Personality Associations With Amyloid and Tau: Results From the Baltimore Longitudinal Study of Aging and Meta-analysis

Supplementary Information

PET imaging - Amyloid.

Amyloid was measured using ^{11}C-Pittsburgh compound B (PiB) on a GE Advance scanner for 137 participants and a Siemens High Resolution Research Tomograph (HRRT) for 79 participants. Details of the GE Advance scan acquisition protocol have been described previously (Ziontz et al., 2019). On the HRRT scanner, a transmission scan was acquired using a rotating ^{137}Cs point source prior to the emission scan. Transmission images were segmented to suppress noise and scaled to 511 keV. Emission scans were obtained over 70 minutes immediately following an intravenous bolus injection of approximately 15 mCi of ^{11}C-PiB. Scans were reconstructed using ordered subset expectation maximization (2 iterations, 16 subsets), incorporating corrections for deadtime, attenuation, randoms, scatter, and decay. The same frame timing protocol as the one used for the GE Advance scans (Ziontz et al., 2019) was followed to yield 33 time frames with approximately 2.5 mm full width at half maximum at the center of the field of view (image matrix = 256 x 256, 207 slices, voxel size = 1.22 mm isotropic).

To minimize resolution differences between the GE Advance and HRRT scanners, images acquired on the HRRT were blurred using a 3 mm isotropic Gaussian kernel. The same image processing pipeline was then applied to both GE Advance and HRRT scans to perform time frame alignment, MRI coregistration, anatomical label definition in native PET space, and kinetic modeling. Distribution volume ratio (DVR) images were computed in PET native space using the cerebellar gray matter as the reference region. The primary outcome was the mean cortical amyloid burden, calculated as the average of the DVR values in cingulate, frontal, parietal (including precuneus), lateral temporal, and lateral occipital cortical regions, excluding the sensorimotor strip. To harmonize mean cortical DVR across scanners, we scaled and translated the mean cortical DVR computed for HRRT scans such that for individuals who had scans on both scanners, the difference between the HRRT measurements and the expected values given the individuals' longitudinal trends based on the GE Advance measurements were minimized. A mean cortical DVR threshold of 1.067, derived from a Gaussian mixture model, was used to categorize participants as PiB –/+ (Ziontz et al., 2019).

Ziontz J, Bilgel M, Shafer AT, Moghekar A, Elkins W, Helphrey J, et al. (2019): Tau pathology in cognitively normal older adults. *Alzheimer's & dementia (Amsterdam, Netherlands)*. 11:637-645.

GE Advance and HRRT PiB PET harmonization

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Let $\mathbf{y}_{\text{GE}}$ and $\mathbf{y}_{\text{HRRT}}$ be the vectors of all mean cortical DVRs computed using GE and HRRT scans, respectively. We seek to find the transformation parameters (α, γ) such that $\alpha\mathbf{y}_{\text{HRRT}} + \gamma$ is "harmonized" with $\mathbf{y}^{\text{GE}}$. To define "harmonization", we leverage individual-level data. Extrapolation of an individual-level longitudinal linear fit to the GE Advance measurements should coincide with the "harmonized" values of the HRRT measurements for that individual. We can capture this using a linear mixed effects model that characterizes mean cortical DVR as a function of time and allows for individual-level variation in the slopes:

$$\begin{bmatrix} \mathbf{y}_{\text{GE}}^{(i)} \\ \alpha\mathbf{y}_{\text{HRRT}}^{(i)} + \gamma \end{bmatrix} = \beta_0 + \beta_1 x_1^{(i)} + \beta_2 \mathbf{x}_2^{(i)} + z_0^{(i)} + z_1^{(i)}\mathbf{x}_2^{(i)} + \boldsymbol{\epsilon}^{(i)} \quad (1)$$

$$\begin{bmatrix} z_0^{(i)} \\ z_1^{(i)} \end{bmatrix} \sim \mathcal{N}_2(\mathbf{0}, \Sigma) \quad (2)$$

$$\epsilon^{(ij)} \sim \mathcal{N}(0, \sigma^2), \quad (3)$$

where the superscript (i) indicates individual i, $\mathbf{y}_{\text{S}}^{(i)}$ is the vector of measurements on scanner S (i.e., GE or HRRT) for individual i (or the empty vector if there are none), $x_1^{(i)}$ is the age at first amyloid PET scan (regardless of scanner), $\mathbf{x}_2^{(i)}$ is a vector containing time from first amyloid PET scan, $\beta_0, \beta_1, \beta_2$ are regression coefficients, and $z_0^{(i)}, z_1^{(i)}$ are individual-level random effects.

Model parameters, including the HRRT transformation parameters α and γ can be estimated using standard linear mixed effects model fitting methods. To see this, we subtract from both sides of Eqn. 1 and obtain:

$$\begin{bmatrix} \mathbf{y}_{\text{GE}}^{(i)} \\ \alpha\mathbf{y}_{\text{HRRT}}^{(i)} + \gamma \end{bmatrix} - \begin{bmatrix} \mathbf{0}_{n_{\text{GE}}^{(i)}} \\ \alpha\mathbf{y}_{\text{HRRT}}^{(i)} + \gamma \end{bmatrix} = \beta_0 + \beta_1 x_1^{(i)} + \beta_2 \mathbf{x}_2^{(i)} + z_0^{(i)} + z_1^{(i)}\mathbf{x}_2^{(i)} - \begin{bmatrix} \mathbf{0}_{n_{\text{GE}}^{(i)}} \\ \alpha\mathbf{y}_{\text{HRRT}}^{(i)} + \gamma \end{bmatrix} + \boldsymbol{\epsilon}^{(i)} \quad (4)$$

$$\begin{bmatrix} \mathbf{y}_{\text{GE}}^{(i)} \\ \mathbf{0}_{n_{\text{HRRT}}^{(i)}} \end{bmatrix} = \beta_0 + \beta_1 x_1^{(i)} + \beta_2 \mathbf{x}_2^{(i)} + z_0^{(i)} + z_1^{(i)}\mathbf{x}_2^{(i)} + (-\alpha)\begin{bmatrix} \mathbf{0}_{n_{\text{GE}}^{(i)}} \\ \mathbf{y}_{\text{HRRT}}^{(i)} \end{bmatrix} + (-\gamma)\begin{bmatrix} \mathbf{0}_{n_{\text{GE}}^{(i)}} \\ \mathbf{1}_{n_{\text{HRRT}}^{(i)}} \end{bmatrix} \quad (5)$$

$$\tilde{\mathbf{y}}_{\text{GE}}^{(i)} = \beta_0 + \beta_1 x_1^{(i)} + \beta_2 \mathbf{x}_2^{(i)} + (-\alpha)\tilde{\mathbf{y}}_{\text{HRRT}}^{(i)} + (-\gamma)\mathbf{s}^{(i)} + z_0^{(i)} + z_1^{(i)}\mathbf{x}_2^{(i)} + \boldsymbol{\epsilon}^{(i)}, \quad (6)$$

where $n_{\text{S}}^{(i)}$ is the number of scans on scanner S, $\mathbf{0}_n$ is an n-dimensional vector of 0's, $\mathbf{1}_n$ is an n-dimensional vector of 1's, $\mathbf{s}^{(i)}$ is a binary scanner indicator (coded as 0 for GE and 1 for HRRT), $\tilde{\mathbf{y}}_{\text{GE}}^{(i)} = \begin{bmatrix} \mathbf{y}_{\text{GE}}^{(i)} \\ \mathbf{0}_{n_{\text{HRRT}}^{(i)}} \end{bmatrix}$, and $\tilde{\mathbf{y}}_{\text{HRRT}}^{(i)} = \begin{bmatrix} \mathbf{0}_{n_{\text{GE}}^{(i)}} \\ \mathbf{y}_{\text{HRRT}}^{(i)} \end{bmatrix}$.

After estimating the model parameters of this rearranged formulation, we then compute the harmonized HRRT values as $\alpha\mathbf{y}_{\text{HRRT}} + \gamma$, and replace the original HRRT values with these harmonized values in subsequent analyses.

Figure S1: Mean cortical DVR vs. age for individuals with both GE Advance and HRRT PiB scans. Left: prior to scanner harmonization. Right: after affine transform harmonization.

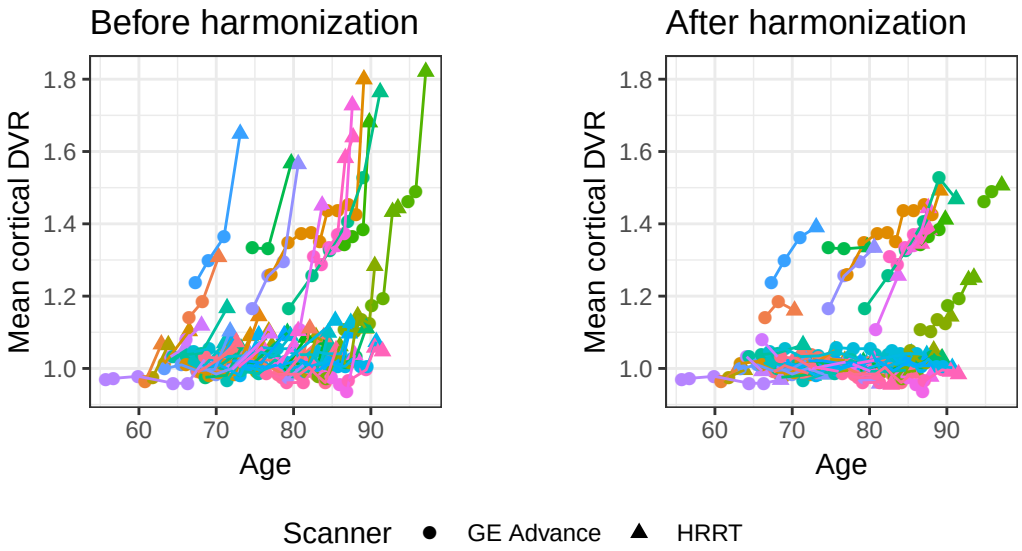


Figure S2. Plot of neuroticism (top panel) and conscientiousness (bottom panel) with mean cortical PiB.

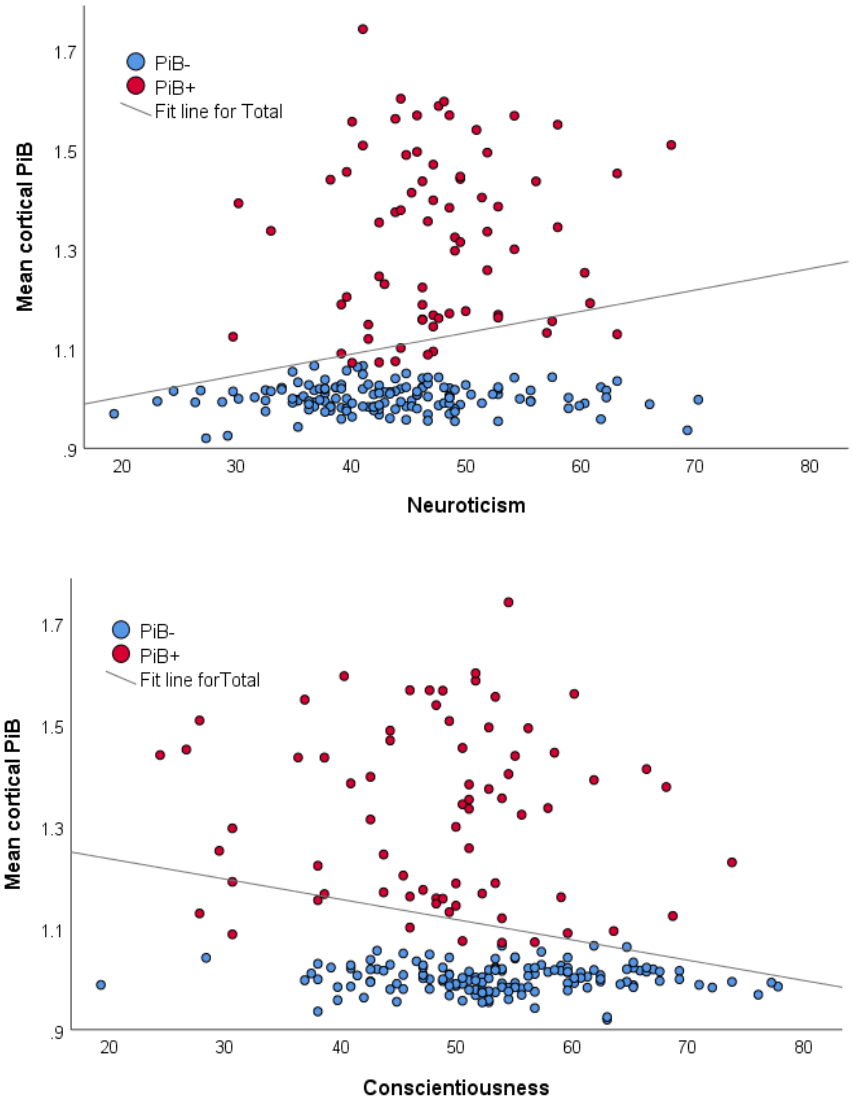


Figure S3. Funnel plots

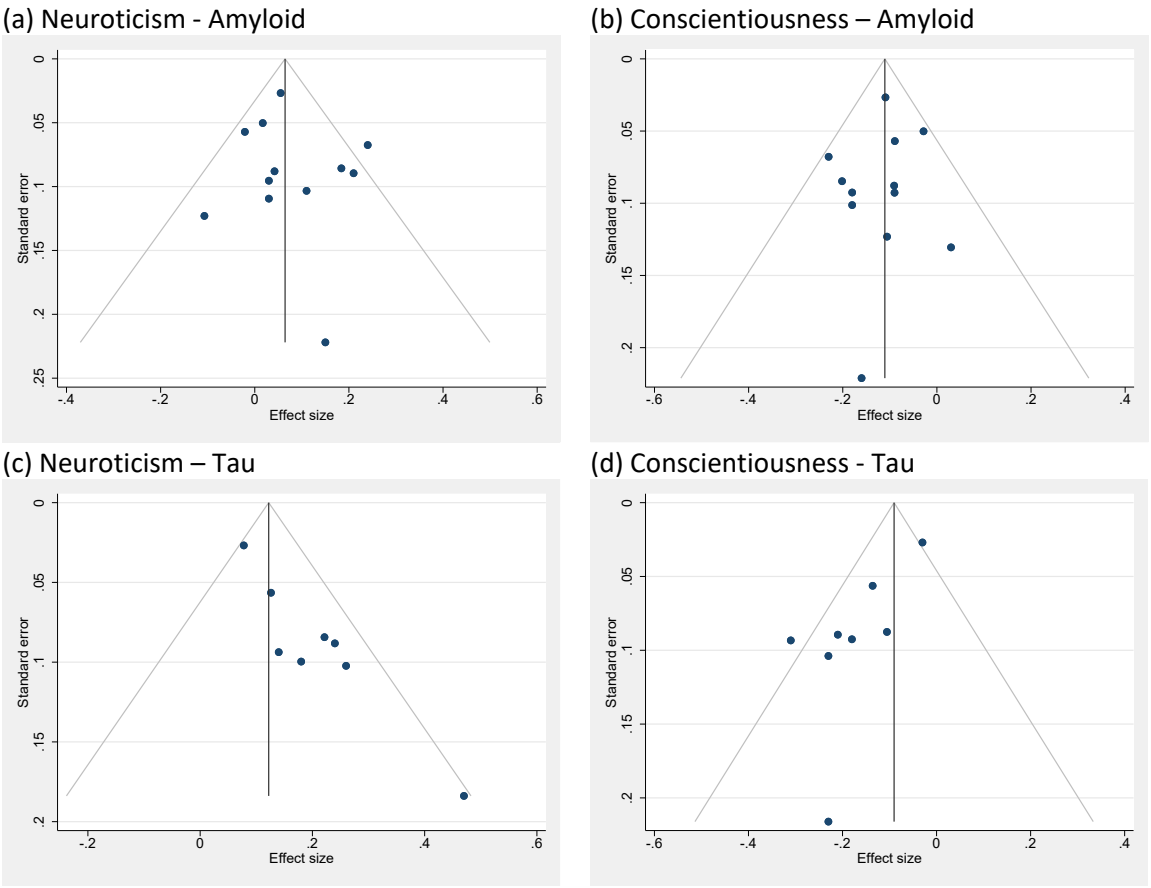
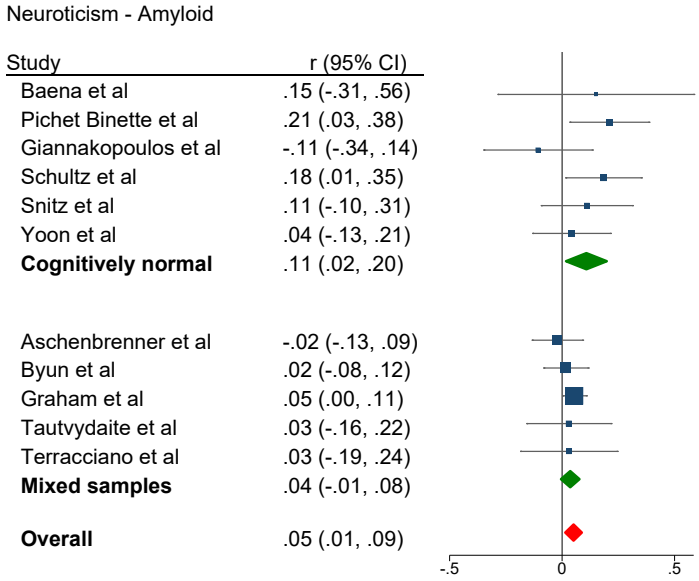
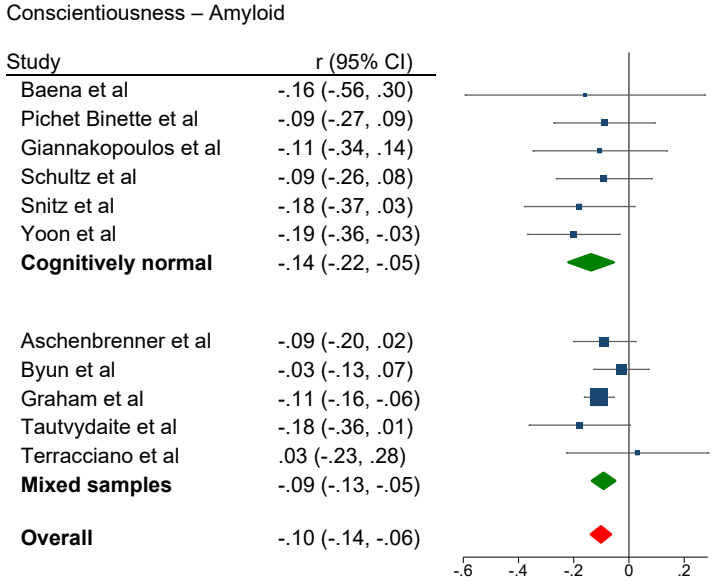


Figure S4. Forest plot excluding the new BLSA sample.

A

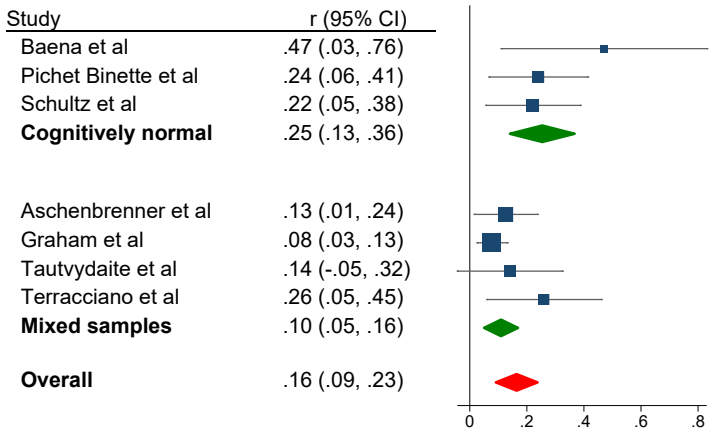


B



C

Neuroticism – Tau



D

Conscientiousness – Tau

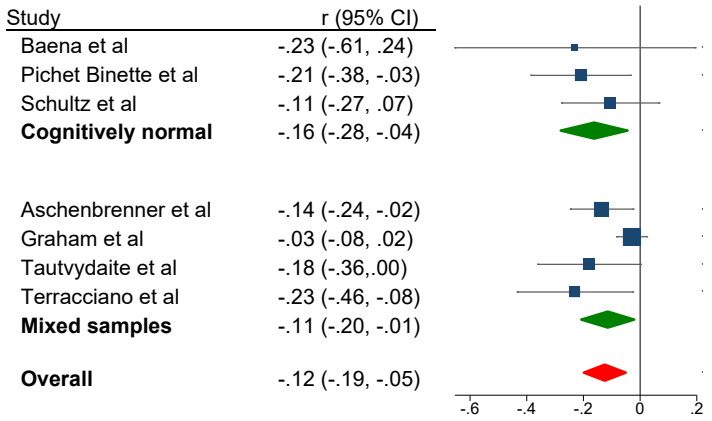


Table S1. Associations between personality traits and amyloid and tau regions in the cognitively normal participants and full sample.

	Amyloid Precuneus			Tau Fusiform			Tau Inferior temporal gyrus			Tau Hippocampus		
	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Cognitively normal												
Neuroticism	.26**	.28**	.27**	.11	.11	.16	.15	.15	.19	-.08	-.09	.04
Extraversion	-.07	-.03	-.01	-.13	-.11	-.15	-.12	-.10	-.12	-.06	-.04	-.16
Openness	-.10	-.11	-.09	-.15	-.15	-.17	-.14	-.14	-.15	.07	.07	.00
Agreeableness	-.13	-.12	-.13	-.15	-.11	-.13	-.20	-.14	-.15	.09	.13	.12
Conscientiousness	-.25**	-.23**	-.22**	-.28**	-.33**	-.40**	-.27**	-.32**	-.37**	-.03	-.03	-.16
Full sample												
Neuroticism	.23**	.23**	.23**	.10	.10	.15	.15	.15	.19	.03	.02	.10
Extraversion	-.05	.01	.03	-.12	-.09	-.12	-.13	-.09	-.11	-.03	-.01	-.09
Openness	-14*	-.12	-.09	-.16	-.15	-.17	-.15	-.14	-.16	.09	.10	.02
Agreeableness	-.12	-.09	-.09	-.12	-.08	-.09	-.15	-.11	-.11	.06	.07	.08
Conscientiousness	-.24**	-.20**	-.19**	-.24*	-.28**	-.33**	-.24*	-.28*	-.31**	-.02	.01	-.05

Note. For CN, N = 196 for amyloid and N = 95 for tau. For full sample, N = 216 for amyloid and N = 103 for tau. M1 = No covariates; M2 = Partial correlations accounting for age, sex, and time interval between personality and imaging; M3 = Partial correlations accounting for M2 covariates, education and depressive symptoms.
*p<.05; **p<.01.

Table S2. Meta-analytic results for amyloid and tau.

Amyloid	K	N	r	LL 95%CI	UL 95%CI	P	Q	P	I^2	τ
Neuroticism	12	3015	.07	.02	.12	.008	16	.132	32	0.05
Extraversion	11	2431	.01	-.03	.05	.549	9	.524	0	0.00
Openness	11	1675	-.04	-.09	.02	.185	10	.288	16	0.04
Agreeableness	11	1650	-.03	-.08	.02	.188	10	.422	2	0.01
Conscientiousness	12	2990	-.11	-.14	-.07	<.001	9	.613	0	0.00
Tau	K	N	r	LL 95%CI	UL 95%CI	P	Q	P	I^2	τ
Neuroticism	8	2231	.15	.09	.22	<.001	10	.173	32	0.05
Extraversion	7	1927	-.09	-.21	.04	.170	22	.001	72	0.13
Openness	7	1171	-.14	-.29	.01	.065	29	<.001	79	0.17
Agreeableness	7	1146	-.07	-.16	.03	.151	11	.089	45	0.08
Conscientiousness	8	2206	-.14	-.22	-.06	<.001	13	.066	47	0.07

Table S3. Publication bias indices.

	Kendall τ	P-value	Egger	SE	P-value	Trimm and Fill	Imputed r
Amyloid							
Neuroticism	0.05	0.78	0.46	0.7	0.53	0	NA
Extraversion	0.00	1.000	-0.75	0.49	.160	2	0.016
Openness	-0.15	0.53	-1.38	0.74	0.09	4	0.002
Agreeableness	-0.25	0.28	-1.17	0.68	0.12	5	0.02
Conscientiousness	-0.02	.950	-0.29	0.52	.584	3	-0.09
Tau							
Neuroticism	0.61	0.035	1.89	0.26	0.00034	5	0.096
Extraversion	-0.19	0.55	-2.22	0.83	0.045	2	-0.02
Openness	-0.1	0.76	-2.3	1.69	0.23	1	-0.08
Agreeableness	-0.57	0.07	-2.07	0.73	0.037	4	0.01
Conscientiousness	-0.32	0.27	-1.97	0.42	0.004	5	-0.06

Note. NA = not applicable.