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Study Partner Report of Apathy in Older Adults is Associated with AD Biomarkers: Findings from the Harvard Aging Brain Study

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ABSTRACT

Objectives: *We examined relationships between apathy (self and study-partner-reported) and markers of Alzheimer's disease (AD) in older adults.* ***Design:*** *The study utilized a well-characterized sample of participants from the Harvard Aging Brain Study (HABS), a longitudinal cohort study. Participants were cognitively unimpaired without clinically significant neuropsychiatric symptoms at HABS baseline. The dependent variables, apathy evaluation scale-self (AES-S) and informant (AES-I), were administered cross-sectionally between years 6–9 and compared to the independent variables, amyloid and tau PET neuroimaging, from the same year.* ***Setting:*** *Community-dwelling participants assessed at research visits in an academic medical center.* ***Participants:*** *Participants (n = 170) completed assessments within 1.5 years of their neuroimaging visit. At the time of apathy assessment, N = 156 were cognitively unimpaired and 14 had progressed to mild cognitive impairment (n = 8) or dementia (n = 6).* ***Measurements:*** *We utilized linear regression*

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models to assess cross-sectional associations of AES-S and AES-I with AD PET imaging measures (beta-amyloid (Pittsburgh Compound B) and tau (Flortaucipir)), covarying for age, sex, education, and the time between PET scan-apathy assessment. ***Results:*** *AES-I was significantly associated with beta-amyloid and temporal lobe tau, and the associations were retained after further adjusting for depressive symptoms. The associations between AES-S and AD biomarkers were not significant. In an exploratory subgroup analysis of cognitively unimpaired individuals with elevated Aβ, we observed an association between AES-I and inferior temporal tau.* ***Conclusions:*** *Study-partner-reported, but not self-reported, apathy in older adults is associated with AD pathology, and we observed this relationship starting from the preclinical stage. Our findings highlight the importance of collateral information in capturing AD-related apathy.* (Am J Geriatr Psychiatry 2024; ■■:■■−■■)

OBJECTIVE

As the population ages, the global prevalence of dementia with Alzheimer's disease (AD dementia) is projected to grow substantially.[1] The impact of AD extends beyond the patient to families, caregivers, and society as a whole by inducing tremendous physical, emotional, work-related, and demographic stress.[2,3] Therefore, there is an increasing urgency to develop measures to prevent or target AD early in its course and mitigate its psychological and economic consequences.

Cognitive and behavioral symptoms manifest starting from the early stages of AD well before dementia diagnosis. Evidence supports neuropsychiatric symptoms (NPS) as clinical indicators and modifiers of cognitive impairment and AD progression.[4−6] Among NPS, apathy, defined as a lack of motivation or goal-directed behavior and indifference to one's surroundings,[7] is one of the most common symptoms seen in mild cognitive impairment (MCI) and dementia due to AD.[8] Moreover, regional tau and cortical beta-amyloid burden are associated with baseline apathy and increased apathy over time in individuals with MCI or AD dementia, indicating that apathy might be a direct manifestation of AD pathology.[9−11]

However, the majority of previous studies of apathy and AD pathology have focused on individuals with MCI or dementia. It remains unclear when and how AD-pathology-driven- apathy emerges in the continuum of preclinical and prodromal AD. This contrasts with other NPS, including depression, that have been studied in cognitively unimpaired (CU) older adults and have been variably found to be associated with AD pathology, beta-amyloid and tau burden,[12−14] in addition to other neurobiological mechanisms.

Moreover, how to capture AD-related apathy in preclinical and prodromal AD needs further investigation. Apathy is not always reported consistently by patients relative to family and/or care partners.[15] This may stem in part from the nature of the symptom, as individuals experiencing apathy, by definition, may be less bothered by it and less inclined to report it compared to those around them. In one prior study by our group, cognitively unimpaired individuals self-reported having greater apathy than was reported about them by their study partners (typically a spouse, child, or close friend).[16] However, the reverse was true for participants with MCI−they tended to self-report less apathy compared to what their study partner reported about them.[16] This suggests a lack of awareness or concern about apathy as individuals reach the stage of cognitive impairment.[17] Thus, whether we should use self-reported or study partner-reported apathy measures in the earliest stages of AD remains unclear.

To address this gap, we leveraged the Harvard Aging Brain Study (HABS), a longitudinal observational study of cognitive aging and preclinical AD. HABS, at study years 6−9 when apathy data were collected, represents the continuum of disease progression rather than separately recruited subgroups of CU and MCI participants who often prove to be very distinct, and thus provides a unique dataset to study AD-related apathy in the earliest disease continuum. In the current study, our objective was to examine cross-sectional relationships between self

and study-partner reported apathy and *in vivo* regional AD pathology in older adults on a continuum of CU and MCI/dementia.

METHODS

Participants

The Harvard Aging Brain Study (HABS) is a longitudinal cohort study that recruited CU individuals between the ages 50 and 90 from the greater Boston area. All participants provided informed consent, and the Mass General Brigham Institutional Review Board approved the study procedures. Inclusion criteria at the beginning of HABS included: Clinical Dementia Rating (CDR) global score of 0, Mini Mental State Exam (MMSE) greater than 25, and performance within 1.5 SD on adjusted norms of Logical Memory delayed recall (LM).[18–20] We excluded individuals with major medical or neurological disorders that might contribute to cognitive impairment, including a history of alcoholism, drug abuse, head trauma, or a family history of autosomal dominant AD. We excluded individuals at study entry with active depressive symptoms in the clinically significant range, defined as a Geriatric Depression Scale-30 (GDS) score of 12 or greater.[21] Of note, individuals were not excluded at subsequent follow up even if they developed clinically significant depressive symptoms or other NPS.

All participants and their study partners included in the current study completed the apathy evaluation scale (AES)[22] within 1.5 years of a neuroimaging-related visit (n = 170). The timing of this scale fell between years 6 and 9 of the participant's HABS participation and was given at a single time point per participant (cross-sectional).

Clinical Assessments

Participants and their study partners completed the AES-S and AES-I surveys respectively.[22] This survey consists of 18 items rated on a 4-point Likert-type scale and a score range from 18 to 72 with lower scores indicating greater apathy. Self (AES-S) and study partner (AES-I) completions occurred at the same time.

Moreover, participants completed the GDS in each year of study participation.[21] For our study sample analyses, we used the GDS completed at the time of AES collection.

Each participant's progression to MCI or dementia was assessed through consensus meetings by neurologists, psychiatrists, and neuropsychologists.

PET Imaging

PET acquisition methods have been detailed previously.[23,24] Briefly, PET images were collected on a Siemens HR+ scanner at the Mass General Hospital Gordon Center for Biomedical Imaging. To quantify neocortical fibrillar beta-amyloid plaque burden,[11] C-Pittsburgh Compound B (PiB) tracer was used. The distribution volume ratio (DVR), including the frontal, lateral parietal, lateral temporal, and retrosplenial cortical regions, was calculated with cerebellar gray matter reference to determine cortical beta-amyloid burden. Continuous measures of PiB PET values were used in all analyses. For purposes of clinical sample description and model visualizations, each PiB-PET image was classified as Aβ positive or Aβ negative using a Gaussian mixture modeling approach.[25] Regional tau burden was measured by ^{18}F-Flortaucipir (FTP) tracer uptake. Given that our study sample was predominantly cognitively unimpaired, we focused on two bilateral regions of interest (ROIs) in the temporal lobe: the bilateral entorhinal cortex (EC) and inferior temporal (IT) that have been previously identified as among the earliest sites of tau accumulation and FTP PET signal in aging and preclinical AD.[23] To quantify tau burden, the bilateral FTP mean standardized uptake value ratios (SUVRs) were calculated in each ROI using a cerebellar gray reference region. For both PiB-PET and FTP-PET scan data, partial volume correction (PVC) was performed using the geometric transfer matrix method as previously described.[26] PET scans are acquired in years 1, 4, 6, 9, and 12. In this study, we used PET data closest in time to AES data collection. As mentioned above, all PET data were obtained within 1.5 years of apathy assessment administration (Table 1).

Statistical Analyses

All statistical analyses were carried out in R version 4.3.1. In separate linear regression models, we

TABLE 1. Demographics of Study Sample The demographics and clinical characteristics of the study sample are shown. The columns show the entire study sample (n = 170), and also the breakdowns between participants with stable cognition (n = 156) and participants who had progressed to cognitive impairment through the course of the study (either mild cognitive impairment or AD dementia, n = 14). The rows include age, sex, education, and Geriatric Depression Scale (GDS) scores of the study sample. Amyloid-β burden was measured using Pittsburgh Compound B (PiB) PET imaging in a cortical aggregate (frontal, lateral temporal/parietal and retro splenial cortices, distribution volume ratio (DVR)). Amyloid positivity (PiB DVR PiB+) was determined using a PiB PET cut-off in the sample derived as previously described. APOEe4 allele carriers (numbers and percentage) are also reported. Apathy Evaluation Scale (AES) reported scores are given for both the study partner and self. Date differences between time of PET scan and time of AES collection are also reported in years.

Characteristic	All (N = 170[a])	Stable Cognition (N = 156[a])	Impaired (N = 14[a])
Age, years	80 (6.74)	79.57 (6.71)	85.05 (4.85)
Female sex	101 (59.4%)	92 (59.0%)	9 (64.3%)
Education, years	16.36 (2.87)	16.29 (2.86)	17.14 (2.88)
PiB DVR PiB+	67 (39.4%)	54 (34.6%)	13 (92.9%)
PiB DVR FLR	1.59 (0.48)	1.44 (0.42)	2.23 (0.44)
GDS[b]	4.14 (4.16)	4.12 (4.20)	4.38 (3.78)
APOE4 Carrier[c]	47 (28.0%)	39 (25.3%)	8 (57.1%)
Apathy evaluation scale-informant (AES-I)	64.76 (7.37)	65.72 (6.40)	54.07 (9.15)
Apathy evaluation scale-self (AES-S)	64.19 (7.21)	64.47 (6.70)	61.07 (11.38)
Absolute tau-AES date difference, years	1.15 (1.46)	1.14 (1.46)	1.34 (1.59)
Absolute PiB-AES date difference, years	1.27 (1.53)	1.25 (1.51)	1.48 (1.77)

[a] Mean (SD) for all characteristics except female sex, PiB DVR PiB+, and APOE4 carrier, which are reported as total number (percentage of sample).
[b] Missing: 1 observation in the Impaired Group.
[c] Missing: 2 observations in the Stable Cognition Group.

assessed the associations between AES-S or AES-I and PET imaging measures, covarying for age, sex, education, and the time difference (in years) between AES-S/I (dependent variable) and beta-amyloid or tau level as measured by PET scans (independent variable).

We performed diagnostic analyses to ensure that our results would not be driven by deviations from the assumptions of linear regression. We observed no large deviation from the assumptions of linearity, homoscedasticity, and normality of residuals. Our study design ensures the independence of observations, as AES-S and AES-I are done once for each participant and study partner. Further, we used Cook's distance method to identify strong outliers that could act as leverage points and found none. The AES-S and AES-I distributions had ceiling effects, reflecting a large number of participants having high scores on the measure (indicating low levels of apathy). This was expected due to both the nature of the measure and the composition of the study sample, consisting of predominantly cognitively unimpaired individuals without psychiatric disease burden. To ensure robustness of results, a log transformation (log(73-AES score)) was applied to AES scores and all primary models were repeated using these log-transformed values.

We performed four additional sensitivity linear regression analyses. First, we controlled for depressive symptoms using the participant-reported GDS (N = 169 due to 1 participant missing score) as apathy can be comorbid with depressive symptoms in older adults.. Next, to examine the influence of cognitive symptom progression on the associations between apathy and AD pathology, we repeated linear regression analyses, limiting our sample to CU participants (N = 156) after excluding those who had progressed to MCI or dementia by the time of apathy assessments (N = 14). To rule out potential confounding effects of the COVID-19 pandemic including diminished social activities that could mimic the social withdrawal of apathy, we repeated linear regression analyses, adding a covariate to indicate whether AES assessments were completed before or after the onset of COVID-19 pandemic. Finally, we controlled for participant cognitive performance using their Preclinical Alzheimer Cognitive Composite (PACC96) scores as a covariate to examine whether the association between apathy and AD biomarkers is independent of cognitive decline. We also ran separate linear

regression models with age, depressive symptoms, or cognitive performance as moderators (interactive predictors with PET measures).

RESULTS

Demographics and clinical characteristics of our study sample are shown in Table 1. In our study sample, 156 participants had stable cognition, while 8 participants had clinically progressed to MCI and 6 had progressed to AD dementia at the time of apathy assessment.

We confirmed that our models met the assumptions for linear regression models (see Methods and Supplementary Fig. 1), and thus it is unlikely that our results are driven by the skewness of the data or outliers. Of note, results were concordant using log-transformed and non-log-transformed AES values (data not shown). For ease of interpretability, we present primary results of models using non-log-transformed AES values.

In our primary linear regression analysis focusing on self-reported apathy, we did not observe significant relationships between AES-S and measures of AD pathology (amyloid-β, EC tau or IT tau) (Table 2). In contrast, in the linear regression models focused on study-partner-reported apathy, lower AES-I, corresponding to greater SP-reported participant apathy symptoms, was associated with elevated EC tau, IT tau, and cortical amyloid-β (Table 2, Fig. 1) where B indicates unstandardized coefficients. Of note, we observed small to medium effect sizes for the associations between AES-I and AD biomarkers (ΔR^2 0.030 −0.070 Table 2). Age moderated the effect between AES-I and cortical amyloid-β (B = -0.40, t = -2.30, df = 163, p = 0.02).

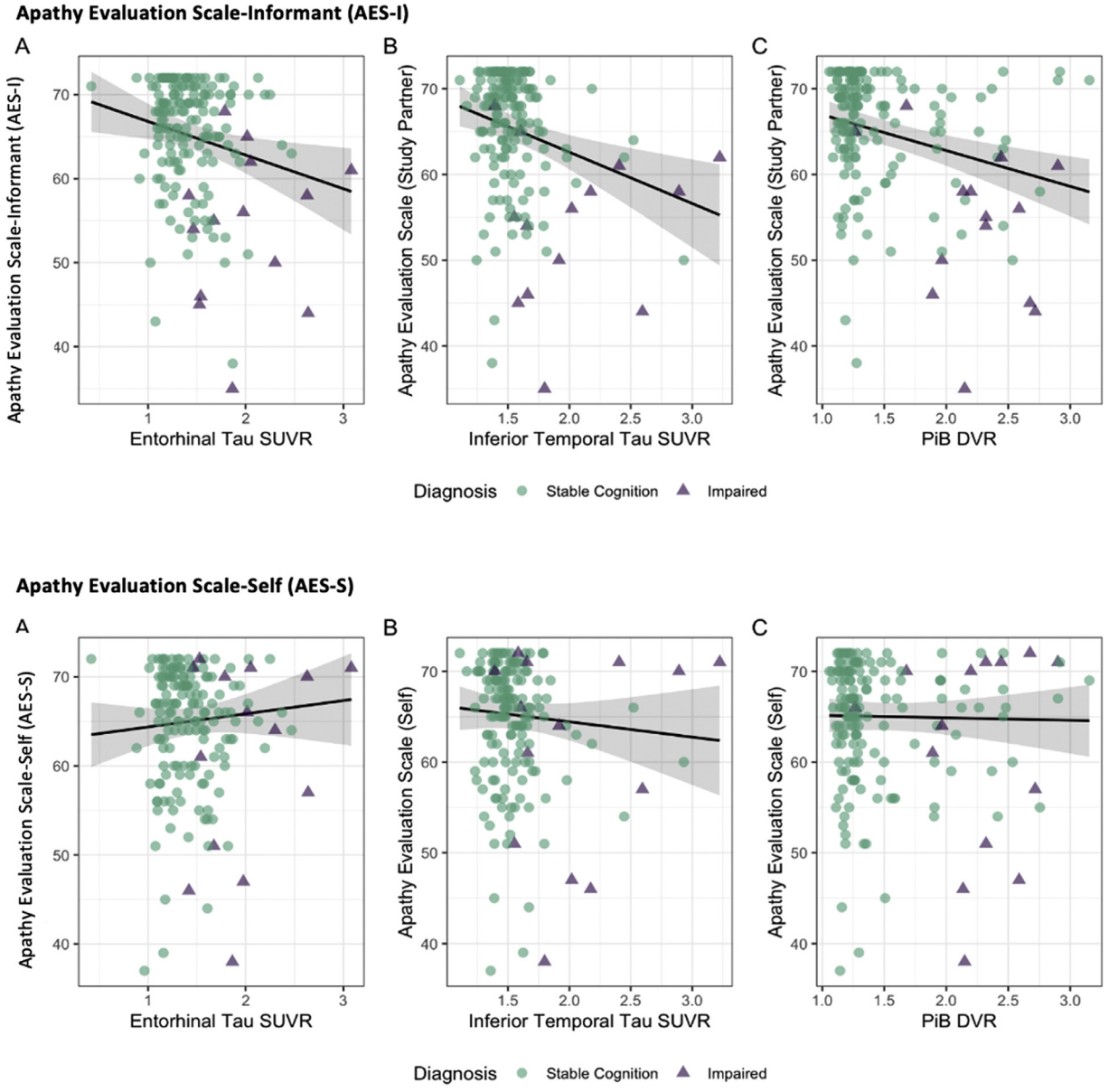
To consider co-occurring depressive symptoms, we carried out sensitivity linear regression analyses adjusting for participant scores on the GDS administered at the same time point as the AES measure. Of the 169 participants who had GDS data available, 11 participants reported clinically significant depression (defined as a GDS greater than or equal to 12) at the time of apathy assessment. The relationship between SP-reported apathy and AD biomarkers remained significant when adjusting models for participant GDS scores: lower AES-I, or greater SP-reported participant apathy, was associated with elevated EC tau (B = -4.46, t = -2.93, df = 162, p = 0.004), IT tau (B = -6.67, t = -3.45, df = 162, p <0.001), and amyloid-β (B = -4.10, t = -3.80, df = 162, p <0.001) where B indicates unstandardized coefficients. Similarly, in additional sensitivity linear regression analyses adjusting for time between AES assessment and onset of the COVID-19 pandemic, the relationships between AES-I and AD biomarkers remained unchanged (elevated EC tau (B = -4.06, t = -2.61, df = 145, p = 0.010), IT tau (B = -5.95, t = -3.28, df = 145, p = 0.001), and amyloid-β (B = -4.28, t = -3.90, df = 145, p <0.001) where B indicate unstandardized coefficients. As observed in primary analyses, we did not observe significant relationships between AES-

TABLE 2. Results of Primary Models Examining Associations Between AES-S (Self-Reported Apathy) or AES-I (Study-Partner-Reported Participant Apathy) and AD Neuroimaging Biomarkers (Ab, EC Tau, and IT Tau)

AES Measure	PET Measure	B	95% CI	SE	t	p	ΔR^2
AES-S	EC tau	1.48	(-1.62, 4.59)	1.57	0.94	0.35	−0.001
AES-S	IT tau	−1.69	(-5.35, 1.97)	1.85	−0.91	0.36	−0.001
AES-S	PiB FLR	−0.28	(-2.54, 1.98)	1.14	−0.24	0.81	−0.005
AES-I	EC tau	−4.01	(-7.08, -0.93)	1.56	−2.57	0.011*	0.030
AES-I	IT tau	−5.99	(-9.57, -2.42)	1.81	−3.31	0.001**	0.051
AES-I	PiB FLR	−4.18	(-6.35, -2.02)	1.09	−3.82	<0.001***	0.068

AES-S: apathy evaluation scale- self; **AES-I:** apathy evaluation scale- informant; **EC Tau:** entorhinal tau; **IT Tau:** inferior temporal tau; **PiB FLR:** amyloid- β in a frontal, lateral, temporal/parietal, and retrospenial cortical composite; *Linear regression analyses were performed and unstandardized effects sizes & r-squared values are reported, (df = 163).* Regional tau (18F-Floftaucipir (FTP) PET, entorhinal cortex (EC) and inferior temporal cortex (IT) regions of interest (ROI)) and amyloid-β (Pittsburgh Compound B (PiB) PET in a cortical composite (FLR) burden were associated with greater study partner-reported participant apathy (lower AES-I scores) in older adults. Results of each linear regression model is shown in each row. For all models, associations between outcome—Apathy Evaluation Scale, either participant (self-rated) (AES-S) or study-partner-rated participant apathy (AES-I)–were examined relative to one of the PET biomarker predictors of interest: (EC tau PET, IT tau PET, or cortical amyloid-β PET), adjusting for covariates: age, sex, and education. The unstandardized B values, 95% confidence intervals (CI), standard error (SE) for each analysis, t-scores, and p-values are listed. Asterisks denote statistical significance.

FIGURE 1. AES-S and AES-I relation to biomarkers. **Regional tau and amyloid burden are associated with greater study partner-reported participant apathy (lower AES-I scores) in older adults. Scatter plots depict entorhinal tau (A), inferior temporal tau (B), and amyloid-β (C) in relation to study partner-reported participant apathy (AES-I) (top panel) and self-reported apathy (AES-S) (bottom). Tau is measured using FTP PET SUVR in the entorhinal and inferior temporal regions. Amyloid-β burden is measured using PiB PET DVR in a frontal, lateral, and retro splenial (FLR) cortical aggregate. Black solid lines indicate lines of best fit for each linear regression model, shading represents a 95% confidence interval (CI), and data points represent individual study participants. Green dots denote participants who have stable cognition (unimpaired), and purple triangles denote participants who progressed to cognitive impairment in the study at the time of AES assessment. AES-S: apathy evaluation scale, self-rated; AES-I: apathy evaluation scale, study-partner rated; SUVR: standardized uptake volume ratio; DVR: distribution volume ratio.**



S and AD biomarkers in sensitivity analyses. Finally, to take cognitive status into account, we carried out sensitivity linear regression analyses adjusting for participant scores on the Preclinical Alzheimer Cognitive Composite (PACC96) administered at the same time as the AES measure. When PACC96 score was added to models as a covariate, no significant associations were seen between apathy and tau, but there was a significant association between study-partner-reported apathy, AES-I, and amyloid-β (B = -3.09, t = -2.68, df = 163, p = 0.008) where B indicates an unstandardized coefficient.

While the majority of our cohort (>90%) had stable cognition, 14 participants had progressed to a consensus diagnosis of MCI or dementia at the time of AES assessment. Given previously reported discrepancies in self versus study-partner-reported apathy at stages of cognitive impairment, we repeated our primary analyses excluding these 14 individuals. In these secondary linear regression analyses, we did not observe significant relationships between self-reported apathy and AD pathology measures. Further, the associations between lower AES-I scores (higher study-partner-reported participant apathy) and AD pathology were marginal and/or no longer significant (Supplementary Table 1). Nonetheless, in an exploratory subgroup analysis focusing on the CU individuals with preclinical AD (CU and amyloid-β positive), we observed a significant association between AES-I and IT tau (B = -7.12, t = -2.61, p = 0.012; Supplementary Fig. 2). This result suggests that the association between AD pathology and AES-I starts to emerge in CU amyloid-β positive individuals, or pre-clinical individuals, who represent a population of future interest.

CONCLUSIONS

Leveraging participants from the Harvard Aging Brain Study with well-characterized longitudinal follow-up, we observed that higher study partner-reported apathy in participants, but not self-reported apathy, is cross-sectionally associated with AD pathology (cortical amyloid-β and tau burden in the temporal lobe [an early site of tau accumulation in aging and AD]). Even though >90% of our study participants had stable cognition at the time of apathy assessments, the associations between SP-reported apathy and AD biomarkers were no longer significant when we excluded the few participants who had progressed to the stage of cognitive impairment (MCI or dementia) from the analyses. Together, our results indicate that AD-driven apathy can be better captured by the SP even in the earliest disease stages. Further, our results suggest that AD-driven apathy might become apparent only at the transition to cognitive impairment.

Consistent with prior literature, our results support apathy as an early symptom in the spectrum of cognitive-behavioral changes in AD. Our results additionally provide a unique perspective, highlighting the emergence of care partner-recognized apathy at the transition from CU to cognitive impairment in older adults. Even at this early disease stage, self-report of apathy may lack reliability relative to study-partner observation when associated with AD biomarkers. This may be due to either the nature of apathy, such that it concerns observers—friends and family—more than it does the individual, versus loss of awareness of cognitive and behavioral symptom progression in early AD, or the combination of both. Distinguishing between these alternatives warrants future study and has implications for early clinical detection and management of AD.

Previous studies of apathy and AD neuroimaging biomarkers have largely been carried out in clinically symptomatic cohorts utilizing informant (study partner) reports of apathy, such as captured by the Neuropsychiatric Inventory (NPI). However, many of these investigations have not differentially assessed self versus study-partner-reported apathy. In a cross-sectional study in a cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI), apathy assessed by the study-partner rated NPI apathy item was cross-sectionally associated with AD pathology (amyloid and tau PET imaging).[11] This study sample consisted of 410 CU, 199 MCI and 61 AD dementia participants. When secondary analyses were carried out in CU or cognitively impaired participants separately, apathy-biomarker associations were only observed in the cognitively impaired participants. This is concordant with our findings. Though we examined individuals who had progressed from stable to impaired cognition over the course of the longitudinal HABS cohort study, representing incident cognitive impairment, results from both studies suggest apathy as emerging at the stage of early cognitive impairment, or in the transition from CU to MCI. Indeed, findings from our

manuscript additionally suggest apathy associated with AD pathology emerges at the stage of preclinical AD, highlighting CU amyloid-β positive individuals as a group of particular interest for future study. Building on prior work, our results suggest that study partner reported apathy may more closely track with AD pathology, and that self-reported apathy in CU or MCI older adults may not reflect underlying AD pathology. This underscores the importance of capturing collateral history, for example from a study partner or family member, when assessing apathy in AD clinical research and practice.

In addition to NPS such as apathy, subjective cognitive concerns may also be early cognitive-behavioral manifestations in preclinical AD. Previous studies from the HABS cohort evaluating associations between subjective cognitive concerns and *in vivo* AD pathology in CU older adults found that a composite of self-reported cognitive concerns was cross-sectionally associated with temporal lobe tau pathology, most prominently EC tau.[26] An additional longitudinal study using the HABS cohort further probed self- versus study-partner reported cognitive concerns over time relative to AD pathology.[27] This study found that longitudinal study-partner reported versus self-reported cognitive concerns, the latter of which were influenced by participant mood symptomatology, more closely tracked with baseline levels of AD pathology. In contrast to these prior study findings focused on subjective cognitive concerns, we found weaker/no significant cross-sectional associations between apathy and AD pathology when we limited our sample to CU participants. While future longitudinal studies of self-versus study-partner reported apathy in relation to AD biomarkers and subjective cognitive concerns are needed, these findings together raise the possibility that in community-dwelling older adults, subjective cognitive concerns may emerge prior to apathy in the cognitive behavioral trajectory of early AD.

Apathy and depression can be challenging to differentiate clinically and may co-occur. Yet, we observed that the association between SP-reported apathy and AD biomarkers remained significant when we controlled for depressive symptoms using the GDS. However, this must be interpreted in the context of our study sample, which was comprised of individuals who did not have clinically significant depression at the time of HABS enrollment. Furthermore, the majority of participants had no prior history of depression. In future studies it will be important to explore apathy-depression-AD biomarker relationships in older adults with a history of depression who meet diagnostic criteria for Major Depressive Disorder (MDD) or Persistent Depressive Disorder (PDD).

It is important to note some of the limitations of our study, beginning with our sample.

Though we leveraged a unique, well-characterized cohort of largely unimpaired older adults, our study sample was predominantly Non-Hispanic, White, and highly educated. Thus, these findings might not extrapolate to the entire population. In addition, the majority of our sample did not have concurrent psychiatric diagnoses. While this poses some limitations, it also allowed us to examine symptoms of apathy that may be more likely associated with AD rather than premorbid psychiatric illness. Although the effect sizes of associations between apathy and PET measures were in the small to medium range, they are consistent with ranges we have observed in previous analyses of cognitive symptom-biomarker relationships in our sample and are of high theoretical interest. Moreover, apathy, measured with the AES, and depression, measured with the GDS, are among the primary neuropsychiatric symptoms assessed in our sample. In future work, it will be of interest to assess a broader range of neuropsychiatric symptoms longitudinally in our sample. In our study, we focused on early regions of tau deposition in AD, and these may not be explicitly implicated in the neurobiology of apathy. Finally, though the AES is a validated scale, it may be useful to include additional scales to capture the complexity of apathy as an NPS of AD. The AES encompasses emotional, motoric, and cognitive aspects of apathy, but here we focused on the construct as a whole because our sample size was too small to carry out item-based analyses. Thus, it will be useful for future studies to look at these specific components as well as to incorporate standardized diagnostic criteria for apathy in neurocognitive disorders, as were recently developed by a working group led by the International Society for CNS Clinical Trials Methodology and the Alzheimer's Association.[28]

In summary, in a sample of older adults from the Harvard Aging Brain Study, apathy as measured by study partner, but not self-report, was cross-sectionally associated with *in vivo* AD pathology (cortical amyloid

and temporal lobe tau). Moreover, these results were driven by individuals who had progressed to cognitive impairment at the time of apathy assessment. Together, this highlights a particularly vulnerable group of older adults who may manifest AD-pathology-driven-apathy that is best captured by study-partner report. Further studies examining longitudinal relationships among apathy, other early NPS, cognition, and regional amyloid and tau pathology are needed to clarify the temporal sequence of cognitive-behavioral changes in early AD. It will be important to examine these relationships in both clinically impaired and unimpaired populations, and to include not only self and study partner reports of apathy, but also potentially novel and more objective measures. Such work has important implications for older adults presenting with early NPS who may be appropriate candidates for newly emerging AD interventions.

AUTHOR CONTRIBUTIONS

Jessa Burling, Jennifer Gatchel, and Hyun-Sik Yang lead this project and collaborated on statistical methods and content with the following co-authors: Zoe Katz, Ziwen Yuan, Catherine Munro, Kayden Mimmack, Grace Ma, Bernard Hanseeuw, Kate Papp, Rebecca Amariglio, Patrizia Vannini, Dorene Rentz, Yakeel T. Quiroz, Keith Johnson, Reisa Sperling, Deborah Blacker, Gad A. Marshall.

DATA STATEMENT

Both imaging and neuropsychological data are publicly available upon request and agreement to our data use agreement (DUA). Please visit https://habs.mgh.harvard.edu to inquire.

A poster presentation of the preliminary results of this work was presented at the Alzheimer's Association International Conference from July 31, 2022 to August 4, 2022 in San Diego California.

DISCLOSURES

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SUPPLEMENTARY MATERIALS

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