Title: 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

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Abstract (247/250 words)

Background: Major prevention trials for Alzheimer's disease (AD) are now focusing on multi-domain lifestyle interventions. However, the exact combination of behavioral factors related to AD pathology remains unclear. In two cohorts of cognitively unimpaired individuals at risk of AD, we examined which combinations of personality traits, neuropsychiatric symptoms, and cognitive lifestyle (years of education or lifetime cognitive activity) related to the pathological hallmarks of AD, amyloid-beta and *tau* deposits.

Methods: Some 115 older adults with a parental or multiple-sibling family history of sporadic AD (PREVENT-AD cohort) underwent amyloid and *tau* positron emission tomography (PET) and answered several questionnaires related to behavioral attributes. Separately, we studied 117 mutation carriers from the Dominantly Inherited AD (DIAN) cohort with amyloid PET and behavioral data. Using partial least squares analysis, we identified latent variables relating amyloid or *tau* pathology with combinations of personality traits, neuropsychiatric symptoms, and cognitive lifestyle.

Results: In PREVENT-AD, lower neuroticism, neuropsychiatric burden and higher education were associated with less amyloid deposition ($p=0.014$). Lower neuroticism and neuropsychiatric features, along with higher measures of openness and extraversion, were related to less *tau* deposition ($p=0.006$). In DIAN, lower neuropsychiatric burden and higher education were also associated with less amyloid ($p=0.005$). The combination of these factors accounted for up to 14% of AD pathology.

Conclusions: In the preclinical phase of both sporadic and autosomal dominant AD, multiple behavioral features were associated with AD pathology. These results may suggest potential pathways by which multi-domain interventions might help delay AD onset or progression.

1. Introduction

Given the limited successes of pharmacological treatments for Alzheimer's disease (AD), attention has shifted toward risk or protective factors that might prevent or postpone disease onset(1, 2). Estimates suggest that a multi-domain lifestyle intervention that achieved a 10% reduction in risk factors could prevent more than a million cases worldwide(3). The mechanisms that link protective factors and AD risk are not well understood, but current notions of resilience and resistance may be helpful (4). While resilience refers to the preservation of cognitive abilities in the presence of AD pathology, resistance refers to avoidance of the pathology in the first place(5, 6). These concepts, which are not mutually exclusive, have been tested in the sporadic form of the disease, given the causative genetic mutation in autosomal dominant AD (ADAD). Here, we describe investigations in both disease forms of the relationships between several personality and behavioral features associated with AD risk and presence of AD pathology. Such relationships, tested in asymptomatic individuals, might suggest sources of resistance pathway, thereby hinting at modifiable pathways to postpone manifestation of brain pathology.

In sporadic AD, as much as a third of AD risk appears to be related to modifiable factors such as level of education, depression, and cognitive or physical activity(1, 7). Education and mid-life cognitive activity have been associated with lower levels of pathology in the preclinical phase of the disease, and with increased resilience to pathology in later stages(8, 9). Neuropsychiatric symptoms like depression and apathy are known to increase over the course of the disease(10-12). While some such features are likely a consequence of the disease, mid-life neuropsychiatric symptoms have been associated with increased AD risk in later life(13). Personality traits like

neuroticism and conscientiousness have also been associated with cognitive decline and risk of sporadic AD(14, 15). Admittedly, personality traits may change as a consequence of the disease process, but a recent study showed that personality traits in adolescence — a time when AD pathology is unlikely—are associated with incident dementia 54 years later(16). Furthermore, personality traits usually remain stable in the early stages of the disease(17).

Fewer studies have explored the associations between behavioral/personality features and AD risk in ADAD. Higher resilience has been noted in individuals having higher levels of education, using the estimated years to symptom onset as a proxy for disease severity(18). Less physical activity and lower levels of education have also been associated with increased AD pathology and cognitive decline in preclinical ADAD(19-21). While personality has been studied less in ADAD, neuropsychiatric symptoms such as depression and anxiety have been found to remain stable in asymptomatic individuals but to increase in individuals with cognitive impairment(22). When compared with non-carriers, asymptomatic ADAD mutation carriers have even been found to exhibit fewer depressive symptoms(22).

During the pre-symptomatic phase of either disease, individuals remain cognitively normal despite their accumulation of AD pathological hallmarks, amyloid-beta (Aβ) and *tau* proteins(23, 24). This silent phase, which can span more than two decades, represents an ideal window of opportunity for preventive strategies(25). Given the complex etiology of AD, targeting multi-domain factors is rapidly becoming the norm in prevention trials(26). We therefore used multivariate analyses to investigate combinations of personality traits, neuropsychiatric symptoms, and cognitive lifestyle in relation to Aβ and *tau* deposition in cognitively normal

older adults at increased risk of sporadic or autosomal dominant AD (mutation carriers) (for the latter, Aβ only). We expected to find similar associations in both disease forms, but perhaps weaker associations in ADAD, given the latter's overwhelming genetic diathesis. We reasoned that discovery of such associations in the asymptomatic phase of the disease could suggest that preventive behavioral interventions may be useful in at-risk persons that are still free from pathology.

2. Methods and Materials

2.1 Participants

We studied 232 cognitively unimpaired participants, including 115 individuals at risk of sporadic AD from the PRe-symptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) study and 117 asymptomatic individuals with ADAD from the Dominant Inherited Alzheimer's Network (DIAN) study group. PREVENT-AD enrolls older adults having intact cognition but a parent or two siblings diagnosed with AD-like dementia, who are therefore at increased risk of sporadic AD(27). Participants were above 60 years of age, or between 55 and 59 if their age was fewer than 15 years from their parent's age of symptom onset. Participants were free of major neurological and psychiatric diseases at enrollment. Inclusion criteria included intact cognition based on the Montreal Cognitive Assessment (MoCA; score above 25) (28) and a 45-minute standardized neuropsychological evaluation using the Repeatable Battery for the Assessment of Neuropsychological Status (29). The cognitive status of individuals with questionable neuropsychological status was reviewed in consensus meetings of neuropsychologists (including SV) and/or psychiatrists (including JCSB). Only participants with Aβ-PET, *tau*-PET and data on behavioral factors

were included, resulting in 115 participants (out of 324 active PREVENT-AD participants as of May 2019). The DIAN study group enrolls individuals over 18 years old with a family history of ADAD. We selected mutation carriers who were cognitively normal as evidenced by Clinical Dementia Rating(30) of 0, and who had Aβ-PET and behavioral data available. Those studied comprised 117 participants (85 PSEN1 mutation carriers, 17 PSEN2 mutation carriers and 15 APP mutation carriers) out of 146 mutation carriers archived in the DIAN data-freeze of May 2016).

2.2 Behavioral factors

All participants filled out questionnaires to assess various behavioral factors plausibly related to AD risk (Table S1). For ease of interpretation, we grouped these factors into three categories: "Big Five" personality traits (neuroticism, openness, extraversion, agreeableness, conscientiousness), neuropsychiatric symptoms (depression, anxiety, stress, apathy), and features of cognitive lifestyle (years of education, lifetime cognitive activity). In PREVENT-AD, all questionnaires were answered at home six months to a year prior to PET (mostly electronically, but 10% responded by paper version). Follow-up questionnaires were sent to participants every year or so, resulting in three time points for neuropsychiatric symptoms (2016, 2017, 2018) and two for personality (2016 and 2018). Intraclass correlation coefficients (ICC) and their 95% confidence intervals, based on absolute agreement in two-way mixed-effects models, were computed using SPSS(31). Figures S1 and S2 display correlations between these scores at the different time points.

In DIAN, all questionnaires were answered at the baseline visit, which also included Aβ-PET. The DIAN personality questionnaire (IPIP-NEO-120)(32) was more detailed than the Big Five Inventory used in PREVENT-AD, and yielded scores on 30 personality facets along with the Big Five personality domains. The 30 facets were used only in complementary analyses.

2.3 Image acquisition

PREVENT-AD participants underwent PET using [^{18}F]NAV4694 to assess Aβ burden and flortaucipir ([^{18}F]AV1451) to assess *tau* deposition. DIAN participants underwent Aβ-PET only using Pittsburgh compound B ([^{11}C]PIB). A T1-weighted structural image was also acquired using a similar MPRAGE sequence in both studies (greater detail available in Supplemental Information).

2.4 Image processing

Both PREVENT-AD and DIAN scans were processed locally using the same pipeline (see https://github.com/villeneuvelab/vlpp for more details and Supplementary material for parameters used). Aβ- and *tau*-PET images were registered to the T1-weighted scan of each participant, which had been segmented with the Desikan-Killiany atlas using FreeSurfer version 5.3(33). Images were then masked to remove the scalp and cerebrospinal fluid, to reduce contamination by non-grey and non-white matter voxels. In PREVENT-AD, PET images were smoothed with a Gaussian kernel of 6 mm. Standardized uptake value ratios (SUVR) were obtained using the whole cerebellum as reference region for Aβ-PET(34) and the inferior cerebellar grey matter for *tau*-PET(35).

DIAN PET images were smoothed with a Gaussian kernel of 8 mm to diminish multi-site effect(36) and Aβ-PET SUVRs were obtained using the whole cerebellum as reference region. Mean SUVR from left and right hemispheres in each Desikan-Killiany region was used for further analyses. The frontal pole region was excluded owing to weaker registration to the structural scan. Only a subset of sensitive regions was included for each modality in the analyses. For Aβ, bilateral SUVR in lateral and medial prefrontal, parietal, lateral temporal and cingulate cortical regions were included in multivariate analyses because these are key regions of Aβ deposit in the pre-clinical and clinical phases of AD(37, 38). The weighted average across all these regions is referred to here as global Aβ index SUVR,(38, 39) and used in univariate analyses. For *tau*-PET, bilateral SUVR in the regions of Braak stages I (entorhinal cortex), III and IV were included in the multivariate analysis since those stages capture regions up to early tau accumulation(40, 41) (Table S2). Average SUVRs in separate Braak stages were also computed and used in univariate analyses. Braak stage II (hippocampus) was excluded, however, due to signal contamination from the choroid plexus,(42) and regions of Braak stages V and VI were also excluded, given that they represent later stages of AD progression(43, 44).

2.5 Statistical analyses

2.5.1 Univariate analyses

We first estimated univariate parametric correlations between each individual behavioral feature and pathology. We used global Aβ index SUVR in both PREVENT-AD and DIAN. *Tau* SUVR in Braak stages I, III and IV were used in PREVENT-AD. Also, to evaluate the extent to which behavioral features were related to one another, we

calculated the parametric correlation between all factors. P-values < 0.05 were considered significant. Associations surviving false discovery rate (FDR) of 5% are also reported, to account for multiple comparisons.

2.5.2 Multivariate analyses

The main statistical approach was partial least squares (PLS) analysis[45, 46], implemented using PLS Software v6.15.1 (https://www.rotman-baycrest.on.ca/index.php?section=84) on Matlab v2016a. This approach allowed investigation of relationships between combinations of behavioral factors and AD pathology across the brain. PREVENT-AD permitted two PLS analyses, relating these behavioral features with Aβ and *tau* independently. Two PLS analyses were also performed in DIAN, the primary analysis relating similar behavioral features with Aβ, and a complementary one further detailing personality after including the 30 personality facets available exclusively in DIAN.

A cartoon explains these analyses in Figure 1 (greater detail is available in Supplemental Information). Briefly, PLS finds linear combinations of two sets of variables (organized in two matrices) that correlate maximally with each other. The first matrix enters the behavioral factors in columns with entries corresponding to the score on the various questionnaires, and the rows to individual participants. The behavioral data was z-scored column-wise since all questionnaires were on different scales. The second matrix contains either regional Aβ or *tau* SUVR in columns, and rows corresponding to participants. The output from the PLS analyses are sets of latent variables relating behavioral features and AD pathology. The number of latent variables is equal to the smallest dimension of the matrices, here the number of behavioral factors. Permutation

tests were used to identify which latent variables were significant, with p-value<0.05 being considered significant. The latent variables are a triplet of (1) a singular value, (2) a vector of weights attributed to each behavioral factor, and (3) a vector of weights attributed to the various cortical regions. In the significant latent variable(s), bootstrap resampling was used to identify the most stable features and brain regions contributing to the behavioral factors-pathology relationship. Lastly, the vector of weights from each behavioral factor and each brain region were multiplied by the original data of each participant. These two values correspond to each participant's weighted score of behavioral factors and weighted score of pathology. Correlating these two scores across participants provided an estimate of the strength of the multivariate relationship between the behavioral and pathology features.

2.5.3 Complementary analyses

One complementary question is whether behavioral factors influence AD pathology, pathology influences behavioral factors, or whether these relationships are bi-directional. This question is particularly relevant for neuropsychiatric symptoms, inasmuch as education level and lifetime cognitive activity typically precede AD pathology and personality traits generally remain stable over time, even in individuals with AD-related cognitive impairment(15). Longitudinal PET scans will be needed to address this question more fully. Nonetheless, we sought to take advantage of three-year follow-up for neuropsychiatric symptoms and evaluated whether Aβ (global Aβ index SUVR) and *tau* (entorhinal *tau* SUVR) was associated with change in neuropsychiatric symptom scores. To do this, we used linear mixed-effects models having random slope and

intercept, in which a time-by-Aβ or -tau SUVR interaction predicted longitudinal neuropsychiatric symptom scores. These mixed-effects analyses used the R package lme4 version 1.1-15.

3 Results

Sample characteristics are detailed in Table 1. Information on cognitive data in both cohorts is available in Tables S3 and S4.

3.2 Univariate relationship between behavioral features and Aβ and *tau*

In PREVENT-AD, only neuroticism was related the global Aβ index SUVR, with higher scores on neuroticism related with higher Aβ deposition (R=0.21, p=0.02; Table S5, but does not survive FDR correction). *Tau* SUVR in Braak I (entorhinal cortex) was related with different behavioral features (personality traits, apathy and lifetime cognitive activity [R=0.21-0.34, p<0.001-0.02]), while only lifetime cognitive activity was related to *tau* SUVR in Braak III or IV (Table S5). All associations with *tau* SUVR in Braak I survived FDR correction.

In DIAN, fewer behavioral features were available for analyses (8 rather than 11), and some of the questionnaires differed from those in PREVENT-AD (Table S1). Higher level of education correlated with lower global Aβ index (R=-0.19, p=0.04; Table S5, but does not survive FDR correction). Of note, mutation type had virtually no effect on behavioral features (the only difference being that PSEN2 mutations carriers had lower extraversion scores than PSEN1 carriers in post-hoc testing, p=0.04). There was also no difference on any behavioral features between asymptomatic mutation carriers and 127 non-carriers.

3.3 Inter-correlation among behavioral features

Inter-correlations among behavioral features revealed associations between about half of the features in PREVENT-AD (Figure 2A). The neuropsychiatric symptoms were themselves inter-correlated, and neuropsychiatric symptoms were (unsurprisingly) associated mainly with higher neuroticism and lower extraversion. Furthermore, education, cognitive activity and openness were positively correlated with one another. In DIAN, more years of education was also associated with increased openness, and inter-correlations were found between different personality traits (Figure 2B). These numerous inter-correlations suggest that a wide variety of behavioral features relate to one another, thus justifying our decision to investigate them in combination.

3.4 Relation of AD pathology with multi-domain behavioral features.

In PREVENT-AD there was one significant latent variable relating behavioral features with Aβ ($p=0.014$, 95% of the PLS variance being explained by this variable). Figure 3A displays the different weights of the behavioral features and brain regions that form this latent variable. A combination of lower neuroticism, anxiety and apathy along with higher education and openness were the features that were most strongly associated with lower Aβ burden. All regions of the global Aβ index contributed to the relationship. The correlation between the weighted scores of the behavioral features and of regional Aβ pathology across participants was $R=0.23$, $p=0.013$, accounting for 5.3% of the Aβ variance.

The multivariate analysis with *tau* also revealed one latent variable relating behavioral features with regional *tau* SUVR (p=0.006, 82% of the PLS variance was explained by this variable). Figure 3B displays the different weights of the behavioral features and brain regions forming this latent variable. Almost all behavioral variables contributed to this relationship, with a combination of higher scores on openness and extraversion, higher cognitive activity, lower neuropsychiatric symptoms and neuroticism being related to less *tau* burden. The top region related to behavioral features was the entorhinal cortex (Braak I), followed by others in the medial and lateral temporal lobe. Regions outside the temporal lobe did not contribute, which is in keeping with the known deposition pattern of *tau* in the asymptomatic phase of AD(40, 47). The correlation between the weighted scores of the behavioral features and regional *tau* pathology across participants was R=0.29, p=0.002, accounting for 8.4% of variance explained.

In DIAN, one latent variable related behavioral features with Aβ (p=0.005, 91% of the PLS variance explained, Figure 3C). More years of education and a lower score on the Neuropsychiatric Inventory Questionnaire (NPI-Q) were the factors that related most strongly to lower Aβ burden. All regions included in the global Aβ index contributed to this relationship. The correlation between weighted scores of the behavioral features and regional Aβ pathology across participants was R=0.26, p=0.005, accounting for 6.7% of variance explained. To obtain a more fine-grained picture of these associations in DIAN, the PLS was repeated, now substituting the Big Five personality traits with the 30 personality facets. Again, one latent variable (p=0.004, 88% of PLS variance explained) related behavioral features and Aβ. Higher intellect (a facet of the openness trait), along with more years of

education and a low score on NPI-Q were related to lower Aβ burden (Figure 4). The correlation between the weighted scores of the behavioral features and pathology was R=0.37, p<0.001, accounting for 14% of the variance.

3.4 Stability over time of behavioral features in PREVENT-AD

All analyses presented thus far included the behavioral feature assessments nearest in time to the PET scans. We also evaluated the stability of such self-reported questionnaire responses, taking advantage of the longitudinal assessment of three years for neuropsychiatric symptoms and of two years for personality (Figure S1 and S2). Education and lifetime cognitive activity were only assessed once as they are typically fixed. Overall, there was moderate stability of neuropsychiatric symptoms over three years (ICC between 0.55 and 0.73; Figure S1) and, predictably, better stability of personality traits over two years (ICC between 0.76 and 0.81; Figure S2). Using the three-year data available on neuropsychiatric symptoms, we also found no apparent influence of the level of Aβ or *tau* on change of neuropsychiatric symptoms over time (Table S6; only the relationship of *tau* and stress had a p-value of 0.03, but this did not survive correction for multiple comparisons).

4. Discussion

It has been estimated that up to 35% of AD risk is modifiable by health and behavioral factors such as physical health, psychological health, education and cognitive activity(1, 7). Beyond these factors, facets of personality, such as neuroticism(15), and other behaviors, such as sleep dysregulation(48), have also been associated with a risk of AD, suggesting that even more than 35% of AD risk may be modifiable. Working in the asymptomatic stage of the sporadic and autosomal dominant forms of AD, we tested whether combinations of multi-domain behavioral

features were related to AD pathology, and to what extent. In cognitively unimpaired late-middle-aged individuals at increased risk of sporadic AD, several combinations of factors encompassing personality traits, neuropsychiatric symptoms and cognitive lifestyle were related to Aβ and *tau* deposition in the brain. In asymptomatic ADAD mutation carriers, education and psychiatric symptoms were related to Aβ. Across analyses, the variance explained from behavioral feature-pathology relationships ranged from 5 to 14%. Although this might appear modest, reduction of AD risk factors by such percentages could have a major impact on future disease prevalence, preventing millions of cases(3).

In sporadic AD, personality traits had been described previously as being related to the incidence of dementia(14, 15). Little was known, however, about associations with Aβ and *tau* pathology in the earliest phases of the disease (49, 50). In PREVENT-AD, a higher score on neuroticism was among the key factors related to the presence of both pathologies. Our results are in accord with the aforementioned studies in which neuroticism, characterized by negative emotions (51), is the dominating trait associated with increased risk of AD. Neuropsychiatric symptoms – which are correlated with neuroticism – were also associated with Aβ and *tau* burden. Other personality traits such as openness and extraversion also related to *tau* pathology in both univariate and multivariate analyses.

Our results add to an abundant literature reporting increased prevalence of neuropsychiatric symptoms with disease progression (52-55), and suggest that neuropsychiatric features may be related to pathology even in cognitively normal individuals (56-58). Given that our findings are only correlational, and that pathology accumulates over many years, reverse causality is also

possible, *i.e*. that pathology has already affected the magnitude of neuropsychiatric symptoms even in cognitively unimpaired individuals. Neuropsychiatric symptoms are frequent in individuals with dementia(52, 59) and at that late disease stage they are most certainly a consequence of the disease. Longer follow-up and longitudinal PET scans will be needed to clarify which behavioral features cause, and which are a consequence of, AD pathology. By contrast, given that personality traits are abiding characteristics of an individual, we postulate that they are probably true risk factors of the disease. Clarifying such relationships might help target the right factors at the optimal time for prevention.

In DIAN mutation carriers, the main factors related to Aβ deposition were fewer years of education, lower scores on the intellect personality facet, and higher neuropsychiatric symptom burden. Here, personality traits did not appear to be driving factors related to the pathology. The importance of personality traits in sporadic AD might be due to a lifelong effect of personality, which influences lifestyle choices and how one copes with situations throughout life, eventually affecting pathology accumulation in old age. DIAN mutation carriers, being much younger, may not exhibit such an effect of personality traits on Aβ burden. This idea remains in line with recent studies suggesting the influence of lifestyle factors such as physical activity and education on (later) AD progression in the presence of a fully penetrant genetic mutation(19).

Perhaps importantly, the current work assesses multiple behavioral features in the same analytic design. As shown in Figure 2, many behavioral features are, in fact, highly correlated. The net sum of these factors, rather than one factor alone, may therefore be associated with an altered risk of developing AD pathology. We included protective factors that might contribute to higher

cognitive reserve or brain maintenance(4, 60), but also risk factors that might contribute to "cognitive debt". The concept of "cognitive debt" refers to the constellation of behaviors (mainly stress and neuropsychiatric symptoms) that increase an individual risk to AD(61). As postulated by this hypothesis, lower neuroticism and neuropsychiatric factors might be a way to reduce vulnerability to Alzheimer's dementia. Along with high cognitive reserve, modulating these risk factors might be important target to resist pathology accumulation.

Other important limitations of this study include relatively modest sample sizes in the two samples. It will be important to test whether such findings generalize to populations without the added risk conferred by a family history of AD. Most participants were also highly educated and it will be of interest to know which associations would still be found in individuals with less education. For example, certain associations between high school personality traits and dementia in late life have been reported as being stronger in individuals with higher socioeconomic status(16). Also, associations with openness (or intellect) and education, could reflect an underlying relationship with different intelligence measurements(62, 63) which, unfortunately, were not available in either cohort. Furthermore, in PREVENT-AD, behavioral and PET data were not collected at the same time. We did, however, show that the self-reported behavioral features had good stability over 2-3 years.

Given the failures of many clinical trials, new avenues are needed to prevent or slow AD progression. Multi-domain lifestyle interventions have shown some promises in delaying cognitive decline. We suggest here that such interventions might also postpone accumulation of AD pathology in both sporadic and autosomal dominant AD. In the former, behavioral

interventions might focus on aspects of personality and/or emotional regulation, as both were strongly related to both Aβ and *tau* deposition. Beyond this, acting on personality traits could have a positive impact on lifestyle changes(64). While more work is needed to understand the mechanisms by which behavioral features may influence AD risk, our results may suggest that both personality, neuropsychiatric symptoms and lifestyle features should be considered when assessing multi-domain interventions to postpone the accumulation of AD pathology and its related clinical expression.

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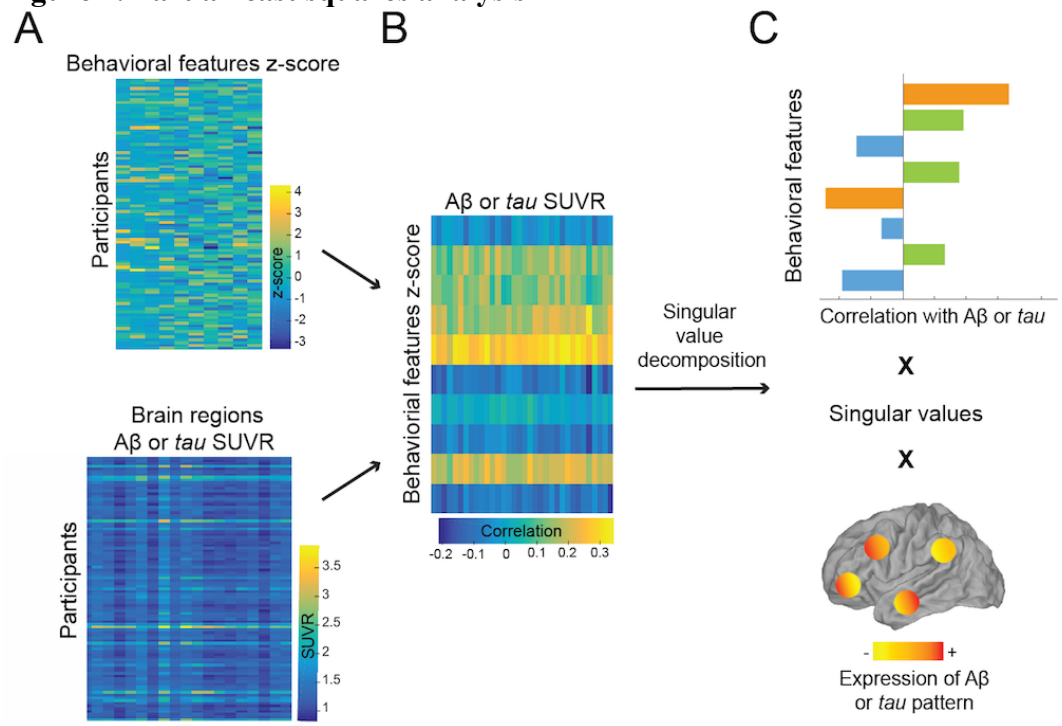
Table 1. Participants demographics and behavioral features

	PREVENT-AD (n=115)	DIAN (n=117)
Age, years	67.6 ± 5.0 (58.6-83.3)	34.6 ± 9.4 (18.0-61.0)
spEYO and EYO respectively	-5.7 ± 7.8 (-20.8.6-16.8)	-12.9 ± 8.0 (-31.5-11.8)
Gender, F:M (%F)	86:29 (75%)	64:53 (55%)
APOE4 carriers (%)	44 (38%)	36 (31%)
Global Aβ SUVR[a]	1.1 ± 0.3 (0.9-2.3)	0.9 ± 0.2 (0.8-1.6)
Tau Braak I SUVR	1.1 ± 0.1 (0.7-1.7)	-
Tau Braak III SUVR	1.2 ± 0.1 (0.8-1.7)	-
Tau Braak IV SUVR	1.1 ± 0.1 (0.9-1.6)	-
MMSE	28.8 ± 1.3 (24-30)	29.1 ± 1.2 (24-30)
Cognitive lifestyle		
Education, years	15.0 ± 3.2 (7.0-22.0)	15.2 ± 3.0 (10.0-24.0)
Lifetime cognitive activity	2.6 ± 0.7 (1.2-4.4)	-
Neuropsychiatric factors		
Depression	1.3 ± 1.9 (0-10.0)	1.5 ± 1.8 (0-9.0)
Anxiety	2.1 ± 3.6 (0-18.0)	-
Stress	4.7 ± 5.2 (0-24.0)	-
Apathy	27.8 ± 6.2 (18.0-46.0)	-
NPI-Q	-	0.7 ± 1.8 (0-11.0)
Personality[b]		
Openness	38.9 ± 6.5 (21.0-50.0)	79.5 ± 11.8 (49.0-107.0)
Neuroticism	17.6 ± 6.1 (8.0-35.0)	60.1 ± 13.8 (31.0-94.0)
Conscientiousness	37.4 ± 5.4 (19.0-45.0)	96.0 ± 12.3 (67.0-120.0)
Agreeableness	39.2 ± 4.0 (26.0-45.0)	95.8 ± 10.2 (62.0-115.0)
Extraversion	26.7 ± 5.6 (14.0-40.0)	85.6 ± 12.1 (47.0-109.0)

Data presented as mean ± standard deviation (range). [a] [^{18}F]NAV4694 is used in PREVENT-AD and [^{11}C]PIB is used in DIAN. [b] Personality traits are assessed with the Big5 Inventory in PREVENT-AD and the IPIP-NEO-120 in DIAN, and the two questionnaires have different scales.

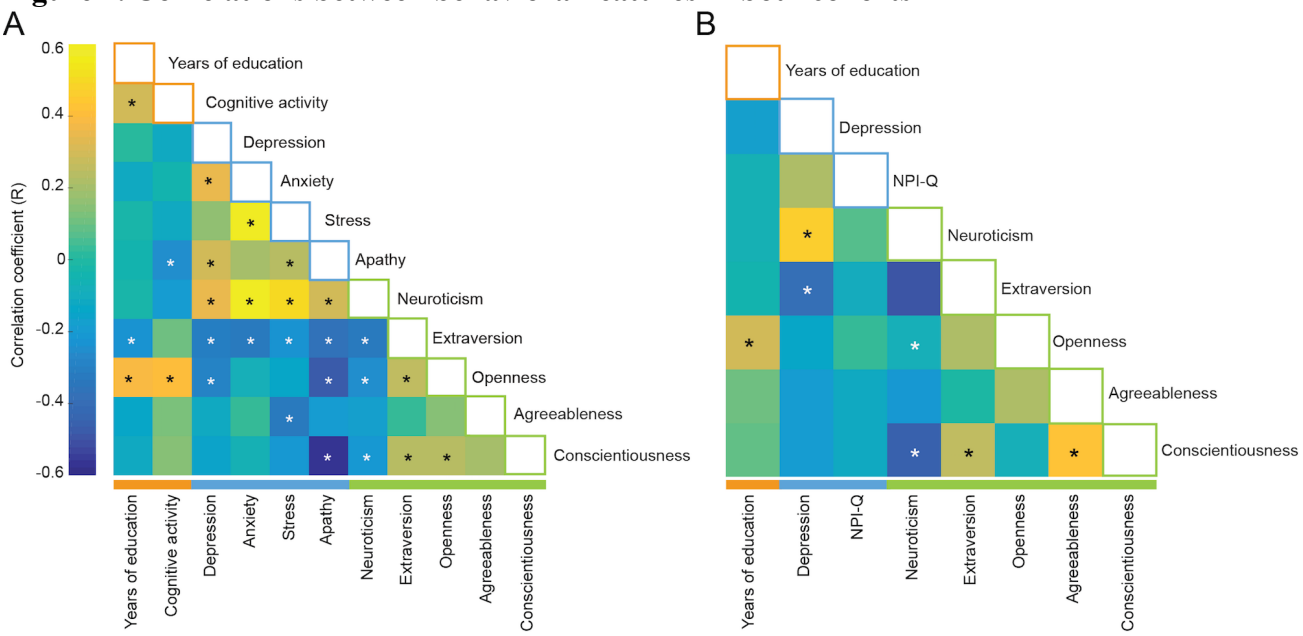
EYO: estimated years to onset (age of participant – age of the parent at symptom onset); spEYO: sporadic estimated years to onset for PREVENT-AD participants (info available for 111 participants); F: female; M: male; APOE: apolipoprotein E; Aβ: beta-amyloid; SUVR: standardized uptake value ratio; MMSE: Mini-Mental State Evaluation; NPI-Q: Neuropsychiatric Inventory Questionnaire.

Figure 1. Partial least squares analysis



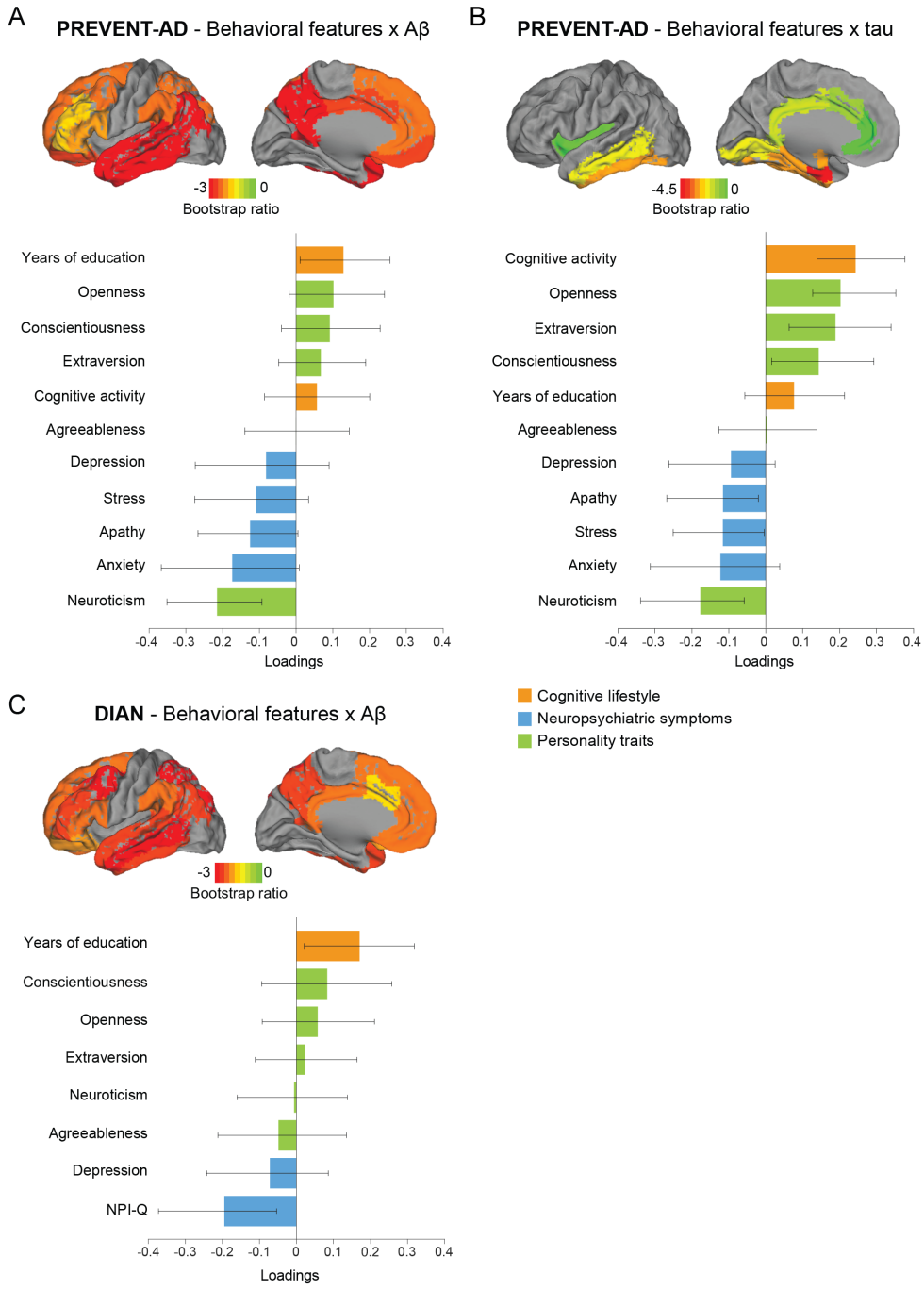
Legend: Partial least squares (PLS) analysis finds maximally correlated linear combinations of two input matrices, one with behavioral features (top matrix in A) and the other with AD pathology across defined cortical regions (bottom matrix in A). These two matrices are then correlated together and this latter matrix (B) is decomposed into multiple latent variables using singular value decomposition. An example of a latent variable is shown in C. Briefly, each latent variable consists of a singular value (related to the covariance between the two input matrices) and two vectors of weights representing how much each behavioral feature and each brain region contribute the overall multivariate relationship.

Figure 2. Correlations between behavioral features in both cohorts



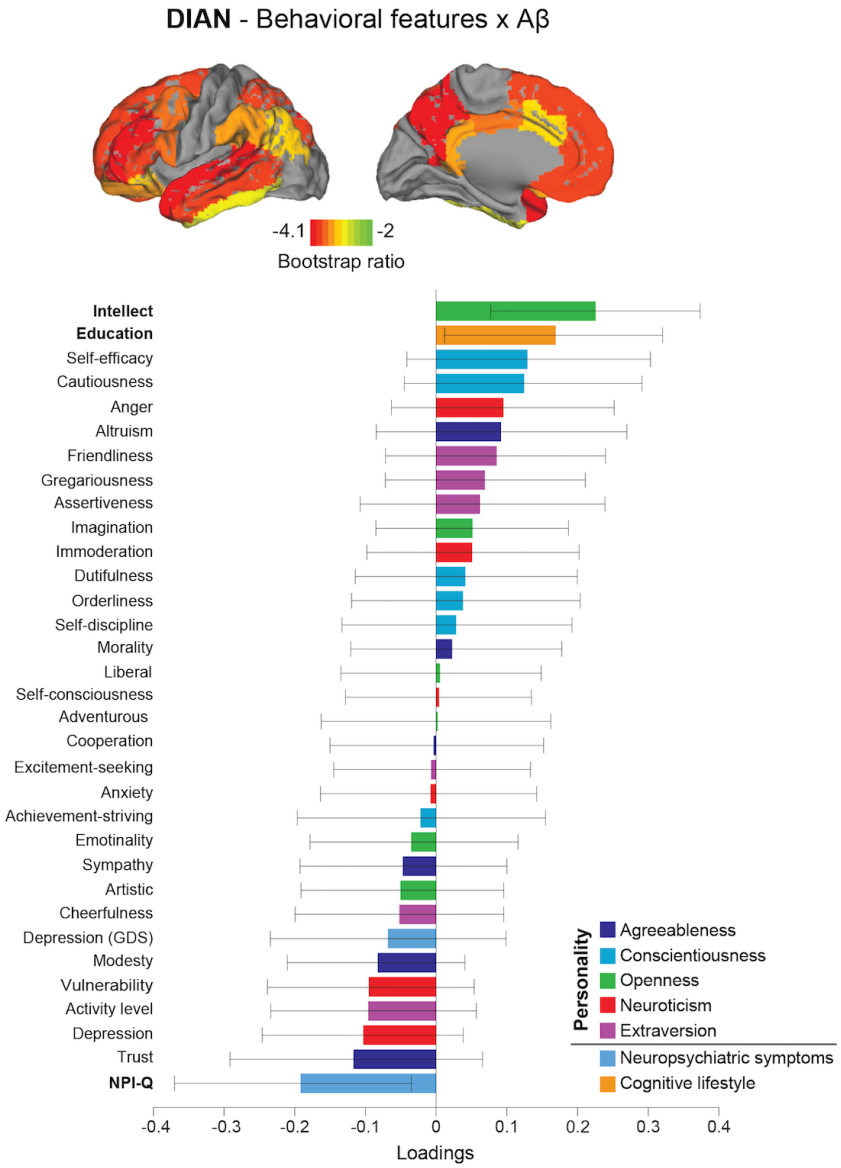
Legend: Inter-correlation (Pearson correlation) between behavioral factors in PREVENT-AD (**A**) and DIAN (**B**). White stars correspond to negative correlations and black stars to positive correlations that remained significant after FDR correction.

Figure 3. Latent variables from partial least squares analysis relating behavioral features and AD pathology in both cohorts



Legend: Results from the different partial least squares analyses representing which combinations of behavioral features relate to Aβ pathology in PREVENT-AD (**A**), tau pathology in PREVENT-AD (**B**), and Aβ pathology in DIAN (**C**). Bar graphs represent the weight of each behavioral feature to the multivariate relationship. Confidence intervals are derived from bootstrap resampling. All brain regions included in the partial least squares analyses are projected on the brains. Bootstrap ratios correspond to the importance of each region to the behavioral feature-pathology relationship.

Figure 4. Latent variable from partial least squares analysis relating personality facets and behavioral features with Aβ in DIAN



Legend: Result from the partial least squares analysis relating behavioral features including the 30 personality facets and Aβ pathology across brain regions in DIAN. Bar graphs represent the weight of each behavioral feature to the multivariate relationship. Confidence intervals are derived from bootstrap resampling. All brain regions included in the analysis are projected on the brain. Bootstrap ratios correspond to the importance of each region to the behavioral feature-pathology relationship.

Supplemental Information

Supplementary methods

Image acquisition

All PET scans in the PREVENT-AD study were performed at the McConnell Brain Imaging Centre at the Montreal Neurological Institute on a brain-dedicated PET Siemens/CT high-resolution research tomograph on two consecutive days between February 2017 and May 2018. Aβ scans were acquired 40 to 70 minutes post-injection (≈6 mCi) and tau scans 80 to 100 minutes post-injection (≈10 mCi). T1-weighted structural magnetic resonance imaging (MRI) scans were acquired on a Magnetom Tim Trio (Siemens) scanner at the Douglas Mental Health Research Institute (in average 8 ± 4 months from PET imaging) using a MPRAGE sequence (TR=2300 ms; TE =2.98ms; FA=9°; matrix size=256x256; voxel size=1x1x1 mm; 160-170 slices). DIAN participants underwent Aβ PET imaging using Pittsburgh compound B ([^{11}C]PIB) (8-18 mCi) either with full dynamic or 40-70 minutes post-injection acquisition. PET and MRI protocols were unified across the different DIAN study sites. For DIAN participants who had a dynamic scan, only the frames 40-70 minutes post-injection were selected to have the same scanning window for all individuals.

Image processing

The processing pipeline that we used is publicly available at https://github.com/villeneuvelab/vlpp. The configuration files that were used to process the data are pasted below:

PREVENT-AD Aβ PET:

```
dataset = "PAD"
tracer = "NAV"
scanner_resolution = "[2.5 2.5 2.5]"
pet2anat {
    pet {
        fwhm = 6
        mask = "gmwm"
    }
}
```

PREVENT-AD tau PET:

```
dataset = "PAD"
tracer = "TAU"
scanner_resolution = "[2.5 2.5 2.5]"
pet2anat {
    pet {
        fwhm = 6
        mask = "gmwm"
    }
 }
```

DIAN Aβ PET:

```
dataset = "DIAN"
tracer = "PIB"
pet2anat {
    pet {
        fwhm = 8
        mask = "gmwm"
    }
}
```

Partial least squares analysis

In the present study, we searched for linear combinations relating behavioral factors and AD pathology through partial least squares (PLS) analyses. The two sets of variables are organized in two matrices (Figure 1). The first one corresponds to the behavioral factors where entries in the columns correspond to the scores on the different questionnaires and each row corresponds to a different participant. The behavioral data was z-scored column-wise since all questionnaires were on different scales. The second matrix contains either Aβ or tau SUVR, with regional SUVR entered in columns and rows corresponding to participants. Briefly, the two input matrices are correlated across participants, resulting in a covariance matrix that is then subjected to singular value decomposition(1). The outcome of this decomposition is a set of mutually orthogonal latent variables. The number of latent variables is equal to the smallest dimension of the covariance matrix, here the number of behavioral factors. Each latent variable is a triplet of (1) a singular value, (2) a vector of weights attributed to each behavioral factor, and (3) a vector of weights attributed to each cortical region. The singular values are related to the covariance between behavioral factors and pathology. The percentage of covariance explained by each latent variable can be calculated as the squared singular value divided by the sum of all squared singular values. The two weighted vectors represent the contribution of each feature(each behavioral factor and each cortical region) to the overall multivariate pattern. In other words, the outputs are a weighted combination of behavioral factors maximally correlated to a weighted combination of cortical regions expressing AD pathology.

We used permutation tests to assess whether any of the latent variables, representing the association between combinations of multi-domain behavioral features and regional AD pathology, were significant. Briefly, the rows of the AD pathology matrix were randomly reordered and PLS analysis was run on the non-permuted behavioral factors matrix and permuted AD pathology matrix. This procedure was repeated 10 000 times, creating a distribution of singular values under the null hypothesis that there is no relationship between behavioral factors and AD pathology. The significance of the latent variable in the original PLS analysis was calculated as the proportion of times the permuted singular values exceeded the original value. Latent variables with a p-value < 0.05 were considered significant, and if so, the contribution of each feature (each behavioral factor and each cortical region) was assessed using bootstrap resampling.

Bootstrap resampling was performed 10 000 times by randomly sampling participants with replacement and subjecting these resampled matrices to PLS analysis. This resampling serves to identify the most stable behavioral factors and brain regions contributing to the multivariate pattern across participants. For the behavioral factors, the standard error of this resampled distribution was calculated. For the brain regions, a bootstrap ratio was calculated by dividing the weight of each region from the original analysis by the standard error from its bootstrap resampling distribution. A large bootstrap ratio means that this brain region contributes strongly to the behavioral factors-pathology relationship (high weight), and is stable across participants (small bootstrap standard error).

Lastly, for each participant, the vector of weights from behavioral factors and the regional AD pathology were multiplied by the original data of the participant. These two values correspond to a total score of "behavioral burden" and of "pathology burden" for each participant. By correlating these two scores across participants, we get an estimate of the strength of the multivariate relationship between the combination of behavioral factors and pathology.

Table S1. Questionnaires to assess behavioral features in both cohorts

	PREVENT-AD	DIAN
Personality traits	**Big5 inventory** (44 items)(2) - Neuroticism - Extraversion - Agreeableness - Conscientiousness - Openness	**NEO-IPIP** (120 items)(3) - Neuroticism - Extraversion - Agreeableness - Conscientiousness - Openness
Neuropsychiatric symptoms	**Geriatric depression short scale** (range 0-15)(4) **Geriatric anxiety inventory** (range 0-20)(5) **Stress subscale** (range 0-42)(6) **Apathy Evaluation Scale** (range 18-72)(7)	**Geriatric depression short scale** **Neuropsychiatric Inventory Questionnaire** (NPI-Q) (range 0-12)(8)
Cognitive lifestyle	**Years of education** **Lifetime Cognitive activity** (mean from cognitive activity at 6, 18, 40 years old and in the last year; range 1-5) (9)	**Years of education**

For all questionnaires included in the neuropsychiatric symptoms category, higher scores represent higher neuropsychiatric burden. The NPI-Q was the only questionnaire filled by an informant/study partner.

Table S2. Brain regions in different Braak stages

Braak stage	FreeSurfer-derived ROIs
I	Entorhinal cortex
III	Parahippocampal gyrus, fusiform gyrus, lingual gyrus, amygdala
IV	Inferior temporal cortex, middle temporal cortex, temporal pole, caudal, rostral, isthmus, posterior cingulate, insula

Table S3. Cognitive profile in PREVENT-AD

Prevent-AD (n=115)	RBANS composite score
Immediate memory	106 ± 11 (76-140)
Visuospatial constructional	98 ± 15 (66-131)
Language	100 ± 11 (68-134)
Attention	107 ± 15 (68-142)
Delayed memory	107 ± 10 (71-129)

Legend: Data presented as Mean ± Standard deviation (Range). A score of 100 represents the expected score given one's age. RBANS: Repeatable Battery for Assessment of Neuropsychological Status

Table S4. Cognitive profile in DIAN

	Mutation carriers (n=117)	Mutation non-carriers (n=127)	p-value
Mini-Mental State Evaluation	29.1 ± 1.2 (24-30)	29.1 ± 1.2 (25-30)	0.85
Logical Memory	14.5 ± 4.4 (4-23)	15.0 ± 3.7 (5-24)	0.32
Digit Symbol Coding	62.7 ± 12.5 (34-93)	61.4 ± 11.2 (39-93)	0.41
List learning immediate recall	5.8 ± 2.2 (2-12)	6.2 ± 2.0 (2-11)	0.22
List learning delayed recall	3.1 ± 2.1 (0-11)	3.5 ± 2.2 (0-13)	0.16

Legend: Data presented as Mean ± Standard deviation (Range). We used independent sample t-test to compare cognitive performance between mutation carriers and non-carriers; there was no significant difference on any task between the two groups.

Table S5. Univariate correlations between pathology and behavioral features

	PREVENT-AD				DIAN
	Global Aβ index	Tau Braak I (entorhinal cortex)	Tau Braak III	Tau Braak IV	Global Aβ index
Cognitive lifestyle					
Education, years	-0.13	-0.09	-0.08	-0.04	-0.19[a]
Lifetime cognitive activity	-0.06	**-0.29**[c]	-0.21[a]	-0.19[a]	-
Neuropsychiatric symptoms					
Depression	0.08	**0.23**[a]	0.06	0.02	-0.05
Anxiety	0.17	0.12	0.10	0.11	-
Stress	0.10	0.11	0.12	0.09	-
Apathy	0.12	**0.24**[b]	0.08	0.05	-
NPI-Q	-	-	-	-	0.11
Personality					
Openness	-0.10	**-0.34**[c]	-0.18	-0.08	-0.05
Neuroticism	0.21[a]	**0.24**[b]	0.17	0.09	-0.13
Conscientiousness	-0.09	**-0.21**[a]	-0.12	-0.10	-0.02
Agreeableness	0.00	-0.07	0.02	0.02	0.06
Extraversion	-0.06	**-0.22**[a]	-0.15	-0.17	0.04

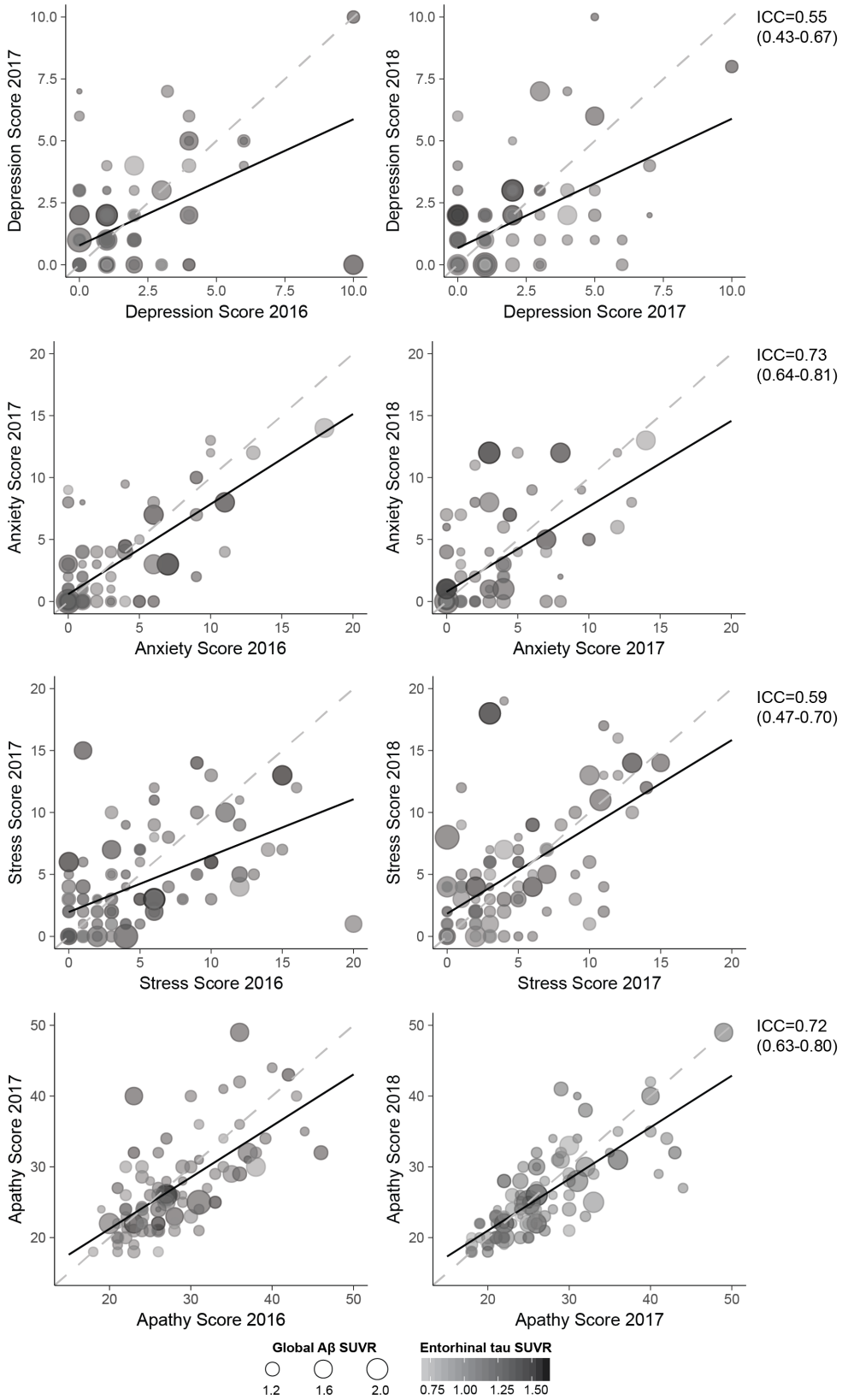
Legend: Correlations coefficients from Pearson correlation. NPI-Q: Neuropsychiatric Inventory Questionnaire. a: $p < 0.05$; b: $p < 0.01$; c: $p < 0.001$. Relationships surviving FDR correction are bolded.

Table S6. Summary of linear mixed-effects models examining the interactive effect of time and Aβ/tau on longitudinal neuropsychiatric symptoms in PREVENT-AD

Neuropsychiatric symptom	Aβ * time			tau * time		
	β (SE)	*t*	P value	β (SE)	*t*	P value
Depression	-0.15 (0.36)	-0.41	0.68	0.27 (0.70)	0.39	0.70
Anxiety	0.34 (0.60)	0.57	0.57	1.49 (1.16)	1.29	0.20
Stress	0.61 (0.90)	0.67	0.50	**3.71 (1.71)**	**2.17**	**0.03**
Apathy	0.16 (0.92)	0.18	0.86	0.95 (1.80)	0.53	0.60

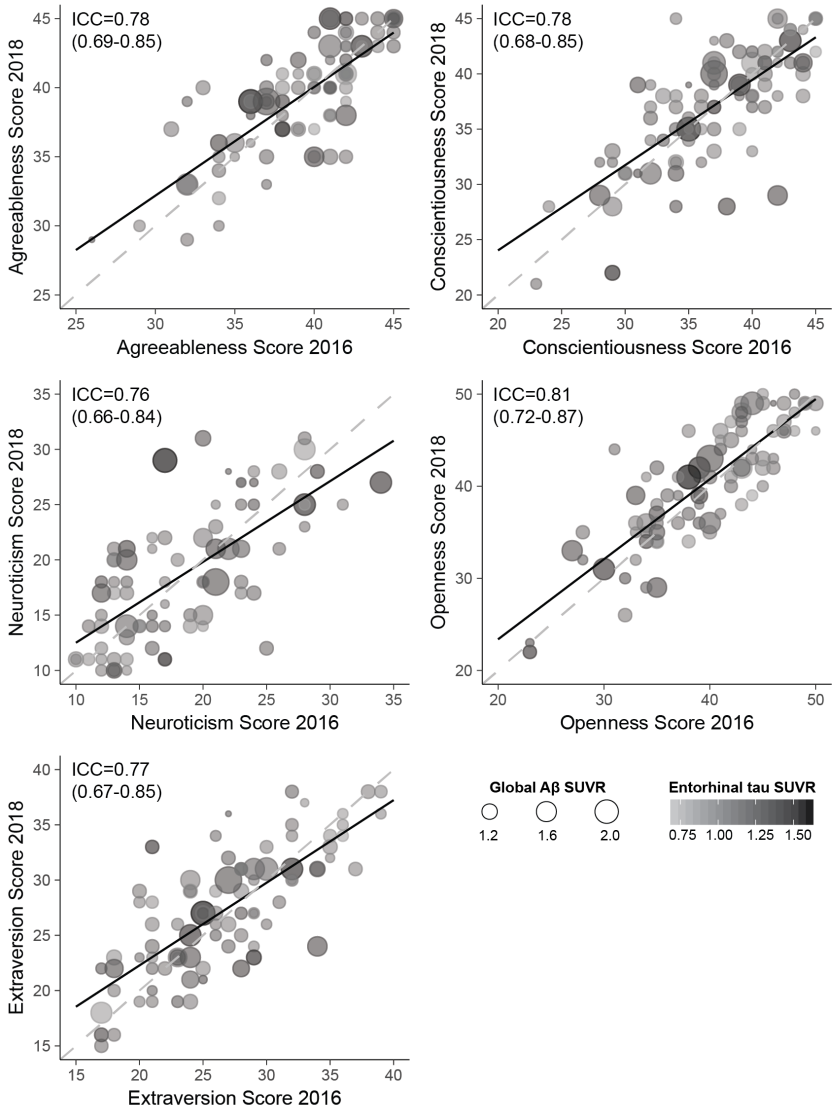
Legend: Results from linear mixed-effects models investigating whether AD pathology influences longitudinal scores on the different neuropsychiatric symptoms over a three-year follow-up (dependent variable).

Figure S1. Correlations between neuropsychiatric symptoms over the three time points in PREVENT-AD



Legend: Correlations between the scores on neuropsychiatric symptoms questionnaires between 2016 and 2017 (left column) and between 2017 and 2018 (right column). The dash line represents the identity line (y=x). The size of the dots corresponds to the global Aβ index and the color of the dots corresponds to the entorhinal tau SUVR. Intraclass correlation coefficients (ICC) and the 95% confidence interval are reported on the right as a measure of reliability of the scores over 3 years.

Figure S2. Correlations between personality traits over the two time points in PREVENT-AD



Legend: Correlations between the scores on five main personality traits between 2016 and 2018. The dash line represents the identity line (y=x). The size of the dots corresponds to the global Aβ index and the color of the dots corresponds to the entorhinal tau SUVR. Intraclass correlation coefficients (ICC) and the 95% confidence interval are reported for each trait as a measure of reliability of the scores over 2 years.

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