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Personality associations with amyloid and tau: Results from the Baltimore Longitudinal Study of Aging and meta-analysis.

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Abstract

Background: Higher neuroticism and lower conscientiousness are risk factors for Alzheimer's disease and related dementias, but the underlying neuropathological correlates remain unclear. Our aim was to examine whether personality traits are associated with amyloid and tau neuropathology in a new sample and meta-analyses.

Methods: Participants from Baltimore Longitudinal Study of Aging (BLSA) completed the Revised NEO Personality Inventory and underwent amyloid (¹¹C-labeled Pittsburgh Compound B) and tau (¹⁸F-flortaucipir) positron emission tomography.

Results: Among cognitively normal BLSA participants, neuroticism was associated with higher (OR = 1.68, 1.20–2.34) and conscientiousness with lower (OR = 0.61, 0.44–0.86) cortical amyloid burden. These associations remained significant after accounting for age, sex, education, depressive symptoms, hippocampal volume, and *APOE* ε4. Similar associations were found with tau in the entorhinal cortex. Random-effect meta-analyses of 12 studies found higher neuroticism (N = 3015, r = .07, *P* = .008) and lower conscientiousness (N = 2990, r = -.11, *P* < .001) were associated with more amyloid deposition. Meta-analyses of 8 studies found higher neuroticism (N = 2231, r = .15, *P* < .001) and lower conscientiousness (N = 2206, r = -.14, *P* < .001) were

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associated with more tau pathology. The associations were moderated by cognitive status, with stronger effects in cognitively normal compared to heterogeneous samples, suggesting that the associations between personality and proteopathies are not phenomena that emerge with neuropsychiatric clinical symptoms.

Conclusions: By aggregating results across samples, this study advances knowledge on the association between personality and neuropathology. Neuroticism and conscientiousness may contribute to resistance against amyloid and tau neuropathology.

Keywords

Personality; Alzheimer's disease; amyloid; tau; neuropsychiatric disorders; meta-analysis

Introduction

Personality traits are defining features of a person's psychological profile. The five major personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) emerge early in life, are fairly stable, and have a broad impact on important life outcomes, including neuropsychiatric disorders(1–4). In the health domain, a growing number of prospective studies have found that high neuroticism and low conscientiousness in cognitively normal (CN) adults predict who is at greater risk of developing Alzheimer's disease (AD) and related dementias (ADRD)(5–10). These same traits also predict cognitive performance on standardized tests(11) and are associated with changes in cognitive and functional status, as rated by knowledgeable informants(12). These associations are robust across samples and extend across the lifespan(13). For example, personality traits assessed in adolescence predict cognitive function in middle-age(13) and dementia risk about 50 years later(14). Two postmortem studies indicate that personality traits may reduce the risk for clinical dementia by increasing *resilience* to AD neuropathology (e.g., high conscientiousness supports coping with AD pathology and delays clinical signs)(15, 16). It is similarly possible that personality modulates *resistance*(17) to AD neuropathology (e.g., high conscientiousness delays or even helps to avoid the development of AD pathology)(8, 18–21).

To better understand the mechanisms underlying the association between personality and risk of dementia, we investigate whether personality traits are associated with two defining markers of AD neuropathology: amyloid and tau deposition. Based on the literature on personality and dementia(9), our primary hypothesis is that high neuroticism and low conscientiousness are associated with greater amyloid and tau burden. We advance the same hypothesis for both biomarkers because amyloid and tau are interrelated and both are part of the cascade of AD neurodegeneration(22). To provide a more comprehensive assessment of the role of personality, we also report results for extraversion, openness, and agreeableness.

To test our hypothesis, we first examined the associations in a well-characterized sample of older adults from the Baltimore Longitudinal Study of Aging (BLSA) who completed a measure of personality and underwent amyloid and tau positron emission tomography (PET). We then conducted a systematic search of the literature to provide a quantitative synthesis of current evidence. The current literature is somewhat mixed, with

some studies reporting associations between AD biomarkers and neuroticism(23–25), or conscientiousness(26), or neither(27). The meta-analytic approach in this context is essential because most studies to date have relied on relatively small sample sizes that are modestly powered to reliably detect the expected associations. We evaluated heterogeneity, publication bias, and tested two potential moderators: measure of neuropathology (postmortem vs. in vivo) and cognitive status (CN vs. CN + cognitively impaired individuals).

Materials and Methods

BLSA participants.

The BLSA ([ClinicalTrials.gov: NCT00233272](https://clinicaltrials.gov/ct2/show/study/NCT00233272)) is an ongoing longitudinal study of community-dwelling adults. Participants were from the BLSA neuroimaging substudy who underwent amyloid and tau PET. At enrollment into the substudy, all participants were free of dementia, stroke, bipolar illness, epilepsy, severe cardiac disease, severe pulmonary disease, and metastatic cancer. Personality data were available for all participants at the PET assessment or a previous visit. The personality assessment was within one year of the PET scan for 70% of participants; time ranged from –11.62 to 0.87 years (mean = –0.96, SD = 1.77) for the time between the personality and amyloid and from –11.62 to 0.86 years (mean = –1.33, SD = 1.96) for the time between the personality and tau imaging. For participants with multiple assessments, we selected the last available PET visit, which had concurrent amyloid and tau scans (the same day or within a few days for all participants except for one participant with the tau scan one year before and one participant one year after the amyloid scan). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocols were approved by local institutional review boards and all participants provided written informed consent before each visit.

Measures

Personality.—Participants completed the 240-item, self-report version of the Revised NEO Personality Inventory (NEO-PI-R)(28). Raw scores were standardized as T-scores ($M = 50$, $SD = 10$) using combined-sex norms(28). The NEO-PI-R factor structure in the BLSA shows high congruence with the normative structure (Tucker $\phi = 0.97$ – 0.99), high internal consistency ($\alpha = 0.88$ – 0.92), and high test-retest correlations ($r_{tt} = 0.78$ – 0.85) over a mean interval of 10 years(29). In addition to BLSA studies, the reliability and validity of the NEO-PI-R (or briefer versions such as the NEO-Five-Factor Inventory) are supported by a large literature across clinical and non-clinical samples, self-report and observer rating methods, and across age groups, languages, and cultures(28–33).

PET imaging - Amyloid.—Amyloid was measured using ^{11}C -Pittsburgh compound B (PiB) as described in the supplementary material. Briefly, scans were obtained over 70 minutes immediately following an intravenous bolus injection of approximately 15 mCi of ^{11}C -PiB. 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. A mean cortical DVR threshold of 1.067, derived from a Gaussian mixture model, was used to categorize participants as PiB $-/+$ (34).

PET imaging - Tau.—Tau was measured using ^{18}F -AV-1451 (^{18}F -flortaucipir) as previously described(34). Briefly, scans were obtained over 30 minutes starting 75 minutes after an intravenous bolus injection of approximately 10 mCi of ^{18}F -flortaucipir. We computed 80–100 minutes standardized uptake value ratio (SUVR) images by dividing the partial volume corrected PET intensities by the mean within the inferior cerebellar gray matter. We computed the average SUVR in four regions of interest (ROIs) corresponding to the early stages of tau pathology: the entorhinal cortex (primary outcome), fusiform, inferior temporal gyrus, and hippocampus.

Clinical status.—The cognitive evaluation was based on a neuropsychological battery and clinical examination, including informant- and participant-structured interviews. Participants with a Clinical Dementia Rating(35) score ≤ 0.5 or Blessed Information-Memory-Concentration Test(36) ≤ 4 were reviewed through consensus conference. Mild cognitive impairment (MCI) was based on the Petersen criteria(37). Diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) (38) criteria, and diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria(39).

Statistical Analyses

We examined the association between each personality trait and the neuropathology markers using unadjusted correlations (Model 1), partial correlations with age, sex, and time between personality and imaging as covariates (Model 2), and education and depressive symptoms (Center for Epidemiological Studies-Depression score ≥ 16 (40)) as additional covariates (Model 3). The primary outcomes were the mean cortical amyloid burden and entorhinal tau, respectively. Secondary outcomes presented in supplementary material were amyloid in the precuneus and tau in the fusiform, inferior temporal gyrus, and hippocampus. Separate logistic regressions were used to evaluate each personality trait as a predictor of PIB+, including the same covariates. We used z-scores to obtain odds ratios per 1 SD difference on the personality trait. In follow-up analyses, Apolipoprotein E (*APOE*) $\epsilon 4$ carrier status or hippocampal volume (adjusted for intracranial volume) were included as additional covariates in the logistic regressions and in the partial correlations between personality and entorhinal tau. In additional analyses, we included individuals with MCI or dementia.

Literature search and Meta-Analyses

The meta-analyses were prepared in line with the MOOSE guidelines for meta-analyses of observational studies. The protocol was not preregistered and the risk of bias of individual studies was not assessed. The PICO framework was used to form the research questions: Participants = *human subjects*; Intervention = *no intervention/exposure, observational (cohort study)*; Comparison = *level of personality traits (individual differences)*, and Outcome = *amyloid and/or tau (in vivo or postmortem)*.

Eligibility criteria.—We included studies that measured at least one of the five personality traits and post-mortem or in-vivo (PET or CSF) measures of amyloid or tau. We had no exclusion criteria based on study design, type of population, publication status, or language of the article.

Systematic Literature Search.—A systematic literature search covering all years from inception up to 7 May 2021 was conducted using PubMed, PsycInfo, and Web of Science. We used the terms *neuroticism* OR *extraversion* OR *openness* OR *agreeableness* OR *conscientiousness* for personality, *amyloid* OR $A\beta$ OR *Pittsburgh Compound B* OR *PIB* OR ^{18}F -*florbetapir* OR ^{18}F -*Florbetaben* OR ^{18}F -*Flutemetamol* for amyloid, and *tau* or *neurofibrillary tangles* OR *floratacipir* OR ^{18}F -*AV-1451* or ^{18}F -*T807* for tau. The reference lists of published articles were also screened. The literature search was conducted independently by two researchers (AT and DA). We screened the titles and keywords of each article for eligibility. Next, we screened abstracts and if an article seemed eligible, the full text was obtained. The full-text articles were then assessed for inclusion, and the data extracted from selected studies. Google Scholar was used to conduct a similar search and to identify additional studies through forward searches. We contacted study authors for effect estimates(41) and to clarify sample overlap(8).

Meta-Analyses: Random-effect meta-analyses were based on reported correlation coefficients and sample sizes, or the exact p-values, or the t value (derived from beta/SE), and sample sizes. When multiple articles from the same cohort were identified, we used estimates from the largest sample and with PET over CSF(42). For consistency with PET, associations with CSF $A\beta_{1-42}$ were reversed because CSF $A\beta_{1-42}$ decreases with advancing neuropathology. When results were provided for multiple ROIs, we used global measures of amyloid deposition. For tau, we focused on the association with the entorhinal cortex because it is one of the first regions to manifest detectable elevated tau PET signal, and it is commonly reported in PET studies(24, 25, 34). Heterogeneity was quantified using Q , I^2 , and τ . Publication bias was evaluated by examining funnel plots, the Egger intercept, Kendall tau, and trim-and-fill method. We examined whether effect sizes differed between postmortem vs. in vivo measures and between samples of CN vs. CN + cognitively impaired individuals.

Results

BLSA

Descriptive statistics for demographics and other variables of interest are in Table 1 for the CN and full samples.

Amyloid.—Unadjusted correlations (Model 1) and partial correlations accounting for age, sex, time between personality assessment and PET (Model 2), education, and depressive symptoms (Model 3) indicated that higher neuroticism and lower conscientiousness were associated with higher mean cortical amyloid deposition (Table 2; Figure S2; see Table S1 for precuneus). Neuroticism and conscientiousness each accounted for about 5% of the variance in the mean cortical amyloid deposition. Similar associations for neuroticism

and conscientiousness were found with the non-parametric Kendall and Spearman rank correlations ($ps < .01$). As illustrated in Figure S2, the associations were most evident in the contrast between the PIB- and PIB+ groups, but also in PIB+ group. There was very low variability in the PIB- group and therefore no clear associations. In additional regression analyses, we found that neuroticism ($p = .007$) and conscientiousness ($p = .046$; but $p = .063$ when accounting for age and sex) interacted with PIB grouping in predicting mean cortical amyloid burden. Most important, relations between personality and PiB as a continuous measure were consistent with those obtained with logistic regression to predict the PiB+ group: A difference of 1 SD higher neuroticism and 1 SD lower conscientiousness were both associated with about 60% higher risk of PiB+. Adding *APOE* $\epsilon 4$ (to Model 3) had little effect on the associations of neuroticism (OR = 1.70, 1.17 – 2.48) and conscientiousness (OR = 0.66, 0.45 – 0.96) with risk of PiB+. Similarly, adding hippocampal volume (to Model 3) had little effect on the associations of neuroticism (OR = 1.70, 1.17 – 2.47) and conscientiousness (OR = 0.66, 0.45 – 0.94) with risk of PiB+. The associations were mostly unchanged in analyses that included individuals with cognitive impairment (Table 2). Among the other traits, higher openness was associated with lower risk of PiB+, but the effect was not consistently significant in models that accounted for education and depressive symptoms and with the continuous measure of mean cortical PiB (Table 2).

Tau.—Both the unadjusted and partial correlations indicated that lower conscientiousness was associated with more tau in the entorhinal cortex, and explained 8% or more of the variance in tau (Table 2; see Table S1 for fusiform, inferior temporal gyrus, and hippocampus). The correlation coefficients were in the hypothesized direction for neuroticism but did not reach statistical significance except for the fully adjusted Model 3. The associations were essentially unchanged when either *APOE* (e.g., conscientiousness: $r = -.42, P < .001$) or hippocampal volume (e.g., conscientiousness: $r = -.41, P < .001$) was added as a covariate and were similar including individuals with cognitive impairment. Among the other traits, a notable finding was that higher openness was consistently associated with lower tau in the entorhinal cortex ($R^2 \sim 4\%$).

Meta-analyses

The flow chart of the literature search is in Figure 1. Table 3 presents the characteristics of the included samples. Two studies assessed AD pathology at autopsy and personality on average 9 and 30 years before death (15, 16). All other studies were essentially cross-sectional and assessed AD pathology with PET or CSF (23–27, 41, 43–45).

Amyloid.—The meta-analysis of 12 studies ($N = 3015$) found that higher neuroticism was associated with higher amyloid burden ($r = .07, P = .008$) (Figure 2), low heterogeneity ($I^2 = 32\%$) (Table S2), and no evidence of publication bias (Table S3, Figure S3). Cognitive status was a significant moderator (meta-regression, $Z = -2.57, P = .010$): there was a stronger association in the CN ($r = .14, P = .002$) compared to mixed cognitive status samples ($r = .04, P = .087$). The results were similar in the postmortem vs. in vivo as well as CSF vs. PET studies.

For conscientiousness, the meta-analysis of 12 studies ($N = 2990$) indicated that more conscientious individuals had lower amyloid burden ($r = -.11$, $P < .001$), low heterogeneity ($I^2 = 0\%$), and no evidence of publication bias. There were no significant moderators (meta-regression, $P = .10$), but the association was stronger in CN ($r = -.16$, $P < .001$) compared to mixed cognitive status samples ($r = -.09$, $P < .001$). The results were similar in the postmortem vs. in vivo as well as CSF vs. PET studies.

There were no significant associations for extraversion (11 studies, $N = 2431$, $r = .01$, $P = .55$), openness (11 studies, $N = 1675$, $r = -.04$, $P = .19$), or agreeableness (11 studies, $N = 1650$, $r = -.03$, $P = .19$), and low heterogeneity ($I^2 = 16\%$). Among the in vivo studies, higher openness was associated with lower amyloid (9 studies, $r = -.08$, $P = .018$).

Tau.—The meta-analysis of 8 studies ($N = 2231$) found that higher neuroticism was associated with more tau pathology ($r = .15$, $P < .001$; heterogeneity: $I^2 = 32\%$). Cognitive status was a significant moderator ($Z = -2.33$, $P = .02$) with a significantly stronger association in the CN ($r = .23$, $P < .001$) compared to mixed cognitive status samples ($r = .10$, $P < .001$). The results were similar in the postmortem and in vivo studies and CSF vs. PET. With only 8 studies, publication bias tests are not recommended(46), but we noted asymmetry in the funnel plot. The asymmetry was driven by one disproportionately large sample(16), which found a significant association ($P = .0039$), but smaller than the effects in the other samples. The difference may arise from clinical and methodological differences across studies or selective reporting.

For conscientiousness, the meta-analysis of 8 studies ($N = 2206$) found that more conscientious individuals had lower tau pathology ($r = -.14$, $P < .001$; heterogeneity: $I^2 = 47\%$). Associations were significantly stronger among studies that used CN ($r = -.19$, $p < .001$) compared to mixed cognitive status samples ($r = -.11$, $P = .02$)(meta regression, $Z = -2.26$, $P = .02$), and in vivo ($r = -.17$, $P < .001$) compared to postmortem assessment ($r = -.09$, $P = .33$)(meta regression, $Z = -2.93$, $P = .003$). Results were similar for CSF vs. PET studies. There was asymmetry in the funnel plot again due to the larger postmortem study(16).

There were no significant associations between tau and extraversion (7 studies, $N = 1927$, $r = -.09$, $P = .17$), openness (7 studies, $N = 1171$, $r = -.14$, $P = .065$), or agreeableness (7 studies, $N = 1146$, $r = -.07$, $P = .15$) with substantial heterogeneity ($I^2 = 45\%$). Among the five in vivo studies, higher openness ($r = -.22$, $P = .004$) and extraversion ($r = -.16$, $P = .009$) were associated with lower tau pathology.

Discussion

In new data from the BLSA and meta-analyses, we found that high neuroticism and low conscientiousness were associated with higher amyloid and tau deposition. For example, 1 SD higher neuroticism or lower conscientiousness was associated with about 60% higher risk of being PiB+ in the BLSA. The pooled estimates indicated stronger associations for tau compared to amyloid. Further, we found a pattern of stronger associations in CN samples compared to samples inclusive of MCI and dementia. These patterns

suggest that the associations are not emerging phenomena due to personality change with disease progression, as would be expected with reverse causality. Overall, the findings corroborate long-term prospective studies that personality predicts the risk of incident ADRD(5–10). Personality traits, which emerge early in life and are relatively stable throughout adulthood(47), may modulate ADRD risk by conferring resistance(17) against AD neuropathology (i.e., delaying or preventing its emergence).

The in vivo assessment of amyloid and especially tau is relatively recent, and most studies included in the meta-analyses were published in the last two years. Most studies were also based on relatively small samples, typically <200 individuals. Because of the limited power, these studies have often reported null findings, but the effects were generally in the same direction. For example, in the BLSA, the association between neuroticism and entorhinal tau was significant in some models but not in others, but the effect across models was consistent with the meta-analytic estimate. As such, the meta-analyses represent a major advance by achieving the required power to provide robust estimates of the associations between personality and neuropathology. The observed associations should be interpreted in the context of other ADRD risk factors. Current evidence, however, indicates that early-life cognitive ability or enrichment(48, 49), physical activity(50, 51), or vascular risk factors(51–54) are inconsistently associated with amyloid or tau deposition.

Neuroticism is a major risk factor for anxiety and mood disorders, as well as for behavioral and psychological symptoms of dementia(55, 56). While we limited our meta-analyses to personality traits, there is tentative evidence that depressive and anxiety symptoms are also associated with amyloid or tau(57–61). Late-life elevations in depressive symptoms may emerge during preclinical or prodromal AD(59, 62), and neuroticism may increase with amyloid and tau deposition as an early sign of preclinical AD. However, this latter hypothesis is less likely because (a) we found stronger associations in CN compared to mixed samples, (b) longitudinal data indicate that there are no increases in neuroticism in the preclinical phase of AD(63)[changes occur later with the onset(64) and progression of dementia(32, 33)], and (c) the associations of personality traits with amyloid and tau were independent of depressive symptoms. Future work is needed to disentangle the timing of these associations, and test whether neuroticism interacts with proteinopathies to increase the risk of depression and other behavioral and psychological symptoms of dementia. Future studies should also focus on the underlying mechanisms; a potential pathway is inflammation given the links of personality with inflammatory markers from younger ages(65), which over time may increase the risk of neuropathology(66, 67). Personality-linked differences in functional brain network connectivity(68) may also modulate the spread of neuropathology(69). Low neuroticism has been found to increase resilience(15, 16) and differences in network connectivity could partly explain how low emotional vulnerability helps maintain cognitive function despite neuropathologic changes(70). Recent evidence suggest that alterations of transcriptome of the frontal cortex, especially in modules related to tau pathology, may mediate the impact of neuroticism on cognitive decline and AD(71). Genetic factors may also play a role(72); genome-wide association studies (N = 449,484) of neuroticism(73) have found top hits (including an exonic nonsynonymous variant, $P \sim 10^{-28}$) in the microtubule-associated protein tau (*MAPT*) gene, which is

implicated in AD, frontotemporal dementia, and other tauopathies. The *MAPT* transgenic mouse model also displays abnormal fear-related behaviors(74).

We found consistent evidence that high conscientiousness is associated with lower risk of amyloid and tau neuropathology in both the BLSA and the meta-analyses. This finding is consistent with the evidence from prospective studies that consistently find high conscientiousness associated with lower risk of AD and related dementia(10). High conscientiousness is also associated with other measures of brain integrity, such as white matter fractional anisotropy(20). These associations are thought to arise in part from the healthier lifestyle of conscientious individuals, who tend to engage in more physical activity and avoid health risk behaviors, such as cigarette smoking(75, 76). Furthermore, conscientious individuals tend to have better sleep(77), better hearing(78), fewer chronic conditions such as diabetes and depression(56, 79), and spend more time in cognitively demanding activities, like studying, working, and reading(80, 81). Over time, this healthier profile and greater engagement in cognitive activities is likely to build cognitive reserve and reinforce compensation and optimization mechanisms that protect against AD neuropathology(82).

There were also significant associations between openness and the AD biomarkers in the BLSA, which were supported in the meta-analysis of the in vivo studies but not in the full meta-analyses. This again parallels the mixed findings from prospective studies linking low openness to dementia risk(10). It is of note that individuals with high openness tend to achieve higher education and engage in a variety of cognitively stimulating activities (e.g., watching less TV, more reading, more computer use)(80). The intrinsic interest in complex, diverse, and engaging activities is likely to partly explain the protective effects of openness.

Limitations and Future directions

While the meta-analysis included samples from four continents (North and South America, Europe, and Asia), a limitation of current work is the reliance on samples with high education and from high-income countries; ideally, future studies should include samples with lower education and income and from diverse communities that are at considerable risk for ADRD(84). Recent studies, however, found similar associations in samples from Colombia and Brazil(23, 85). Future studies could be further strengthened by using observer ratings as well as self-reported personality. More research is also needed to further understand the spatial specificity of these associations across the brain, especially for tau; the results for the entorhinal region were similar to those found for the fusiform and the inferior temporal gyrus, but not for the hippocampus region, which may be contaminated by choroid plexus binding (Table S1). For tau, there were only eight studies and there was asymmetry in the funnel plot, which could be due to selective reporting or methodological and substantive differences across studies(46). For amyloid, there was limited heterogeneity, despite methodological differences across studies that spanned post-mortem, imaging and CSF measures. The assessment of amyloid and tau has evolved rapidly in recent years, which may partly explain the limitations of the broad differences in study design, analytic approach, and reporting of findings. More methodological and reporting consistency will

help future meta-analytic efforts and potentially explain some of the differences across studies.

In conclusion, the meta-analytic synthesis of current evidence found that neuroticism was a risk factor and conscientiousness was protective against amyloid and especially tau pathology burden; these associations were stronger in CN samples, which include preclinical AD. We and others(15, 16) had previously hypothesized that personality modulates the risk of clinical dementia mainly by providing resilience against the AD neuropathology, but these new findings support the hypothesis that personality traits may also confer resistance to neuropathology. Future longitudinal studies are essential to determine the temporal order of these associations and gain more insight into the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data and materials availability:

The anonymized BLSA data is publicly accessible upon request at <https://www.blsa.nih.gov>. All data used in the meta-analysis are available in the main text or the supplementary materials.

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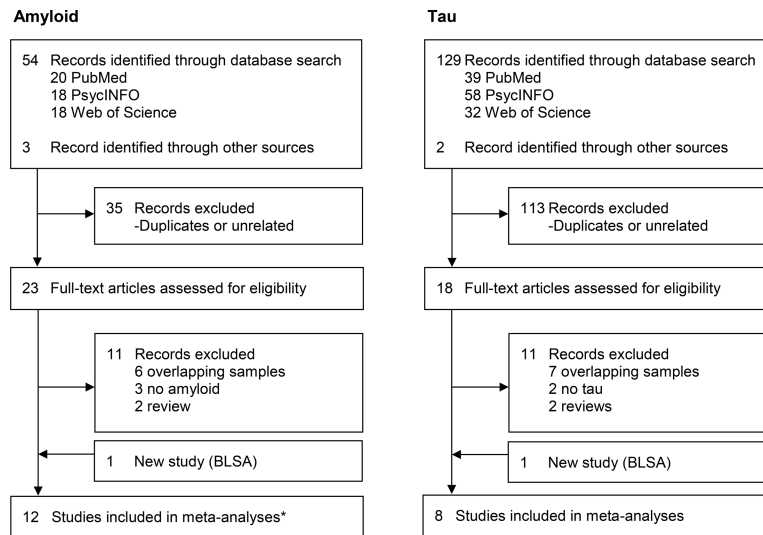
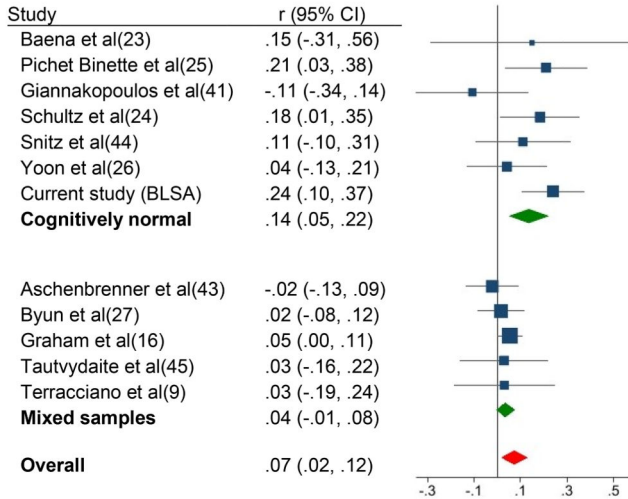


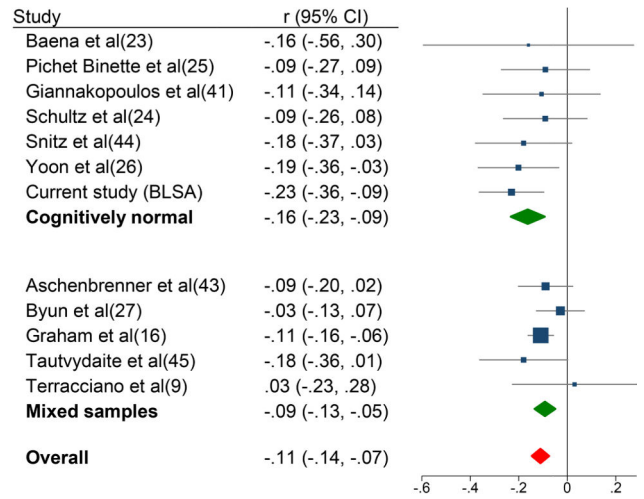
Figure 1.
Flow chart of literature search and selection.

Note. * Up to 12 studies included in the meta-analyses, but data came from 13 records as listed in Table 3.

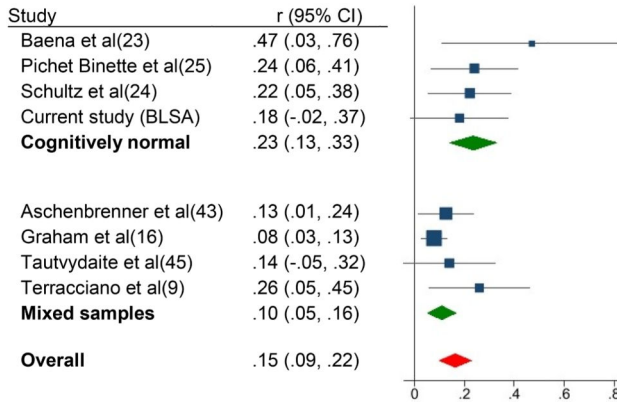
A Neuroticism - Amyloid



B Conscientiousness – Amyloid



C Neuroticism – Tau



D Conscientiousness – Tau

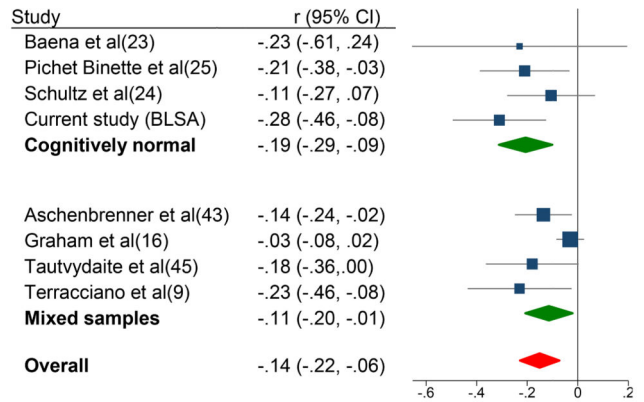


Figure 2. (a – d). Forest plots of the associations between personality traits and amyloid and tau in cognitively normal, mixed samples, and overall.

Note. Effect sizes are correlation coefficients with corresponding 95% confidence intervals. Results were similar if the current BLSA sample was excluded from the meta-analysis (Figure S4).

Table 1.

Demographic, clinical, imaging, and personality descriptive statistics of BLSA study participants.

	Amyloid		Tau	
	CN (N=196)	Full (N=216)	CN (N=95)	Full (N=103)
Age, years	77.74 (8.56)	78.55 (8.72)	76.04 (8.59)	76.85 (8.89)
Female	101 (51.5%)	107 (49.5%)	55 (57.9%)	58 (56.3%)
Black	35 (17.9%)	38 (17.6%)	17 (17.9%)	19 (18.4%)
Other	10 (5.1%)	10 (4.6%)	6 (6.3%)	6 (5.9%)
White	151 (77.0%)	168 (77.8%)	72 (75.8%)	78 (75.7%)
Education, years	17.18 (2.39)	17.24 (2.43)	17.66 (2.43)	17.60 (2.51)
Diagnosis: MCI [^]	0 (0%)	13 (6%)	0 (0%)	6 (5.8%)
Diagnosis: Dementia [^]	0 (0%)	5 (2.3%)	0 (0%)	0 (0%)
<i>APOE</i> e4 carrier	56 (28.9%)	63 (29.6%)	26 (28.0%)	29 (29.0%)
<i>Hippocampus</i> (cm ³)	7.29 (0.76)	7.25 (0.80)	7.34 (0.76)	7.29 (0.77)
CESD 16	12 (6.1%)	16 (7.4%)	5 (5.3%)	6 (5.8%)
Amyloid PiB+	57 (29.1%)	72 (33.3%)	21 (22.1%)	26 (25.2%)
Amyloid mean cortical	1.09 (0.18)	1.11 (0.18)	1.07 (0.15)	1.11 (0.18)
Amyloid Precuneus	1.17 (0.23)	1.19 (0.24)	1.15 (0.19)	1.19 (0.24)
Tau Entorhinal	1.03 (0.17)	1.04 (0.18)	1.03 (0.17)	1.04 (0.18)
Tau Fusiform	1.16 (0.22)	1.16 (0.21)	1.16 (0.22)	1.16 (0.21)
Tau Inferior temporal gyrus	1.30 (0.21)	1.31 (0.20)	1.30 (0.21)	1.31 (0.20)
Tau Hippocampus	1.31 (0.27)	1.32 (0.29)	1.31 (0.27)	1.32 (0.29)
Neuroticism	44.37 (8.65)	44.74 (8.76)	43.44 (9.19)	43.76 (9.27)
Extraversion	49.59 (10.12)	49.63 (10.14)	49.46 (11.79)	49.43 (11.65)
Openness	51.63 (9.93)	51.07 (9.89)	52.10 (10.03)	51.33 (10.16)
Agreeableness	54.46 (9.29)	54.30 (9.18)	55.19 (10.05)	55.09 (10.07)
Conscientiousness	52.33 (9.87)	51.87 (10.08)	54.12 (10.47)	53.99 (10.49)

Notes. CN = Cognitively normal. CESD = Center for Epidemiological Studies-Depression. MCI = Mild Cognitive Impairment. PiB = ¹¹C-Pittsburgh compound B. In parenthesis are SD or percentages. Age at the time of personality assessment. *APOE* data was missing for 3 individuals. PiB statistics are distribution volume ratio (DVR) and tau are standardized uptake value ratio (SUVR).

[^]The difference between CN and Full sample includes impaired participants, of whom two had impairment other than MCI or dementia.

Table 2.

Associations between personality traits and amyloid and tau in BLSA study participants.

Cognitively	PiB mean cortical						Entorhinal Tau									
	PiB-			PiB+			M1			M2			M3			
	r	r	r	OR (95% CI)	OR (95% CI)	OR (95% CI)	r	r	r	OR (95% CI)	OR (95% CI)	OR (95% CI)	r	r	r	
Normal (CN)																
Neuroticism	.24**	.26**	.24**	1.68 (1.20–2.34)**	1.69 (1.20–2.38)**	1.72 (1.18–2.49)**	.18	.18	.24*				.18	.18	.24*	
Extraversion	-.08	-.04	-.01	.80 (.58–1.09)	.84 (.60–1.18)	.89 (.63–1.25)	-.20	-.20	-.24*				-.20	-.20	-.24*	
Openness	-.12	-.13	-.09	.71 (.52–.98)*	.71 (.51–.99)*	.76 (.54–1.07)	-.20*	-.21*	-.22*				-.20*	-.21*	-.22*	
Agreeableness	-.14*	-.14	-.14	.81 (.59–1.10)	.80 (.57–1.11)	.78 (.56–1.10)	-.12	-.11	-.15				-.12	-.11	-.15	
Conscientiousness	-.23**	-.20**	-.18*	.61 (.44–.86)**	.64 (.45–.91)*	.64 (.44–.93)*	-.28**	-.30**	-.42**				-.28**	-.30**	-.42**	
Full sample																
Neuroticism	.21**	.20**	.20**	1.64 (1.21–2.22)**	1.64 (1.19–2.25)**	1.65 (1.16–2.35)**	.19	.18	.23*				.19	.18	.23*	
Extraversion	-.07	-.01	.01	.80 (.60–1.06)	.89 (.66–1.21)	.95 (.69–1.30)	-.20*	-.17	-.20				-.20*	-.17	-.20	
Openness	-.16*	-.14	-.12	.63 (.47–.85)**	.66 (.48–.91)*	.70 (.50–.97)*	-.23*	-.22*	-.23*				-.23*	-.22*	-.23*	
Agreeableness	-.12	-.10	-.11	.80 (.60–1.07)	.81 (.59–1.11)	.81 (.59–1.12)	-.09	-.08	-.09				-.09	-.08	-.09	
Conscientiousness	-.22**	-.17*	-.16*	.57 (.42–.78)**	.62 (.45–.85)**	.63 (.45–.89)**	-.26**	-.25*	-.30**				-.26**	-.25*	-.30**	

Notes. 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 = Includes age, sex, and time interval between personality and imaging; M3 = Includes M2 covariates, education and depressive symptoms. OR (95% CI) = Odds Ratios (95% Confidence Interval) from logistic regression with personality (z-scores) predicting risk of PiB+.

* p<.05

** p<.01.

Table 3. Characteristics of samples included in the amyloid (top panel) and tau (bottom panel) meta-analysis.

Study	Cohort or Institution, Country	N	Mean age	Female	AD biomarker	Cognitive status	Personality Measure
Amyloid							
Terracciano et al 2013	BLSA, US	84	72.4	38%	Postmortem	mixed	NEO-PI-R ^a
Snitz et al 2015	U. of Pittsburgh, US	92	81.2	49%	PET ¹¹ C-PIB	CN	NEO-FFI
Tautvydaite et al 2017	Lausanne U., CH	110	~70	~60%	CSF	CN + MCI	NEO-PI-R
Aschenbrenner et al 2020	DIAN, International	304	37.7	58%	PET ¹¹ C-PIB	mixed	IPIP-NEO ^b
Byun et al 2020	KBASE, KR	397	70.5	56%	PET ¹¹ C-PIB	CN + MCI	NEO-FFI
Giannakopoulos et al 2020	U. of Geneva, CH	65	74.2	63%	PET ¹⁸ F-Florbetapir	CN	NEO-PI-R ^c
Pichet Binette et al 2020	PREVENT-AD, CA	115	67.6	75%	PET [¹⁸ F]NAV4694	CN	BFI
Pichet Binette et al 2020	DIAN, International	117	34.6	55%	PET ¹¹ C-PIB	CN	IPIP-NEO ^b
Schultz et al 2020	WashU, US	128	66.7	61%	PET ¹⁸ FAV-45	CN	NEO-FFI
Yoon et al 2020	BACS, US	129	72.1	54%	PET ¹¹ C-PIB	CN	BFI
Graham et al 2021	RUSH, US	1375	89.6	68%	Postmortem	mixed	NEO ^d
Baena et al in press	COLBOS, CO	20	35.7	60%	PET ¹¹ C-PIB	CN	NEO-FFI
Current study	BLSA, US	196	78.6	50%	PET ¹¹ C-PIB	CN	NEO-PI-R
Tau							
Terracciano et al 2013	BLSA, US	84	72.4	38%	Postmortem	mixed	NEO-PI-R ^a
Tautvydaite et al 2017	Lausanne U., CH	110	~70	~60%	CSF	CN + MCI	NEO-PI-R
Aschenbrenner et al 2020	DIAN, International	304	37.7	58%	CSF	mixed	IPIP-NEO
Pichet Binette et al 2020	PREVENT-AD, CA	115	67.6	75%	PET ¹⁸ F-flortaucipir	CN	BFI
Schultz et al 2020	WashU, US	128	66.7	61%	PET ¹⁸ F-flortaucipir	CN	NEO-FFI
Graham et al 2021	RUSH, US	1375	89.6	68%	Postmortem	mixed	NEO ^d
Baena et al in press	COLBOS, CO	20	35.7	60%	PET ¹⁸ F-flortaucipir	CN	NEO-FFI
Current study	BLSA, US	95	76.9	56%	PET ¹⁸ F-flortaucipir	CN	NEO-PI-R

Notes. BACS = Berkeley Aging Cohort Study; BLSA = Baltimore Longitudinal Study of Aging; COLBOS = Colombia-Boston Longitudinal Biomarker Study; DIAN = Dominant Inherited Alzheimer Network; KBASE = Korean Brain Aging Study; PREVENT-AD = Evaluation of Experimental or Novel Treatments for AD; RUSH = Rush University, Memory and Aging Project and Religious Orders Study; U. = University; WashU = Knight Alzheimer Disease Research Center, Washington University; CA = Canada; CH = Switzerland; CO = Colombia; KR = South Korea; US = United States of

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America; PET = positron emission tomography; CSF = cerebrospinal fluid; ^{11}C -PIB = ^{11}C Pittsburgh compound B; MCI = Mild cognitive impairment; CN = Cognitively normal; mixed = CN, MCI and/or dementia; IPIP = International Personality Item Pool; BFI = Big Five Inventory; NEO-FFI = NEO-Five Factor Inventory; NEO-PI-R = NEO-Personality Inventory Revised.

^aThe BLSA postmortem study (15) included 84 participants for neuroticism, extraversion, and openness and 59 for agreeableness and conscientiousness; there was no overlap between the previous BLSA postmortem (15) and current PET sample.

^bEffect estimates for neuroticism and conscientiousness were from (43) while for extraversion, openness and agreeableness were from (25).

^cSixty-one ^{18}F -Flortetapir and four ^{18}F -Flutemetamol-PET.

^dRush ROS participants completed 6 items for Extraversion and 12 for each of the other traits. Openness and agreeableness were not assessed in MAP (16).

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use "this paper" if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources .	Include any additional information or notes if necessary.
Antibody	n/a			
Bacterial or Viral Strain	n/a			
Biological Sample	n/a			
Cell Line	n/a			
Chemical Compound or Drug	n/a			
Commercial Assay Or Kit	n/a			
Deposited Data; Public Database	Baltimore Longitudinal Study of Aging (BLSA), Humans, female and male		RRID:SCR_013148	NIA/NIH
Genetic Reagent	n/a			
Organism/Strain	n/a			
Peptide, Recombinant Protein	n/a			
Recombinant DNA	n/a			
Sequence-Based Reagent	n/a			
Software; Algorithm	n/a			
Transfected Construct	n/a			
Other	n/a			

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Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information