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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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)

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

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

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

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).

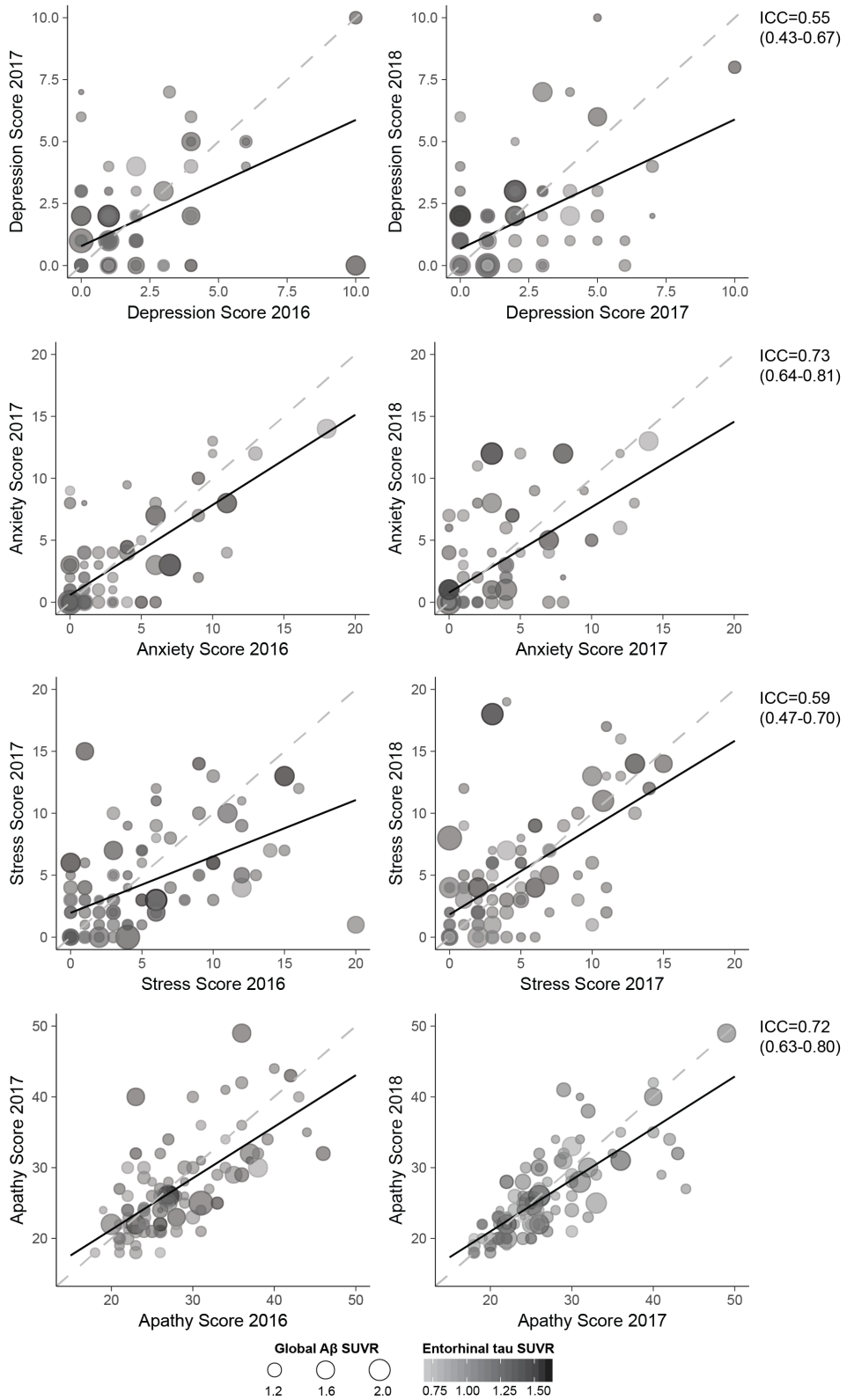

Figure S1. Correlations between neuropsychiatric symptoms over the three time points in PREVENT-AD

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.

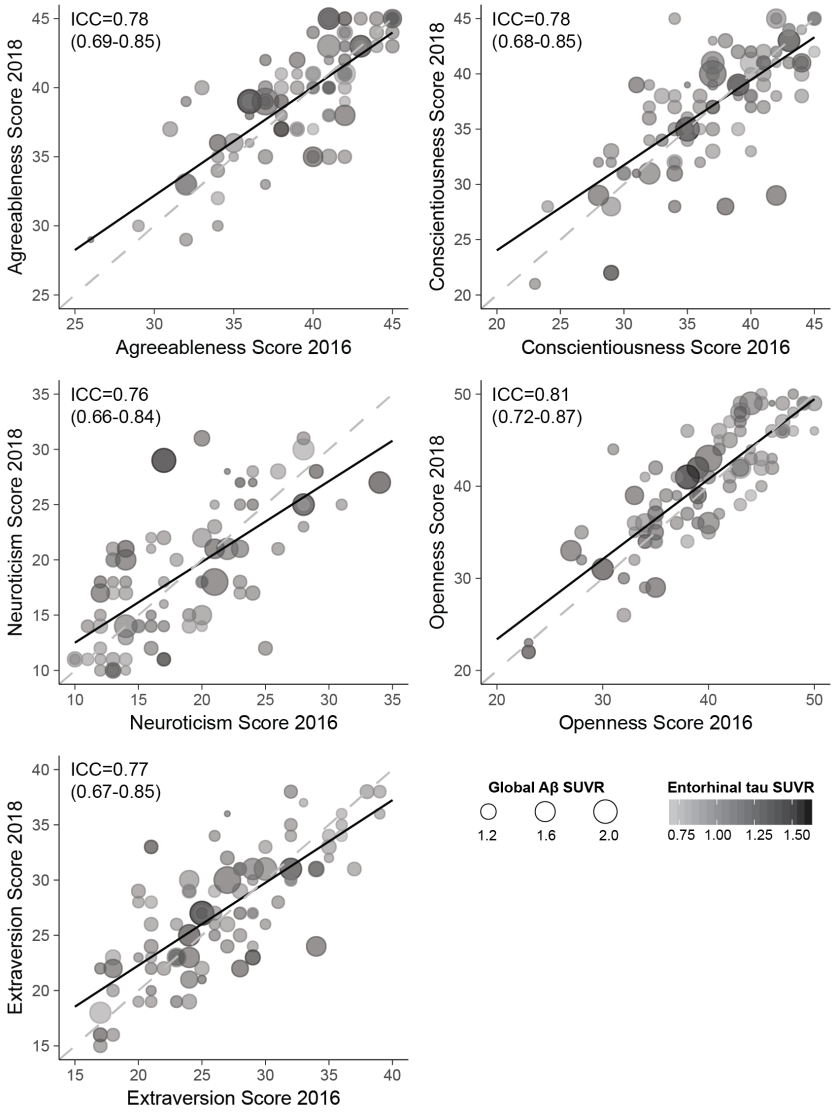

Figure S2. Correlations between personality traits over the two time points in PREVENT-AD

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.

Supplemental References

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