP, Chiew H, Rosa-Neto P, Kandiah N, Ismail Z, Gauthier S (2021): Associations of AT(N) biomarkers with neuropsychiatric symptoms in preclinical Alzheimer's disease and cognitively unimpaired individuals. Transl Neurodegener 10:11.
9. Hanseeuw BJ, Jonas V, Jackson J, Betensky RA, Rentz DM, Johnson KA, *et al.* (2020): Association of anxiety with subcortical amyloidosis in cognitively normal older adults [published correction appears in Mol Psychiatry 2020; 25:2644]. Mol Psychiatry 25:2599–2607.
10. Bensamoun D, Guignard R, Furst AJ, Derreumaux A, Manera V, Darcourt J, *et al.* (2016): Associations between neuropsychiatric symptoms and cerebral amyloid deposition in cognitively impaired elderly people. J Alzheimers Dis 49:387–398.
11. Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS (2016): Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: Systematic review and meta-analysis. Int J Geriatr Psychiatry 31:905–911.
12. van Dalen JW, van Wanrooij LL, Moll van Charante EP, Brayne C, van Gool WA, Richard E (2018): Association of apathy with risk of incident dementia: A systematic review and meta-analysis. JAMA Psychiatry 75:1012–1021.
13. Pietrzak RH, Lim YY, Neumeister A, Ames D, Ellis KA, Harrington K, *et al.* (2015): Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: A multicenter, prospective cohort study. JAMA Psychiatry 72:284–291.
14. Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, *et al.* (2016): Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement 12:195–202.
15. Johansson M, Johansson P, Stomrud E, Hagell P, Hansson O (2017): Psychometric testing of a Swedish version of the Apathy Evaluation Scale [published correction appears in Nord J Psychiatry 2018; 72:157]. Nord J Psychiatry 71:477–484.
16. Djukanovic I, Carlsson J, Årestedt K (2017): Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65–80 years old? A psychometric evaluation study. Health Qual Life Outcomes 15:193.
17. Folstein MF, Folstein SE, McHugh PR (1975): "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.
18. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC (2017): Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. Alzheimers Dement (N Y) 3:668–677.
19. Wiig EH, Nielsen NP, Jacobson JM (2007): A Quick Test of Cognitive Speed: Patterns of age groups 15 to 95 years. Percept Mot Skills 104:1067–1075.
20. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, *et al.* (2020): Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 324:772–781.
21. Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, *et al.* (2014): The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. JAMA Neurol 71:961–970.
22. Mattsson-Carlgren N, Janelidze S, Palmqvist S, Cullen N, Svenningsson AL, Strandberg O, *et al.* (2020): Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. Brain 143:3234–3241.
23. Jonaitis EM, Koscik RL, Clark LR, Ma Y, Betthauser TJ, Berman SE, *et al.* (2019): Measuring longitudinal cognition: Individual tests versus composites. Alzheimers Dement (Amst) 11:74–84.
24. Palmqvist S, Zetterberg H, Blennow K, Vestberg S, Andreasson U, Brooks DJ, *et al.* (2014): Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β-amyloid 42: A cross-validation study against amyloid positron emission tomography. JAMA Neurol 71:1282–1289.
25. Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K, *et al.* (2019): Performance of fully automated plasma assays as screening tests for Alzheimer disease-related β-amyloid status. JAMA Neurol 76:1060–1069.
26. Sánchez-Benavides G, Suárez-Calvet M, Milà-Alomà M, Arenaza-Urquijo EM, Grau-Rivera O, Operto G, *et al.* (2021): Amyloid-β positive individuals with subjective cognitive decline present increased CSF neurofilament light levels that relate to lower hippocampal volume. Neurobiol Aging 104:24–31.
27. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P (2019): Advantages and disadvantages of the use of the CSF amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's disease. Alzheimers Res Ther 11:34.
28. Mattsson N, Insel PS, Palmqvist S, Portelius E, Zetterberg H, Weiner M, *et al.* (2016): Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol Med 8:1184–1196.
29. Schmidt P, Gaser C, Arsic M, Buck D, Förschler A, Berthele A, *et al.* (2012): An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. Neuroimage 59:3774–3783.
30. Marshall GA, Donovan NJ, Lorius N, Gidicsin CM, Maye J, Pepin LC, *et al.* (2013): Apathy is associated with increased amyloid burden in mild cognitive impairment. J Neuropsychiatry Clin Neurosci 25:302–307.
31. Mori T, Shimada H, Shinotoh H, Hirano S, Eguchi Y, Yamada M, *et al.* (2014): Apathy correlates with prefrontal amyloid β deposition in Alzheimer's disease. J Neurol Neurosurg Psychiatry 85:449–455.
32. Pichet Binette A, Vachon-Presseau É., Morris J, Bateman R, Benzinger T, Collins DL, *et al.* (2021): Amyloid and tau pathology associations with personality traits, neuropsychiatric symptoms, and cognitive lifestyle in the preclinical phases of sporadic and autosomal dominant Alzheimer's disease. Biol Psychiatry 89:776–785.
33. Donovan NJ, Locascio JJ, Marshall GA, Gatchel J, Hanseeuw BJ, Rentz DM, *et al.* (2018): Longitudinal association of amyloid beta and

anxious-depressive symptoms in cognitively normal older adults. Am J Psychiatry 175:530–537.

34. Babulal GM, Roe CM, Stout SH, Rajasekar G, Wisch JK, Benzinger TLS, *et al.* (2020): Depression is associated with tau and not amyloid positron emission tomography in cognitively normal adults. J Alzheimers Dis 74:1045–1055.
35. Harrington KD, Lim YY, Gould E, Maruff P (2015): Amyloid-beta and depression in healthy older adults: A systematic review. Aust N Z J Psychiatry 49:36–46.
36. Chung JK, Plitman E, Nakajima S, Chakravarty MM, Caravaggio F, Gerretsen P, *et al.* (2016): Cortical amyloid β deposition and current depressive symptoms in Alzheimer disease and mild cognitive impairment [published correction appears in J Geriatr Psychiatry Neurol 2016; 29:237–241]. J Geriatr Psychiatry Neurol 29:149–159.
37. Madsen K, Hasselbalch BJ, Frederiksen KS, Haahr ME, Gade A, Law I, *et al.* (2012): Lack of association between prior depressive episodes and cerebral [11C]PiB binding. Neurobiol Aging 33:2334–2342.
38. Perin S, Harrington KD, Lim YY, Ellis K, Ames D, Pietrzak RH, *et al.* (2018): Amyloid burden and incident depressive symptoms in preclinical Alzheimer's disease. J Affect Disord 229:269–274.
39. Mackin RS, Insel PS, Landau S, Bickford D, Morin R, Rhodes E, *et al.* (2021): Late-life depression is associated with reduced cortical amyloid burden: Findings from the Alzheimer's Disease Neuroimaging Initiative Depression project [published correction appears in Biol Psychiatry 2021; 89:836]. Biol Psychiatry 89:757–765.
40. Babulal GM, Ghoshal N, Head D, Vernon EK, Holtzman DM, Benzinger TLS, *et al.* (2016): Mood changes in cognitively normal older adults are linked to Alzheimer disease biomarker levels. Am J Geriatr Psychiatry 24:1095–1104.
41. Harrington KD, Gould E, Lim YY, Ames D, Pietrzak RH, Rembach A, *et al.* (2017): Amyloid burden and incident depressive symptoms in cognitively normal older adults. Int J Geriatr Psychiatry 32: 455–463.
42. Yasuno F, Kazui H, Morita N, Kajimoto K, Ihara M, Taguchi A, *et al.* (2016): High amyloid-β deposition related to depressive symptoms in older individuals with normal cognition: A pilot study. Int J Geriatr Psychiatry 31:920–928.
43. Krell-Roesch J, Lowe VJ, Neureiter J, Pink A, Roberts RO, Mielke MM, *et al.* (2018): Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: The Mayo Clinic Study of Aging. Int Psychogeriatr 30:245–251.
44. Krell-Roesch J, Syrjanen JA, Rakusa M, Vemuri P, Machulda MM, Kremers WK, *et al.* (2021): Association of cortical and subcortical β-amyloid with standardized measures of depressive and anxiety symptoms in adults without dementia. J Neuropsychiatry Clin Neurosci 33:64–71.
45. Lussier FZ, Pascoal TA, Chamoun M, Therriault J, Tissot C, Savard M, *et al.* (2020): Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. Alzheimers Dement 16:192–199.
46. Gatchel JR, Donovan NJ, Locascio JJ, Schultz AP, Becker JA, Chhatwal J, *et al.* (2017): Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: A pilot study. J Alzheimers Dis 59:975–985.
47. Theleritis C, Politis A, Siarkos K, Lyketsos CG (2014): A review of neuroimaging findings of apathy in Alzheimer's disease. Int Psychogeriatr 26:195–207.
48. Brodaty H, Altendorf A, Withall A, Sachdev P (2010): Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. Int Psychogeriatr 22:426–436.
49. Guercio BJ, Donovan NJ, Munro CE, Aghjayan SL, Wigman SE, Locascio JJ, *et al.* (2015): The Apathy Evaluation Scale: A comparison of subject, informant, and clinician report in cognitively normal elderly and mild cognitive impairment. J Alzheimers Dis 47:421–432.
50. Cacciamani F, Houot M, Gagliardi G, Dubois B, Sikkes S, Sánchez-Benavides G, *et al.* (2021): Awareness of cognitive decline in patients with Alzheimer's disease: A systematic review and meta-analysis. Front Aging Neurosci 13:697234.
51. Siafarikas N, Selbaek G, Fladby T, Šaltytė Benth J, Auning E, Aarsland D (2018): Frequency and subgroups of neuropsychiatric symptoms in mild cognitive impairment and different stages of dementia in Alzheimer's disease. Int Psychogeriatr 30:103–113.
52. Palmqvist S, Schöll M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H, *et al.* (2017): Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat Commun 8:1214.
53. Munro CE, Donovan NJ, Guercio BJ, Wigman SE, Schultz AP, Amariglio RE, *et al.* (2015): Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. J Alzheimers Dis 46:727–735.
54. Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, *et al.* (2018): Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry 54:71–76.
55. Kawagoe T, Onoda K, Yamaguchi S (2017): Apathy and executive function in healthy elderly-resting state fMRI study. Front Aging Neurosci 9:124.
56. Esposito F, Rochat L, Van der Linden ACJ, Lekeu F, Quittre A, Charnallet A, Van der Linden M (2010): Apathy and executive dysfunction in Alzheimer disease. Alzheimer Dis Assoc Disord 24:131–137.
57. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS, Alzheimer's Disease Neuroimaging Initiative (2017): Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. JAMA 317:2305–2316.