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Locus coeruleus catecholamines link neuroticism and vulnerability to tau pathology in aging

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Abstract

Higher neuroticism is a risk factor for Alzheimer's disease (AD), and is implicated in disordered stress responses. The locus coeruleus (LC)-catecholamine system is activated during perceived threat and is a centerpiece of developing models of the pathophysiology of AD, as it is the first brain region to develop abnormal tau. We examined relationships among the "Big 5" personality traits, LC catecholamine synthesis capacity measured with [^{18}F]Fluoro-m-tyrosine PET, and tau burden measured with [^{18}F]Flortaucipir PET in cognitively normal older adults (n = 47). β-amyloid (Aβ) status was determined using [^{11}C]Pittsburgh compound B PET (n = 14 Aβ positive). Lower LC catecholamine synthesis capacity was associated with higher neuroticism, more depressive symptoms as measured by the Geriatric Depression Scale, and higher amygdala tau-PET binding. Exploratory analyses with other personality traits revealed that

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Credit authorship contribution statement

Jourdan H. Parent: Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Claire J. Ciampa:** Formal analysis. **Theresa M. Harrison:** Formal analysis, Writing – review & editing. **Jenna N. Adams:** Formal analysis, Writing – review & editing. **Kailin Zhuang:** Investigation, Data curation, Project administration, Formal analysis. **Matthew J. Betts:** Conceptualization, Methodology, Validation, Resources, Supervision, Writing – review & editing, Funding acquisition. **Anne Maass:** Conceptualization, Methodology, Validation, Resources, Supervision, Writing – review & editing. **Joseph R. Winer:** Conceptualization, Methodology, Validation, Resources, Supervision, Writing – review & editing, Funding acquisition. **William J. Jagust:** Conceptualization, Methodology, Validation, Resources, Supervision, Investigation, Data curation, Project administration, Writing – review & editing, Funding acquisition. **Anne S. Berry:** Conceptualization, Methodology, Validation, Resources, Supervision, Investigation, Data curation, Project administration, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition.

Supplementary materials

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low trait conscientiousness was also related to both lower LC catecholamine synthesis capacity, and more depressive symptoms. A significant indirect path linked both high neuroticism and low conscientiousness to greater amygdala tau burden via their mutual association with low LC catecholamine synthesis capacity. Together, these findings reveal LC catecholamine synthesis capacity to be a promising marker of affective health and pathology burden in aging, and identifies candidate neurobiological mechanisms for the effect of personality on increased vulnerability to dementia.

Keywords

Locus coeruleus; Tau; Neuroticism; Conscientiousness; Aging

1. Introduction

Understanding why some individuals are differentially prone to the development of Alzheimer's disease (AD) is an area of active research that includes the analysis of personality traits. Studies linking personality with AD have demonstrated consistent associations between higher neuroticism and greater risk for dementia (Terracciano et al., 2014). Higher neuroticism is also associated with greater vulnerability to stress, anxiety, and depression (Bibbey et al., 2013; Kendler et al., 2004), which are themselves risk factors for dementia (Becker et al., 2018; Ownby et al., 2006). While the mechanisms by which personality confers increased AD vulnerability are manifold, neuroticism's relationship with affective risk factors may represent a principal pathway linking neuroticism and AD (Terracciano et al., 2014; Zufferey et al., 2017).

Previous research associating higher neuroticism with vulnerability to AD has highlighted chronic activation of stress pathways as a possible mechanism (Terracciano et al., 2014) given evidence that stress causally increases AD-related pathology in animal models (Sotiropoulos et al., 2011). To date, the majority of this work has focused on maladaptive activation of the hypothalamic-pituitary-adrenal axis, and resultant increases in glucocorticoids (Arenaza-Urquijo et al., 2020; Green et al., 2006). However, there are concomitant increases in activity in the locus coeruleus (LC)-catecholamine system (Rusnák et al., 2001), which heavily innervates the amygdala (Fallon et al., 1978). Stimulation of LC inputs to the amygdala increases anxiety-like behavior (McCall et al., 2017), and chronic stimulation of LC induces depression-like symptoms in rodent models (Omoluabi et al., 2021). In humans, perceived threat and emotional arousal increase pupil dilation (Bradley et al., 2008; Clewett et al., 2018), a common proxy for LC-catecholamine activity (Joshi et al., 2016). Human pupilimetry studies have implicated the LC-catecholamine system in trait neuroticism (Unsworth and Robison, 2017), and genetic studies have linked inferred reductions in catecholamine synthesis capacity with higher neuroticism (Tochigi et al., 2006).

The LC is one of the earliest regions to accumulate AD-related tau pathology (Braak et al., 2011), and may initiate the spread of tau pathology to connected regions (Iba et al., 2015; Jacobs et al., 2021). Our previous research established relationships between

higher temporal lobe tau pathology measured with [^{18}F]Flortaucipir (FTP) PET and lower LC-catecholamine synthesis capacity measured with [^{18}F]Fluoro-m-tyrosine (FMT; Ciampa et al., 2022). FMT, a substrate for aromatic amino acid decarboxylase, is an irreversible PET tracer sensitive to catecholamine (norepinephrine and dopamine) and monoamine (serotonin) synthesis. Our previous research found that LC catecholamine synthesis capacity predicted temporal lobe tau-PET signal, but we did not find associations between tau and either raphe serotonin synthesis capacity or dopamine synthesis capacity in the midbrain or striatum (Ciampa et al., 2022).

While the LC is considered an important biomarker for the early detection of AD processes (Betts et al., 2019; Matchett et al., 2021), there is a paucity of integrative research considering the ways in which the affective functions of the LC-catecholamine system may impact AD vulnerability (though see Omoluabi et al., 2021). It is possible that the chronic engagement of stress pathways in high-neuroticism individuals (Kruschwitz et al., 2015), including LC-amygdala interactions (Giustino et al., 2020), increases one's vulnerability to the accumulation of tau pathology. There is substantial tau pathology in the amygdala, even in cognitively normal older adults (Abiose et al., 2020). How elevated amygdala tau is associated with affective processes and lifestyle factors is an area of active research (Abiose et al., 2020), though previous work in aging has demonstrated higher amygdala tau pathology in individuals with higher trait neuroticism (Schultz et al., 2020). A recent meta-analysis examining relationships between personality traits and AD-related pathology identified higher neuroticism as the primary personality trait associated with higher pathology, with lower conscientiousness as secondary (see Terracciano et al. (2022) for a recent meta-analysis).

This study in cognitively normal older adults aimed to establish relationships between the LC-catecholamine system, neuroticism, and the development of AD-related tau pathology in the amygdala. Though our hypotheses centered on neuroticism given its clear link with stress and affective processes, exploratory analyses probed LC catecholamines' associations with trait conscientiousness, agreeableness, openness, and extraversion.

2. Methods

2.1. Participants

Participants were cognitively normal older adults (n = 47; mean age = 77.1 years, standard deviation (SD) = 5.9, range = 62–85, 27 females, mean years of education = 16.51 years, SD = 2.01, range = 12–20 years; Table 1) who underwent FMT PET to measure LC-catecholamine synthesis capacity, FTP PET to measure tau pathology, and[^{11}C]Pittsburgh compound B (PiB) PET to measure β-amyloid pathology (Fig. 1). Participants were recruited from the Berkeley Aging Cohort Study (BACS) (Wirth et al., 2013), scored at least 25 on the Mini-Mental State Exam (Folstein et al., 1975) (mean = 28.6, SD = 1.2), scored 10 or less on the Geriatric Depression Scale (GDS) (Yesavage et al., 1982) (mean = 4.00, SD = 3.1), and were characterized as cognitively normal (Berry et al., 2016). The study was approved by the Institutional Review Boards at the University of California, Berkeley and Lawrence Berkeley National Laboratory (LBNL). All subjects provided written consent. All participants in the current analyses were included in our previous report describing

relationships between LC FMT, memory, and temporal lobe FTP (Ciampa et al., 2022). One additional participant was excluded due to structural abnormality that interfered with segmentation and normalization, and one additional participant was excluded due to a gap of greater than 3 years between FMT and FTP PET scans.

2.2. Personality traits

We measured personality traits using the Big Five Inventory (BFI), a 44-item survey questionnaire, to measure neuroticism, conscientiousness, agreeableness, openness, and extraversion (John et al., 1991). Responses were rated on a 5-point Likert scale ranging from 1 =strongly disagree to 5=strongly agree and were summed for each trait.

2.3. Geriatric depression scale

We assessed depressive symptoms in older adults using the GDS (Yesavage et al., 1982), which is a 30-item (yes or no) self-report questionnaire validated for assessing depressive symptoms in older adults. FMT PET studies conducted with BACS only enrolled participants with a GDS of 10 or lower. Data were unavailable for subjects with higher GDS. No measure of self-reported anxiety was available for BACS participants.

2.4. Structural MRI acquisition and processing

Participants each underwent structural MRI within 1.5 years of neuropsychological testing. The median time difference between neuropsychological testing and MRI scanning was 139 days (SD = 85; range = 6–356). Structural MRI was acquired at Henry H. Wheeler Jr. Brain Imaging Center in a 3T TIM/Trio scanner (Siemens Medical System) using a 32-channel head coil. Whole-brain high resolution T_1-weighted volumetric magnetization prepared rapid gradient echo image (MPRAGE) scans were acquired (voxel size = 1 mm isotropic, TR = 2300 ms, TE = 2.98 ms, matrix = 256 × 240 × 160, FOV = 256 × 240 × 160 mm^3 , sagittal plane, 160 slices, 5 min acquisition time). MPRAGE images were processed in native space in FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer parcellations according to FreeSurfer's automatic subcortical segmentation (Fischl et al., 2002) were created for FTP PET analyses.

We generated a study-specific template using a standard pipeline in Statistical Parametric Mapping 12 software (SPM12, www.fil.ion.ucl.ak.uk/spm) to facilitate warping to MNI space. Each native space MPRAGE was segmented into gray matter, white matter, and CSF compartments using DARTEL. Native space MPRAGEs and tissue segments were warped to MNI152 Linear space using DARTEL at 2 mm isotropic resolution.

2.5. FMT PET acquisition and processing

Subjects underwent FMT PET scanning within 3 years of MRI scanning. The median time difference between FMT PET and MRI scanning was 93 days (SD = 285; range = 5–967) and the median time difference between FMT PET and neuropsychological testing was 231 days (SD = 250; range = 42–1099).

All PET imaging was performed at Lawrence Berkeley National Laboratory using a Siemens Biograph Truepoint 6 PET/CT scanner (Siemens Medical System). Participants underwent a

FMT PET scan and ingested 2.5 mg/kg of carbidopa ~1 h before scanning to minimize peripheral decarboxylation of FMT. Participants underwent a short CT scan and then received a bolus injection of approximately 2.5 mCi of FMT. Dynamic acquisition frames were obtained over 90 min in 3D mode (25 frames total: 5 × 1 min, 3 × 2 min, 3 × 3 min, 14 × 5 min). All PET images were reconstructed using an ordered subset expectation-maximization algorithm, with attenuation correction, scatter correction, and smoothing using a Gaussian kernel of 4 mm. PET data underwent a standard preprocessing in SPM12 as previously described by Ciampa et al. (2022). These steps include realignment to the middle (12th) frame for motion correction, averaging, and coregistration to 3T structural images using the mean image of frames corresponding to the first 20 min of data acquisition. Patlak plotting was used to perform graphical analysis for irreversible tracer binding (Patlak and Blasberg, 1985) using a primary visual cortex (lingual gyrus and cuneus) reference region. FMT binding was quantified as net tracer influx (Ki), quantifying the amount of tracer accumulation in the brain relative to the reference region in frames corresponding to 25 to 90 min of acquisition (Ciampa et al., 2022). Ki can be expressed as $Ki = k_2k_3/(k_2+k_3)$, where k_2 is the rate constant for the return of free FMT from brain back to plasma and k_3 is the rate constant for the trapping of brain FMT by AADC. Native space FMT Ki maps were then coregistered and resliced to native space structural scans and warped to MNI152 linear space using DARTEL. Primary FMT analyses relied on a MNI-space LC ROI developed from six existing LC templates (Dahl et al., 2022) that we previously described (Ciampa et al., 2022) (Fig. 2A; ROI available: https://neurovault.org/collections/MPDBCZKT/). Briefly, accurate coregistration to MNI space FMT Ki maps (nearest-neighbor interpolation) was confirmed in Mango (https://www.nitrc.org/projects/mango/). The template was then resliced to match FMT Ki map voxel dimensions. To accommodate PET resolution, we smoothed the MR-derived LC ROI (4 mm FWHM) and thresholded (>0.147) to generate a mask of 479 1 × 1 × 1 mm voxels, which is approximately 6x the size of the original.

FMT is also sensitive to the synthesis capacity of serotonin in the raphe nuclei. While our previous research did not reveal associations between raphe FMT and temporal lobe FTP (Ciampa et al., 2022), we report secondary analyses focused on the raphe-serotonin system for completeness, given the relevance of this system to affective function (Donaldson et al., 2014), connections to the amygdala (Steinbusch, 1981), and associations with neuroticism (Frokjaer et al., 2008, 2010). Analyses measured FMT in the dorsal raphe (Kranz et al., 2012) using an unsmoothed ROI that has previously been used in PET imaging (Doppler et al., 2021) (ROI available: https://neurovault.org/collections/MPDBCZKT/; Fig. 2A).

2.6. PiB PET and FTP PET acquisition and processing

All participants underwent PiB PET scanning to assess β-amyloid status and FTP PET scanning to measure tau pathology within 3 years of their FMT scan. The median time difference between FMT and PiB scans was 170 days (SD = 197; range = 9–791). The median time difference between FMT and FTP scanning was 170 days (SD = 241; range = 9–945). The median time difference between MRI and FTP scanning was 154 days (SD = 166; range = 3–813).

A detailed description of PiB and FTP acquisition has been published previously (Schöll et al., 2016). After PiB injection, dynamic frames were collected for 90 min. These frames were realigned, coregistered, and resliced to the 3T structural T1. Distribution volume ratio (DVR) was calculated using a Logan graphical analysis on frames corresponding to 35–90 min post-injection using a cerebellar gray reference region and mean gray matter DVR was computed. A threshold of 1.065 was used to determine positive or negative amyloid status (Mormino et al., 2012; Villeneuve et al., 2015). There were 14 PiB positive individuals in this study.

FTP Standardized uptake volume ratio (SUVR) images were created based on mean tracer uptake over 80–100 min post-injection normalized using an inferior cerebellar gray reference region. As previously described (Ciampa et al., 2022), SUVR images were partial volume corrected on native space FreeSurfer-derived ROIs (Baker et al., 2017). For analyses of relationships between neuroticism, LC catecholamine synthesis capacity, and tau burden, FTP SUVR was measured within bilateral amygdala ROIs. For completeness, we performed parallel analyses using FTP measures in bilateral entorhinal cortex (EC) ROIs as this region is an early tau-accumulating region, shows uptake in cognitively normal older adults, and is commonly used as the dependent variable in tau-PET studies in aging (Maass et al., 2018). All ROIs were defined by native-space FreeSurfer Desikan-Killiany parcellations (Desikan et al., 2006).

2.7. Statistical analyses

We first performed Shapiro-Wilk tests of normality following removal of two outlier values to determine data distribution. Outliers were identified using ROUT outlier identification ($Q = 1\%$) in GraphPad Prism version 9.1.0 for MacOS (GraphPad Software, San Diego, California USA, www.graphpad.com). Pearson's correlations assessed relationships among GDS, neuroticism, LC FMT, amygdala FTP, and a set of secondary control variables including raphe FMT Ki, EC FTP, and the other four BFI personality traits. Analyses of relationships between LC FMT and neuroticism and GDS and exploratory analyses involving conscientiousness, extraversion, agreeableness and openness were corrected for multiple comparisons using FDR correction. Non-corrected 95% bootstrapped confidence intervals are reported with FDR-corrected p-values. Next, we computed full regression models adjusting for age, sex, years of education, PiB status, and time between measures if not collected on the same date. We report simple correlations in addition to full models due to concerns of model overfitting given the relatively small sample, so that the reader can discern the effect of covariates on our results. Our primary hypotheses center on LC's associations with neuroticism and amygdala tau. For parallel analyses involving raphe serotonin synthesis capacity and EC tau, we formally test the difference between correlation coefficients (overlapping correlations based on dependent groups) using the 'cocor' Package in RStudio (Version 1.2.1335; RStudio, Inc.). Exploratory analyses with each BFI personality trait include correction for multiple comparisons that account for the other four BFI personality traits. For all correlations and regression models we computed 95% bootstrapped unstandardized confidence intervals using simple sampling procedures. Descriptive statistics, correlations, regressions were computed using SPSS v28.0.0 (IBM

Corp). Exploratory path analyses were performed using PROCESS module v4.0 (Hayes, 2013).

3. Results

Table 1 shows the descriptive statistics for all variables. Approximately 30% of the sample was PiB positive ($n = 14$). PiB positive and negative older adults were analyzed together as there were no significant differences between groups for the variables of interest. Specifically, there were no differences between PiB positive and PiB negative participants for GDS, trait neuroticism, amygdala FTP, or LC FMT (Table 1). Post hoc analyses found PiB status did not interact with LC FMT to predict neuroticism, GDS or amygdala tau (all $p > .28$). Additionally, there were no significant differences between men and women for the variables of interest (Table 1). Post hoc analyses found sex did not interact with LC FMT to predict neuroticism, GDS or amygdala tau (all $p > .10$).

3.1. LC catecholamine synthesis capacity is related to neuroticism and depressive symptoms

Consistent with previous reports (Bibbey et al., 2013; Kendler et al., 2004), higher neuroticism was associated with more depressive symptoms as indicated by higher GDS score ($r = .66$, 95% bootstrapped Confidence Interval (CI) [.47, .81], $p = <.001$; Fig. 2B). This relationship remained significant following adjustment for covariates (Table 2A).

Consistent with our hypotheses, lower LC FMT was associated with higher neuroticism ($r = -.38$, CI [−.58, −.13] $p = .012$ FDR corrected; Fig. 2C) and higher GDS score ($r = -.37$, CI [−.58, −.14], $p = .012$ FDR corrected; Fig. 2D). Both relationships survived adjustment for covariates (Table 2B,C).

3.2. Serotonin synthesis capacity in the raphe is marginally related to neuroticism

Secondary analyses found that the relationship between raphe FMT and neuroticism was marginal ($r = -.31$, CI [−.55,−.01], $p = .082$ FDR corrected, Fig. 2E). The relationship with GDS was not significant (GDS: $r = -.16$, CI [−.43, .11], $p = .283$ FDR corrected, Fig. 2F). Correlation coefficients for analyses involving LC FMT were not statistically different from those involving raphe FMT (neuroticism: r difference = −.07, Pearson and Filon's $Z = -0.52$, $p = .60$; GDS: r difference = −.20, Pearson and Filon's $Z = -1.47$, $p = .14$).

3.3. Amygdala tau is directly related to LC catecholamine synthesis capacity but not neuroticism

Amygdala FTP was not directly related to neuroticism ($r = .13$, CI [−.12, .38], $p = .51$, FDR corrected; Fig. 3A) or GDS ($r = .11$, CI [−.22, .42], $p = .51$ FDR corrected; Fig. 3B). We did, however, find an association between higher amygdala FTP and lower LC FMT ($r = -.35$, CI [−.59, −.04], $p = .028$; Fig. 3C). This relationship remained significant following adjustment for covariates (Table 3A). A model including an interaction term (PiB status* LC FMT revealed no significant interaction between FMT and PiB ($p = .81$) suggesting that these relationships were not driven by PiB status. Consistent with our previous research (Ciampa et al., 2022), we did not find a significant association between raphe FMT and amygdala

FTP (r = .05, CI [−.24, .33], p = .74; Fig. 3D). A test of the difference of correlations for amygdala FTP with LC FMT and raphe FMT revealed that these correlations were significantly different from one another (r difference = −.40, Pearson and Filon's Z = −2.72, p=.007).

3.4. LC catecholamine synthesis capacity represents an indirect path linking neuroticism with amygdala tau

Relationships between higher neuroticism and higher amygdala FTP PET binding have been previously reported in aging (Schultz et al., 2020), but were not present in the current dataset. Post hoc exploratory analyses probed LC FMT's mutual association with these variables to test the possibility that lower LC catecholamine synthesis capacity represents a significant pathway associating higher neuroticism with higher amygdala FTP (neuroticism → LC FMT → amygdala FTP (Hayes, 2013). Implicit in this model is the idea that neuroticism can affect the regulation of the LC-catecholamine system. Testing this possibility using model 4 of the PROCESS module v4.0 (Hayes, 2013), we identified a signficiant indirect path suggesting neuroticism is related to amygdala tau through their associations with LC FMT (Table 3B). This path analysis was significant following adjustment for covariates. We did not find significant pathways using control variable raphe FMT (Table 3C).

3.5. Neuroticism is not related to entorhinal cortex tau

Primary analyses focused on amygdala tau as our hypotheses centered on models linking amygdala, LC, and neuroticism in stress responsivity. For completeness, we report parallel analyses for EC FTP given EC is an early tau accumulating region and is ubiquitously reported in tau-PET studies of aging (Harrison et al., 2019; Jacobs et al., 2021), and has been implicated in affective processing via connectivity with the amygdala (Ritchey et al., 2008). EC FTP was not directly related to neuroticism (r = .20, CI [−.09, .44], p = .23, FDR corrected) or GDS (r = .32, CI [−.05, .57], p = .09 FDR corrected). There was no association between EC tau and lower LC FMT (r = −.07, CI [−.33, .20], p = .68). A model including an interaction term (PiB status* LC FMT revealed no significant interaction between FMT and PiB (p = .34). Tests of the difference of correlations for LC FMT relationships with amygdala FTP compared to with EC were marginal EC (r difference = −.26, Pearson and Filon's Z = −1.89, p = .059). Finally, we performed parallel path analyses as reported above neuroticism → LC FMT → EC FTP and found no indirect path linking neuroticism and EC FTP (Table 3D).

3.6. Exploratory analyses using other Big 5 personality traits

A priori analyses focused on neuroticism given our strong predictions based on its association with psychopathology and its role as a risk factor for dementia. Here we report exploratory analyses for the other Big 5 personality traits: conscientiousness, agreeableness, openness, and extraversion. These analyses specifically probe relationships with GDS, LC FMT, and amygdala tau pathology to form the basis for future hypothesis testing.

Together, these exploratory analyses revealed conscientiousness to be a personality trait of particular interest as individuals with lower conscientiousness showed high GDS (r = −.47,

CI [−.67, −.20], p = .003 FDR corrected; Fig. 4A) and low LC FMT (r = .39, CI [.14, .60], p = .028 FDR corrected; Fig. 4B), which is the same pattern of results identified for high neuroticism individuals. These findings survived adjustment for covariates (Table 4A,B). Relationships between other personality traits and GDS and LC FMT did not reach statistical significance (Openness r = .29, FDR corrected p = .087; all other |r| < .25, FDR corrected p = > = .16). Raphe FMT was not related to conscientiousness (r = .09, CI [−.18, .37], p = .57 FDR corrected) or the other personality traits (all |r| ⟨ .31, FDR corrected p ⟩ .10).

Similar to neuroticism, conscientiousness was not directly related to amygdala tau pathology (r = −.004, CI [−.40, .39], p = .98 FDR corrected; Fig. 4C). Like neuroticism, there was a signficiant indirect path relating conscientiousness and amygdala tau through their mutual associations with LC FMT (Table 4C). These findings were significant following adjustment for covariates. Analyses substituting raphe FMT or EC tau were not significant (Table 4D,E).

4. Discussion

This study marries two prominent lines of AD-related research: the role of personality traits in conferring risk of dementia, and the role of the LC in the early pathophysiology of AD. A summary graphic of our findings is depicted in Fig. 5. We found that lower LC catecholamine synthesis capacity was associated with higher neuroticism, more depressive symptoms, and higher amygdala tau burden. Exploratory analyses identified similar patterns of associations with low conscientiousness, another personality trait implicated in dementia risk and elevated AD-related pathology burden (Terracciano et al., 2022). While interrelationships among these measures are complex, our findings identify reduced LC catecholamine synthesis capacity as a central arbiter of both neuroticism's and conscientiousness' relationship with amygdala tau burden. Together, these findings contribute to a developing model by which low LC catecholamine synthesis coincides with vulnerability to affective dysregulation and tau burden within the amygdala.

Our findings are consistent with previous research suggesting a role of the LC-catecholamine system in neuroticism. Pupillometry (Unsworth and Robison, 2017) and genetic studies (Tochigi et al., 2006) have previously implicated the LC-catecholamine system in trait neuroticism. To our knowledge, this is the first study to demonstrate a relationship between an endogenous measure of LC neurochemical function and neuroticism. Our exploratory analyses identified a relationship between lower conscientiousness and higher LC catecholamine synthesis capacity. Low trait conscientiousness is associated with poor executive function (Bell et al., 2020; Fleming et al., 2016), which is consistent with LC's role in attention (Aston-Jones et al., 1999; Sara, 2009). While a previous pupillometry study has implicated the LC in individual differences in trait conscientiousness (Wright et al., 2013), the observed relationship between conscientiousness with an endogenous measure of LC catecholamine function is novel and warrants future investigation.

Individuals with more depressive symptoms were also more neurotic and had lower LC-catecholamine synthesis capacity. These findings are supported by a substantial body of work linking neuroticism with psychopathologies including depression (Bibbey et al., 2013; Kendler et al., 2004) as well as research implicating the LC-catecholamine system in depression (Ressler and Nemeroff, 1999). The positive relationship between neuroticism and depression is not surprising given that self-reported depressive symptoms contribute to trait neuroticism scores. While we had strong *a priori* hypotheses regarding the role of higher neuroticism in affective function, lower conscientiousness was similarly related to more depressive symptoms. This has been demonstrated before (Klein et al., 2011) with suggestion that high conscientiousness is protective against daily-life controllable stressors and low conscientiousness (i.e. low executive function) increases exposure to stressful and depressogenic experiences (Bartley and Roesch, 2011; Gartland et al., 2014; Roberts and Bogg, 2004; Snyder et al., 2019; Snyder and Hankin, 2016). It is necessary to highlight here that we identified these relationships in non-depressed individuals with a restricted range in GDS scores (0–10), which limits our ability to extend these findings to the general population where there is a broad range of depression symptoms. Future research is needed to assess the extent to which LC-catecholamine measures are associated with clinical depression, which would be timely given increasing appreciation of the complexity of neuromodulator contributions to affective disorders (Moncrieff et al., 2022). There is emerging *in vivo* neuroimaging evidence that depression is accompanied by reductions in LC structural integrity (Liu et al., 2017), which are also observed across the AD spectrum (Betts et al., 2019). LC neuroimaging biomarker development will benefit from conjoint consideration of these pathways as the LC may be a target for both psychiatric and pathologic processes.

Future longitudinal analyses with larger samples and parallel studies in animal models will be critical for clarifying the extent to which LC catecholamine function changes across the lifespan and is, itself, altered by neuroticism, chronic stress and the development of tau pathology. Such studies would provide context to aid in the interpretation of the origin of low LC-catecholamine synthesis capacity and potential for therapeutic intervention. Catecholamine systems are highly regulated, and synthesis rates may be reduced in response to greater tonic activity of LC or upregulation of beta adrenergic receptors, as there are known mechanisms of feedback inhibition to suppress catecholamine synthesis (Tekin et al., 2014). How LC catecholamine synthesis capacity is related to catecholamine release (Berry et al., 2018) or density of beta adrenergic receptors in the amygdala is not known. A comprehensive understanding of this system will facilitate the integration of these findings with the greater animal literature, which finds upregulation of norepinephrine synthesis in response to novel stress (Rusnák et al., 2001), and human clinical studies which suggest sensitization of the LC-norepinephrine system in affective disorders (Naegeli et al., 2018).

LC is at the center of active lines of research establishing its early role in the pathophysiology of AD (Matchett et al., 2021). However, it is worth noting that abnormal tau within the LC is present in most middle-aged adults (Braak et al., 2011; Pletnikova et al., 2018). Its early occurrence makes it an attractive target for intervention, though it remains an open question to what extent LC tau is simply a feature of aging versus a meaningful signal of accelerating pathological processes. The majority of *in vivo* studies

in humans have focused on structural measures of LC integrity (Betts et al., 2019), though see Lui et al. (2021), and have demonstrated associations between elevated tau burden and reductions in LC integrity (Dahl et al., 2022; Jacobs et al., 2021, 2021). Our research assessing neurochemical function of the LC complements this work by demonstrating associations between elevated tau burden in the amygdala and lower LC catecholamine synthesis capacity. The relationship between LC catecholamine synthesis capacity and EC tau was not significant, though formal testing of the difference between LC-amygdala vs LC-EC relationships was only marginal ($p = .06$). Additional research will be necessary for determining the extent to which LC neurochemical measures like FMT are preferentially related to amygdala tau rather than EC tau given their interconnections and mutual contributions to affective processing and memory (Ritchey et al., 2008). It is possible signaling from the amygdala to LC (Cedarbaum and Aghajanian, 1978; Wallace et al., 1989) drives alterations in LC neurochemical health, strengthening observed relationships between amygdala tau burden and LC catecholamine synthesis capacity across individuals.

We did not find that LC catecholamine synthesis capacity interacted with Aβ status to predict tau as we have found previously for analyses in which tau pathology was measured within a larger tau “meta” ROI comprised of 6 temporal lobe regions vulnerable to tau pathology (Jack et al., 2017). The observation that the association between LC-catecholamine synthesis capacity and amygdala tau burden was not dependent or limited to Aβ positive individuals is noteworthy and suggests the effects we describe may not be specific to AD mechanisms when considering tau in the amygdala. This possibility warrants further investigation given how little research attention amygdala tau has received (relative to EC) given the high levels of amygdala tau-PET binding in aging.

Here, and in our previous research, we have not found associations between raphe serotonin synthesis capacity and tau burden. There is comparatively little focus on raphe as a key player in the etiology of AD tau spread (Grinberg et al., 2009) despite observations that the dorsal raphe is also vulnerable to tau pathology (Ehrenberg et al., 2017; Grinberg et al., 2009). There is a need for systematic research in this area to understand the converging and diverging pathologic trajectories of raphe and LC nuclei and their possible role in accelerating disease spread.

The current study is not able to determine the directionality of effects among personality traits, depression symptoms and LC catecholamine function. A recent report in rats provides support for the feasibility of a model by which affective dysregulation can exacerbate effects of tau pathology in the LC. Omoluabi et al. (2021) examined the effect of a LC stimulation protocol designed to mimic chronic stress conditions using a rat model of LC pretangle tau. Daily tonic LC stimulation induced depression-like behavior in rats and was associated with anatomical degradation of the LC. In contrast, a daily phasic LC stimulation protocol designed to mimic activity associated with novelty was associated with positive cognitive outcomes and preservation of the LC. Together, these findings shed light on the specific harm of chronic stress and suggest that both depression and the advancement of tau pathologic processes are related to tonic LC activity. Additional work is needed to extend our understanding of mechanisms linking chronic stress with progression of tau pathology to include prefrontal cortex-amygdala circuits specifically (Liu et al., 2020)

There are other mechanisms by which higher neuroticism and lower conscientiousness may be associated with greater tau pathology and risk of dementia including effects on behavior and neural systems. We highlight some of these mechanisms, and their connection to the LC-catecholamine system. For example, higher neuroticism and lower conscientiousness are associated with health and lifestyle factors associated with AD such as reduced tendency to exercise (Courneya and Hellsten, 1998; Kummer et al., 2021). Our previous research identified a relationship between a self-report measure of cognitive and physical engagement across the lifespan, the Lifetime Experiences Questionnaire (Valenzuela and Sachdev, 2007), and higher LC catecholamine synthesis capacity (Ciampa et al., 2022). Indeed, physical exercise is associated with increases in norepinephrine synthesis (Gordon et al., 1966) and basal levels of norepinephrine in brainstem and amygdala (Chaouloff, 1989). Effects of personality on inflammation may also contribute to AD risk, as higher trait neuroticism and lower conscientiousness are associated with elevated inflammatory cytokines (Sutin et al., 2010; Turiano et al., 2013). Low LC catecholamine function may contribute to or worsen the effects of personality on inflammation as norepinephrine has known anti-inflammatory functions (Feinstein et al., 2002).

This study has limitations. There was a relatively low number of participants, which limited our ability to probe effects of Aβ status and possible sex differences. Women are uniquely vulnerable to both mood disorders and AD (Altemus et al., 2014; Laws et al., 2018), which makes the LC-catecholamine system's role in affective function and AD risk a promising target for future research. The cross-sectional data and long time periods between PET and behavioral testing sessions limit our ability to interpret directionality of effects within our exploratory path analyses. Fortunately, adjusting for time between testing session does not affect statistical significance within our regression models. While FMT PET imaging of the LC has supported interpretable findings relevant to cognition and tau pathology in aging (Ciampa et al., 2022), addition of complementary perfusion measures and additional consideration around partial volume effects is needed particularly for the extension of FMT PET in patient populations.

The identification of personality and lifestyle factors that increase risk of AD, and the investigation of the biological mechanisms underlying the conferral of risk represent critical fields of research because of their potential for identifying targets for intervention (McGurran et al., 2019, Bachman et al., 2022). Early intervention may be particularly effective in reducing risk associated with personality traits relevant to stress reactivity as these traits may interact with LC neurochemical function, and tau pathology in older age to create a "vicious cycle" (Justice, 2018). Amygdala tau pathology may cause changes in affective function, increasing neuroticism and disrupting noradrenergic function. Behavioral training (Hoge et al., 2013) or pharmacological control (Sheline et al., 2014) of stress reactivity in early life may prevent this cycle by reducing activity within otherwise well-worn affective pathways involving the LC and amygdala, thus reducing tau spread in aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Metadata are provided in supplementary information. Raw data are available following data use agreement. LC and Raphe ROIs are available at https://neurovault.org/collections/MPDBCZKT/.

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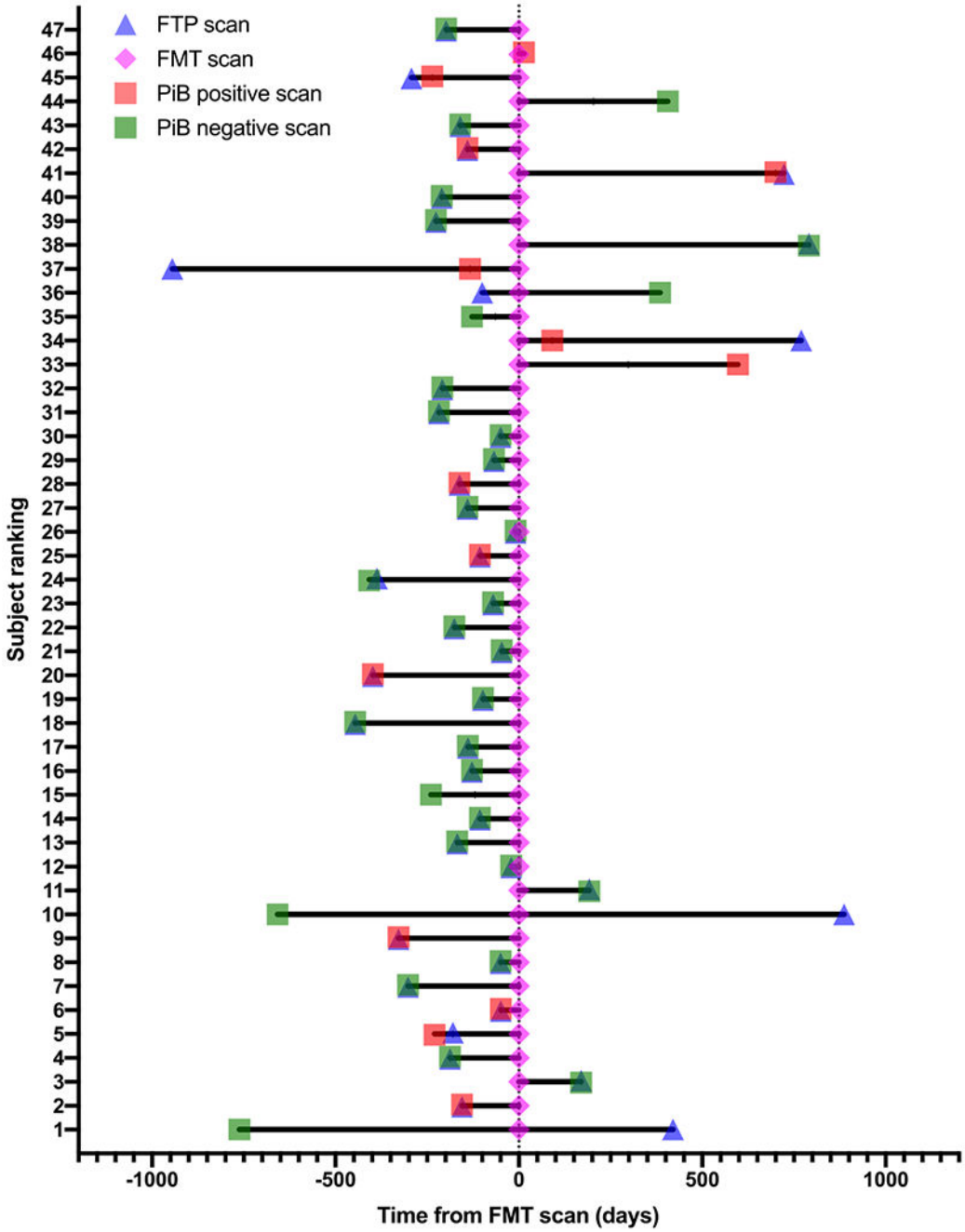

Fig. 1. Plot of the time from FMT scan.

Individual subject data are plotted to display the temporal relationship of FTP PET (blue), PiB negative PET (green), and PiB positive PET (red) relative to FMT PET (pink). Subjects are ranked by LC FMT value for (1 = lowest, 47 = highest). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

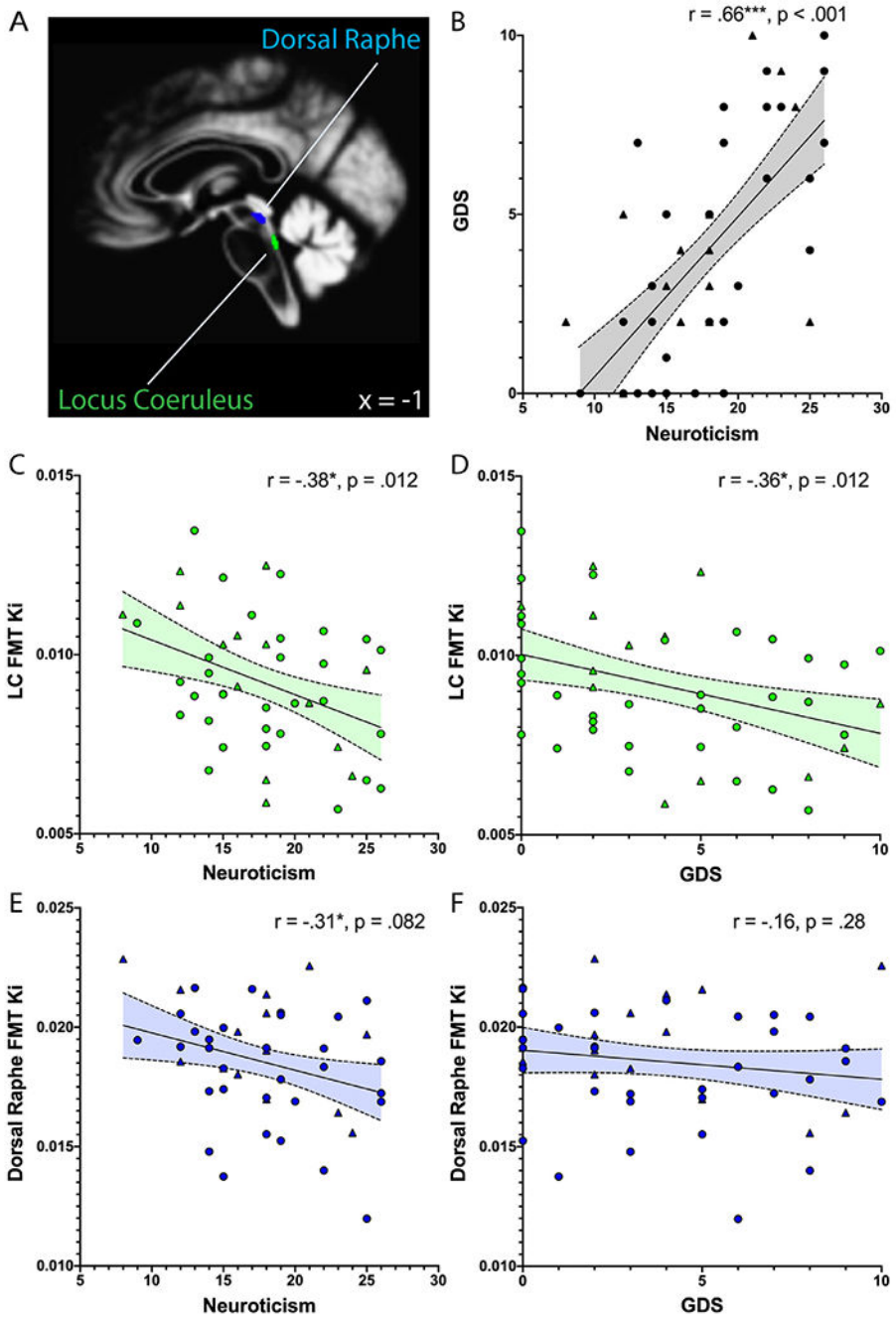

Fig. 2. Relationships among neuroticism, FMT, and Geriatric Depression Risk.

(A) Scatterplot of correlation between neuroticism and GDS scores. (B) dorsal raphe (blue) and locus coeruleus (LC) (green) regions-of-interest overlayed on sample-specific older adult template brain. (C-D) Scatterplots show LC FMT relationship with neuroticism (C) and GDS (D). (E-F) Scatterplots show dorsal raphe FMT relationship with neuroticism (E) and GDS (F). 90% confidence intervals are depicted. Circles indicate PiB negative individuals, triangles indicate PiB positive individuals. *$p < .05$, **$p < .01$, ***$p < .001$.

(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

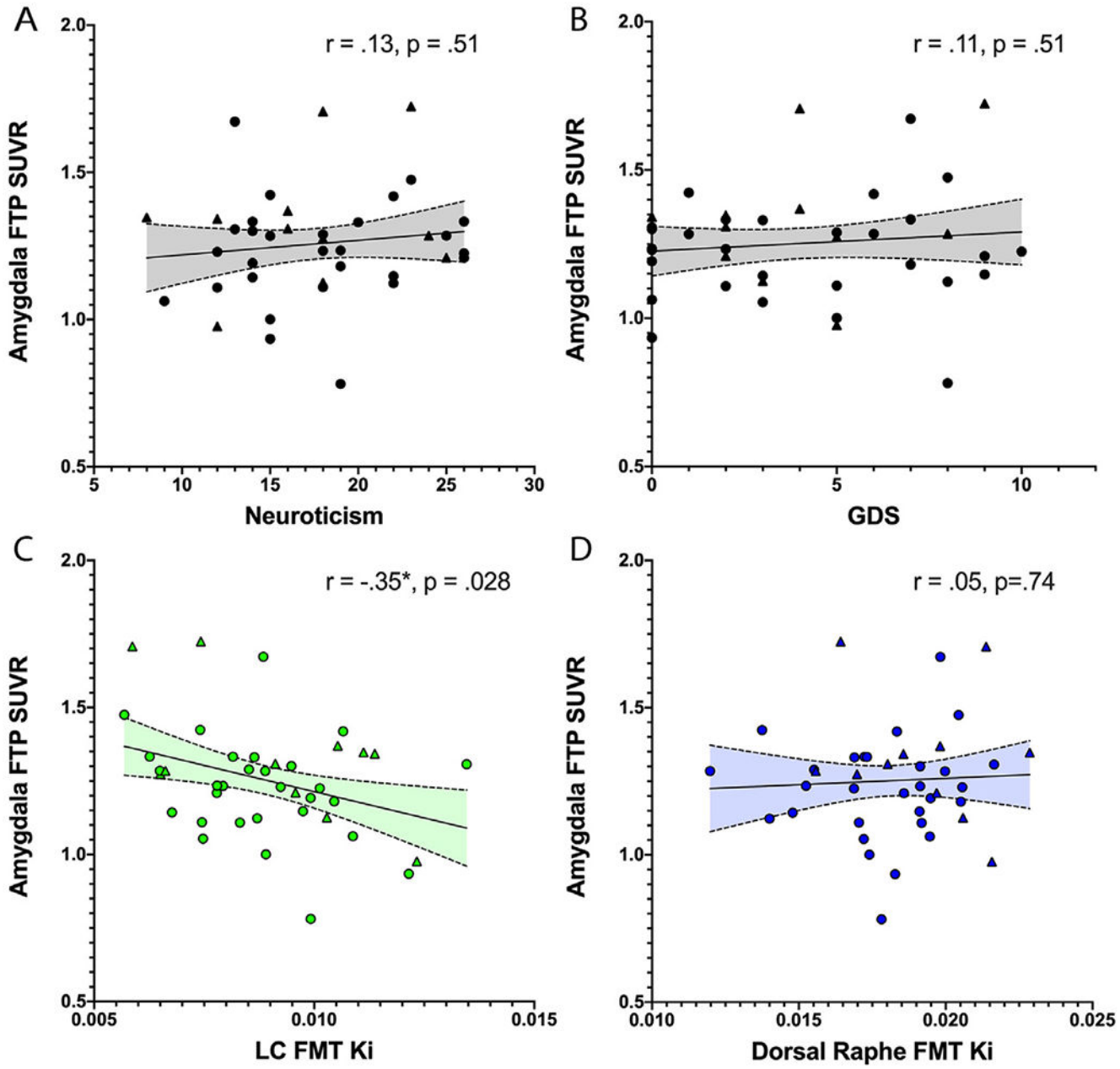

Fig. 3. Relationships among neuroticism, FMT and amygdala FTP.

(A) Scatterplot of correlation between neuroticism and amygdala FTP. (B) Scatterplot of correlation between GDS and amygdala FTP. (C) Scatterplots show LC FMT relationship with amygdala FTP. (D) Scatterplots show raphe FMT relationship with amygdala FTP. 90% confidence intervals are depicted. Circles indicate PiB negative individuals, triangles indicate PiB positive individuals. *$p < .05$.

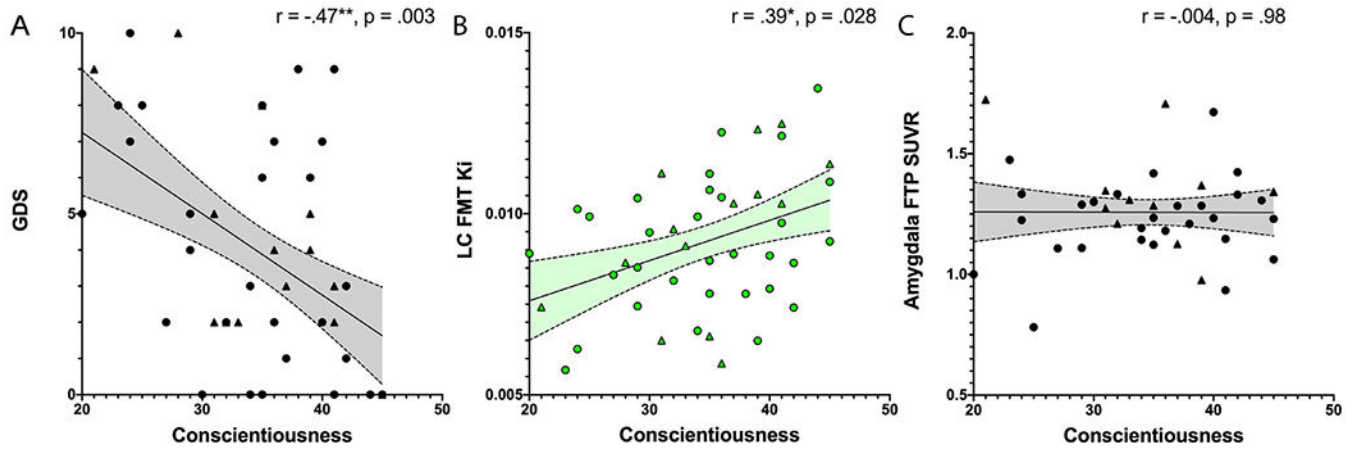

Fig. 4. Relationships among conscientiousness, LC FMT, and amygdala FTP.

(A) Scatterplot of correlation between conscientiousness and GDS. (B) Scatterplot of correlation between conscientiousness and LC FMT. (C) Scatterplot of the relationship between conscientiousness and amygdala FTP. 90% confidence intervals are depicted. Circles indicate PiB negative individuals, triangles indicate PiB positive individuals. *$p <$ .05, **$p <$ .01.

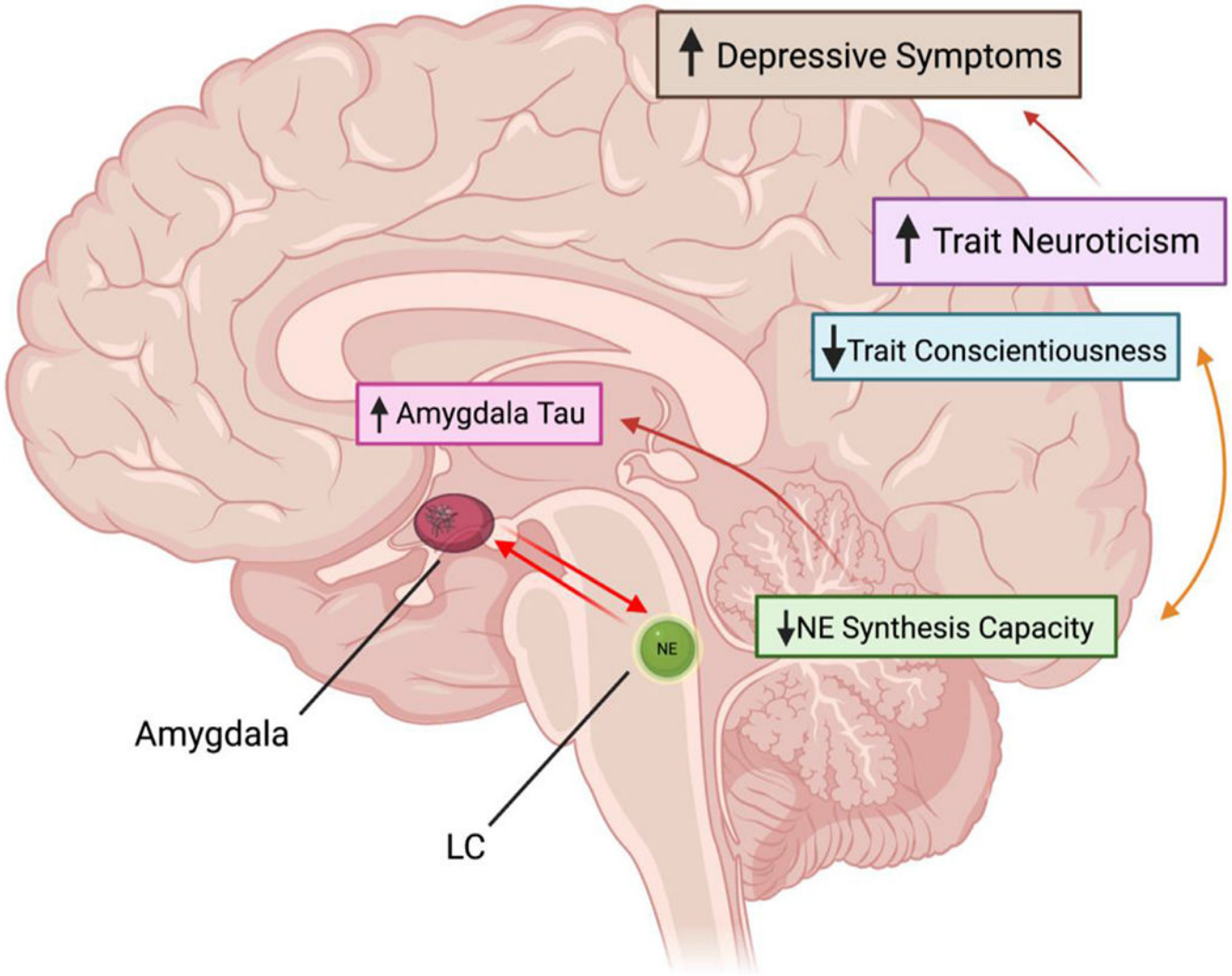

Fig. 5. Bidirectional model of locus coeruleus catecholamine synthesis and personality traits.

We propose that relations between personality traits and catecholamine synthesis in the locus coeruleus (LC) has several implications in aging. Personality traits that affect an individual's sensitivity or exposure to stress may contribute to reductions in LC catecholamine synthesis. Altered LC catecholamine function and engagement of LC-amygdala pathways may then result in increased tau accumulation in the amygdala. Additionally, amygdala tau accumulation may cause decreases in LC catecholamine synthesis, which, in turn, may alter cognitive and affective function. NE = norepinephrine.

Table 1

Sample demographics and descriptive statistics.

Variable	N[b] (%)	Mean	SD	Range (possible Range)	Difference by PiB status[c] t (p)	Difference by sex[d] t (p)
Age	47	77.06	5.86	62–85	1.38 (.17)	0.84 (.41)
Sex						
Male	20 (42.6)					
Female	27 (57.4)					
Race and ethnicity						
White/Non-Hispanic	40 (85.1)					
White/Hispanic	1 (2.1)					
Black or African American/Non-hispanic	3 (6.4)					
Asian	3 (6.4)					
Years of education	47	16.51	2.01	12–20	0.13 (.89)	−0.61 (.54)
MMSE	47	28.64	1.24	25–30	−1.55 (.13)	−0.89 (.38)
GDS	47	4.00	3.14	0–10 (0–10)	0.30 (.76)	−0.19 (.85)
Big five personality traits						
Neuroticism	45	17.84	4.72	8–26 (8–40)	−0.39 (.70)	−0.56 (.58)
Conscientiousness	45	34.56	6.64	20–45 (9–45)	0.25 (.80)	−0.95 (.35)
Agreeableness	45	36.29	4.23	27–45 (9–45)	−0.77 (.45)	−1.34 (.19)
Openness	45	38.56	6.29	26–49 (10–50)	0.57 (.57)	0.089 (.93)
Extraversion	45	29.16	6.17	17–40 (8–40)	1.31 (.20)	−0.29 (.77)
FMT PET						
LC Ki	47	0.0091	0.0019	0.0057–0.013	0.68 (.50)	−1.01 (.32)
Raphe Ki	47	0.019	0.0024	0.012–0.023	1.58 (.12)	−1.62 (.11)
FTP PET						
Amygdala SUVR	40	1.25	0.19	0.78–1.72	1.70 (.10)	1.21 (.23)
Entorhinal cortex SUVR	40	1.24	0.20	0.88–1.95	1.29 (.20)	−0.35 (.73)
PiB PET	47					
PiB DVR positive	14 (29.8)					
PiB DVR negative	33 (70.2)					

[b] N's reflect available data points after ROUT outlier analysis (Q = 1%), 1 EC FTP, 1 amygdala FTP datapoint removed.

[c] PiB positive = 1, PiB negative = 0.

[d] male = 1, female = 0.

Table 2

Linear regression models.

Model outcome variable		B	Bootstrap[a]				
			Bias	Std. error	Sig. (2-tailed)	95% Confidence interval	
						Lower	Upper
A. GDS	(Constant)	−10.51	−0.056	5.85	.075	−21.73	1.74
	Neuroticism	**.46**	**.001**	**.089**	**<0.001**	**.28**	**.64**
	Age	.047	.002	.061	.436	−0.083	.16
	PiB Status[c]	.47	−0.043	.85	.573	−1.28	2.11
	Sex[b]	.18	−0.068	.73	.808	−1.34	1.57
	Years of Education	.15	−0.002	.19	.450	−0.22	.54
B. GDS	(Constant)	4.49	.34	7.059	.531	−8.59	18.15
	LC FMT	**−597.20**	**7.31**	**212.80**	**.005**	**−964.84**	**−141.94**
	Age	.080	−0.006	.076	.275	−0.089	.22
	PiB Status[c]	.43	.045	.95	.632	−1.41	2.30
	Sex[b]	−0.70	−0.066	.99	.462	−2.57	1.25
	Years of Education	−0.058	.006	.21	.771	−0.44	.40
	Days between FMT PET and Neuropsych	−0.00046	.000064	.001	.605	−0.002	.002
C. LC FMT	(Constant)	**.011**	**.0002**	**.005**	**.029**	**.002**	**.021**
	Neuroticism	**−0.00014**	**.0000038**	**.000071**	**.046**	**−.00027**	**−0.0000081**
	PiB Status	.00032	−0.000085	.001	.570	−0.001	.001
	Age	−0.0000040	−0.0000033	.000048	.946	−0.000098	.000092
	Sex[b]	−0.001	.000023	.001	.200	−0.002	.00030
	Years of Education	.000046	−0.0000016	.00017	.775	−0.00033	.00032
	Days between FMT PET and Neuropsych	.00000076	.000000048	.00000091	.381	−0.0000027	.00000085

[a] Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

[b] male = 1, female = 0.

[c] PiB positive = 1, PiB negative = 0.

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Table 3

Models for amygdala FTP.

Model		Bootstrap[a]					
		B	Bias	Std. error	Sig. (2-tailed)	95% Confidence interval	
						Lower	Upper
A. Regression model for amygdala FTP	(Constant)	.50	−0.024	.51	.324	−0.62	1.44
	LC FMT Ki	**−40.48**	**−0.94**	**19.22**	**.044**	**−81.71**	**−7.17**
	Age	.007	.000066	.005	.136	−0.002	.018
	PiB Status[c]	.084	.004	.066	.199	−0.033	.23
	Sex[b]	.018	−0.003	.056	.726	−0.093	.13
	Years of Education	**.031**	**.002**	**.014**	**.029**	**.008**	**.062**
	Days Between FMT PET and FTP PET	.000024	.0000037	.000096	.788	−0.00024	.00016
	Relationship	**Total Effect**	**Direct Effect**	**Indirect Effect**	**Bootstrap Confidence[d] Interval**		**t-statistic**
B. Pathway model for amygdala FTP[e] through LC FMT	Neuroticism -> LC FMT -> Amygdala FTP	.0076 (.248)	.0010 (.881)	.0065	Lower Bound .0002	Upper Bound .017	.15
C. Pathway model for amygdala FTP[e] through raphe FMT	Neuroticism -> Raphe FMT -> Amygdala FTP	.0076 (.248)	.010 (.17)	−0.0027	Lower Bound −0.10	Upper Bound 0.0043	1.41
D. Pathway model for entorhinal Cortex FTP[e] through LC FMT	Neuroticism -> LC FMT -> Entorhinal Cortex FTP	.0065 (.38)	.0059 (.48)	.0006	Lower Bound −0.006	Upper Bound 0.008	.72

[a] Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

[b] male = 1, female = 0.

[c] PiB positive = 1, PiB negative = 0.

[d] bootstrap results are based on 5000 bootstrap samples.

[e] adjusted for age, sex, and years of education.

Table 4

Statistical models for conscientiousness.

Model outcome variable		B	Bootstrap[a]				
			Bias	Std. error	Sig. (2-tailed)	95% Confidence interval	
						Lower	Upper
A. GDS	(Constant)	10.70	−1.028	8.23	.203	−6.63	24.42
	Conscientiousness	**−0.22**	**.005**	**.067**	**.005**	**−0.34**	**−0.075**
	Age	.052	.009	.079	.505	−0.084	.22
	PiB Status[c]	.40	−0.006	.90	.650	−1.43	2.24
	Sex[b]	−0.74	−0.076	.90	.410	−2.56	1.009
	Years of Education	−0.17	.014	.24	.492	−0.64	.32
B. LC FMT	(Constant)	.0038	.00020	.0056	.496	−0.0066	.015
	Conscientiousness	**.000098**	**.00000042**	**.000046**	**.043**	**.000011**	**.00020**
	PiB Status	.00032	−0.000083	.00061	.615	−0.00097	.0014
	Age	−0.0000041	.00000086	.000052	.945	−0.00010	.00011
	Sex[b]	−0.00044	−0.000016	.00054	.410	−0.0015	.00062
	Years of Education	.00014	−0.000016	.00016	.372	−0.00020	.00040
	Days between FMT PET and Neuropsych	.0000010	−0.000000049	.00000084	.205	−0.0000026	.0000007
	Relationship	**Total Effect**	**Direct Effect**	**Indirect Effect**	**Bootstrap Confidence[d] Interval**		**t-statistic**
C. Pathway model for Amygdala FTP[e] through LC FMT	Conscientiousness -> LC FMT -> Amygdala FTP	.0013 (.770)	.0055 (.221)	−0.0041	Lower Bound −0.0099	Upper Bound −0.0002	1.25
D. Pathway model for Entorhinal Cortex FTP[e] through LC FMT	Conscientiousness -> LC FMT -> Entorhinal Cortex FTP	.0040 (.44)	.0054 (.33)	−0.0014	Lower Bound −0.006	Upper Bound 0.0017	0.99
E. Pathway model for Amygdala FTP[e] through Raphe FMT	Conscientiousness -> Raphe FMT -> Amygdala FTP	.0013 (.77)	.0013 (.79)	.0001	Lower Bound −0.0019	Upper Bound 0.0025	0.27

[a]Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

[b] male = 1, female = 0.

[c] PiB positive = 1, PiB negative = 0.

[d] bootstrap results are based on 5000 bootstrap samples.

[e] adjusted for age, sex, and years of education.