Better stress coping associated with lower tau in amyloid-positive cognitively unimpaired older adults

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Abstract

Objective

Research in animals has shown that chronic stress exacerbates tau pathology. In humans, psychological stress has been associated with higher risk of Alzheimer disease clinical syndrome. The objective of this cross-sectional study was to assess the hypothesis that stress coping ability (assessed via the Brief Resilience Scale [BRS]) is associated with tau burden and to evaluate whether these associations differed by sex and amyloid status (A+/A−) in cognitively unimpaired (CU) older adults.

Methods

We included 225 CU participants (mean age 70.4 ± 10.2 years, 48% female) enrolled in the population-based Mayo Clinic Study of Aging who completed the BRS and underwent amyloid-PET (Pittsburgh compound B–PET) and tau-PET (AV1451–PET). We fitted multiple regression and analysis of covariance models to assess the associations between BRS and tau-PET and the interaction with amyloid status and sex. We focused on entorhinal cortex (ERC) tau burden and also performed voxel-wise analyses. Age, sex, education, depression, and anxiety were considered as covariates.

Results

Higher stress coping ability was associated with lower tau burden in the medial temporal lobe (including ERC) and occipito-temporal and cuneal/precuneal cortices. The association was present in both A+ and A− but weaker in A− CU older adults. There was an interaction between amyloid status and stress coping ability that was restricted to the medial temporal lobe tau such that A+ CU older adults with lower stress coping abilities showed higher tau. There were no significant interactions between stress coping and sex.

Conclusions

A faster termination of the stress response (higher coping ability) may limit the negative effects of stress on tau deposition. Conversely, lower stress coping ability may be an early sign of accumulating tau pathology. Longitudinal studies are warranted to clarify whether stress mechanisms act to exacerbate tau pathology or tau influences stress-related brain mechanisms and lowers the ability to cope with stress.

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Glossary

AD = Alzheimer disease; ANCOVA = analysis of covariance; BRS = brief resilience scale; CU = cognitively unimpaired; ERC = entorhinal cortex; HPA = hypothalamus-pituitary-adrenal cortex; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; ROI = region of interest; SUVR = standard uptake value ratio.

Identifying modifiable factors associated with resistance to Alzheimer disease (AD) pathologies—amyloid and tau—is a fundamental step towards designing successful interventions and ultimately towards delaying the onset of AD clinical syndrome.^{1,2}

Several studies have assessed associations of in vivo amyloid measurements and modifiable factors in cognitively unimpaired individuals. Sleep disruption,^{3,4} physical activity levels,^{5–7} and intellectual enrichment^{8–12} have all been associated with amyloidosis, although some of these associations remain controversial.¹¹ While there is increasing interest in the therapeutic potential of targeting tau,^{13,14} studies assessing these types of associations with in vivo tau measurements are sparse.^{15,16}

In the present study, we hypothesized chronic stress as one of the potential factors associated with tau deposition. The major neuroendocrine response to stress is via activation of the hypothalamus-pituitary-adrenal cortex (HPA) axis that leads to glucocorticoid secretion.^{17,18} Research in animals suggests that stress responses—through the mediation of glucocorticoids—may trigger tau-dependent mechanisms and lead to a greater sensitivity to the deleterious action of amyloid.^{19–22}

In humans, chronic stress is associated with increased risk of AD clinical syndrome^{23–27} and high glucocorticoid levels are associated with accelerated brain aging and cognitive decline.^{28–32} Further, patients with mild cognitive impairment (MCI) and patients with AD show higher glucocorticoids levels than controls.^{31,33,34} In cognitively unimpaired (CU) participants, high cortisol levels may exacerbate the effects of amyloid on cognitive decline.³⁵ These studies support a role of stress in exacerbating aging and disease, but the link between chronic stress and AD pathology has not been established in humans.³⁶

There is significant variability in stress responses that ranges from depression^{37,38} to stress resilience, which is defined by the ability to cope well with stressors or to recover after stressor exposure.^{39,40} Older adults with high levels of stress resilience—or stress coping ability—require less time to recover and terminate the stress response after experiencing stressor exposure, which is essential for reducing the damaging effects of chronic elevations of glucocorticoids.⁴¹ Importantly, while stress coping ability can be shaped by individual factors such as age and sex, this ability can be enhanced by training⁴² and uniquely contributes to health outcomes later

in life,⁴³ making it an important target to evaluate for interventions.

Building on the evidence from animal and human research, we hypothesized that better stress coping strategies would be associated with resistance to tau. The specific goals of the study were to (1) examine the cross-sectional association of in vivo measurements of tau burden as measured by tau-PET with stress coping ability in CU older adults and (2) assess the interaction among amyloid status (A+/A–), sex, and stress coping ability on tau burden. We performed regional analyses focused on the entorhinal cortex (ERC), a region showing early tau deposition and highly vulnerable in aging and dementia,⁴⁴ and voxel level associations to further explore the topography of the association.

Methods

Participants

Participants were selected from the Mayo Clinic Study of Aging (MCSA), a population-based study started in 2004 among Olmsted County, Minnesota, residents aged 50–89 years. The Olmsted County population was enumerated using the Rochester Epidemiology Project medical records linkage system.^{45,46} Details about study design and clinical diagnostic criteria are discussed elsewhere.^{46,47} For the present study, we included 225 CU participants aged 50 years and older who had amyloid-PET, tau-PET, and stress coping ability assessments available (see below). Participants completed the assessments between June 2015 and June 2018. The mean time delay between the tau scan and the stress coping ability assessment was 1.4 ± 0.88 years. The results presented in this study are not adjusted by the time delay between assessments, but the relationships between our variables of interest did not differ when the time delay was introduced as covariate in the statistical models.

Standard protocol approvals, registrations, and patient consents

The institutional review boards of both Mayo Clinic and Olmsted Medical Center approved this study. All participants provided written informed consent.

Stress coping ability assessment

Stress coping ability or resilience to stress was assessed using the brief resilience scale (BRS). The BRS includes 6 items that are framed with regard to negative events. Higher scores indicate more resilience. In contrast to other measurements focusing on resilience resources, this scale assesses the ability to recover from stress itself (e-Methods 1, doi.org/10.5061/dryad.0zpc866t7).⁴³

Depressive and anxiety symptoms were measured using the Beck Depression Inventory–II and Beck Anxiety Inventory.^{48,49}

Imaging analyses and preprocessing

Amyloid- and tau-PET scans

Amyloid-PET and tau-PET images were acquired with PET-CT operating in 3D mode. The details of the acquisition and processing were published previously.⁵⁰ In brief, an in-house modified version of the automated anatomic labeling atlas was used and the atlas-based parcellation of the PET images into regions of interest was done in the participant's native anatomical space.

Amyloid deposition

Global cortical amyloid-PET retention ratio was computed as previously reported: the median uptake of voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest (ROIs) for each participant were divided by the median uptake over voxels in the cerebellar crus ROI of the atlas.^{e1} We used a global standard uptake value ratio (SUVR) cutoff of 1.48 to determine amyloid abnormality or positivity, which was established using the methodology we published previously but with updated processing pipelines.⁵⁰

Tau deposition

Tau-PET uptake was divided by the median uptake in the cerebellar crus to create standard uptake value ratios (SUVRs).^{e2} Entorhinal tau-PET was assessed by averaging the uptake in the left and right ERC. For voxel-wise analyses, we used tau-PET images normalized to the Mayo Clinic Adult Lifespan Template^{e3} and smoothed using a 6-mm full-width at half maximum Gaussian kernel. For the main analyses, including the voxel-wise analyses, we did not partial volume correct the tau-PET signal, but the main results presented here did not differ with partial volume correction.

Statistical analyses

The characteristics of the sample are described using mean and SD for continuous variables and count and percentage for categorical variables. The associations between stress coping ability and demographic variables were assessed using Pearson correlations and *t* tests.

ROI analyses were performed in IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL) and voxel-wise analyses were performed in SPM12.

Statistical analyses were carried out first to test the association of BRS with tau region-wise and voxel-wise and second to test the interaction with age and sex, region-wise and voxel-wise.

Association between BRS and tau burden

Regional analyses

We tested the association between ERC tau and BRS scores using an analysis of covariance (ANCOVA) model, with age, sex, and education as covariates.

Voxel-wise analyses

We ran voxel-wise multiple regression analyses in SPM12 including tau-PET scans as the dependent variable and BRS scores as the independent variable with age, sex, and education as covariates.

In both regional and voxel-wise analyses we also examined models adjusted by depression and anxiety scores.

Interaction among BRS, amyloid status, and sex

Regional analyses

We included amyloid status as a factor in the ANCOVA model described above and tested for BRS-by-amyloid and BRS-by-sex interactions.

Voxel-wise analyses

To test for BRS-by-amyloid and BRS-by-sex interactions, we fitted separate one-way ANCOVA models in SPM12. The first model included amyloid status as a factor, tau-PET scans as dependent variables, BRS as independent variables, and age, sex, and education as covariates. The second model included sex as a factor, tau-PET scans as dependent variables, and BRS as independent variable, and was adjusted by age and education.

We restricted the voxel-wise analyses to the gray matter using an explicit mask that included voxels with a gray matter probability greater than 0.2. Voxel-wise results were considered significant at uncorrected $p < 0.005$ at voxel level and family-wise error corrected $p < 0.05$ at cluster level. Taking into account the expected effect, the number of covariates, and the sample size, we applied a more liberal threshold of uncorrected $p < 0.005$ at voxel level and a $K > 500 \text{ mm}^3$ (150 voxels) when testing voxel-wise interactions.

Data availability

Data that support the findings of this study are available upon reasonable request from the Mayo Clinic Study of Aging investigators.

Results

Sample characteristics

Demographic characteristics of the study sample are provided in the table. Stress-coping was not associated with age ($r = -0.09$; $p = 0.20$), amyloid status (amyloid positivity) ($p = 0.27$), or sex ($p = 0.99$). Higher BRS was associated with higher education ($r = 0.24$; $p < 0.001$). There were moderate associations between higher BRS and lower scores in depression ($r = 0.4$; $p < 0.001$) and anxiety scales ($r = -0.3$; $p < 0.001$).

Association between BRS and tau burden

Regional analyses with ERC tau

Results from the multiple regression model to predict ERC tau showed a significant effect of BRS ($F = 13.89$, $p < 0.001$) adjusted by age, sex, and education. Further adjustments by

Table Demographic characteristics of the study sample (n = 225)

	Mean (SD) or n (%)	Range
Age, y	70.44 (10.20)	52–98
Male sex	117 (52)	—
Education, y	14.96 (2.47)	7–20
MMSE	28.74 (1.14)	23–30
Stress coping scale	3.80 (0.68)	1.33–5
Beck Anxiety Inventory	2.20 (3.80)	0–23
Beck Depression Inventory	4.29 (4.35)	0–22
Pittsburgh compound B–positive	78 (35)	—
APOE4	65 (30)	—

Abbreviation: MMSE = Mini-Mental State Examination.

anxiety and depression scores did not alter the results ($F = 9.7$, $p = 0.002$). Neither anxiety nor depression scores were significant contributors to the model (anxiety: $F = 0.30$, $p = 0.60$; depression: $F = 0.80$, $p = 0.37$).

Voxel-wise associations between stress coping ability and tau

Higher BRS scores were associated with lower tau deposition in the inferior temporal gyrus, ERC, parahippocampus, hippocampus, lingual gyrus, fusiform cortex, occipital pole, and cuneal and precuneus cortices after adjusting for age, sex, and years of education (figure 1). The topographic pattern was unchanged with partial volume correction (figure e-1, doi.org/10.5061/dryad.0zpc866t7) and when adjusting for depression and anxiety (figure e-2, doi.org/10.5061/dryad.0zpc866t7). In a sensitivity analysis, we found that BRS was not associated with neurodegeneration in AD regions ($F = 0.78$, $p = 0.38$; adjusted by sex, age, and education), further supporting the tau associations with BRS.

We assessed the association separately in A+ and A– subgroups. While the association was present in both subgroups, the effect was weak in A– and moderate in A+ (figure 2).

Overall, results from regional and voxel-wise analyses show a main effect of BRS on tau burden including, but not restricted to, areas of early tau accumulation.

Interaction among BRS, amyloid status, and sex

Regional analyses on ERC tau

There was a significant BRS-by-amyloid status interaction ($F = 6.98$, $p < 0.009$). When tested separately in A+ and A– subgroups, the association was reduced to a trend in A– older adults ($F = 2.93$, $p = 0.089$) but was still significant in the A+ group ($F = 11.16$, $p = 0.001$). To assess the specificity of the interaction to this region, we repeated the model in the

inferior temporal lobe, a region of early tau deposition but outside the medial temporal lobe. There was no significant interaction between BRS and amyloid on inferior temporal lobe tau ($F = 1.50$, $p = 0.22$). The results of these 2 areas are contrasted in figure 3. Finally, there was no significant interaction between sex and BRS on ERC tau ($F = 0.5$, $p = 0.82$).

Further adjustments by anxiety and depression scores did not alter the significance of the results (BRS-by-amyloid: $F = 6.6$, $p < 0.01$; BRS-by-sex: $F = 0.01$, $p = 0.91$). Neither anxiety nor depression scores were significant contributors to the model (anxiety: $F = 0.14$, $p = 0.71$; depression: $F = 0.72$, $p = 0.40$).

Voxel-wise analyses

We found a BRS-by-amyloid status interaction that was restricted to medial temporal regions including mainly the bilateral parahippocampal cortex and amygdala (left greater than right) and the left ERC, and to a lesser extent, the bilateral anterior hippocampus (figure 3). The pattern of results was similar when we further controlled for anxiety and depression scores (figure e-3, doi.org/10.5061/dryad.0zpc866t7), and there were no significant effects of anxiety or depression scores on tau. There was no significant BRS-by-sex interaction.

Overall, results from regional and voxel-wise analyses show an interaction of BRS and amyloid status restricted to the medial temporal lobe and notably the ERC. The results were unchanged when we repeated the analyses without the participant showing the lowest BRS scores and higher tau-PET uptake.

Discussion

The availability of in vivo measurements of amyloid and tau has increased interest in identifying modifiable factors that may play a role in the development and promotion of AD

Figure 1 Results from the voxel-wise multiple regression analysis between stress coping ability and tau-PET adjusted by sex, age, and education

pathologies. In this study, we investigated stress coping ability—or resilience to stress—in relation to tau deposition in cognitively unimpaired older adults. The main findings were (1) better stress coping ability was associated with lower tau deposition in the inferior and medial temporal lobes, occipito-temporal (fusiform and lingual gyri), and cuneal/precuneus cortices; (2) although this association was present

in both A+ and A− participants, the effect was moderate in the full sample, stronger among A+ and weaker among A− older adults; (3) amyloid status interacted with stress coping ability on regions showing early tau accumulation, that is, on medial temporal regions including the ERC, such that A+ participants with lower stress coping abilities were associated with higher tau.

Figure 2 Plots show the association between mean tau-PET uptake of the areas from the voxel-wise analysis (inferior and medial temporal lobes, occipito-temporal and cuneal/precuneus cortices, Y axis) and stress coping scale in amyloid-positive and amyloid-negative participants (X axis)

(A) Amyloid-positive group. (B). Amyloid-negative group. The discontinuous line in the A+ group plot (A) represents the regression line without the participant showing the lowest stress coping score ($r = -0.36$; $p = 0.002$). SUVR = standard uptake value ratio.

Figure 3 Results from the regional analyses showing an interaction between stress coping scale and amyloid status on entorhinal tau standard uptake value ratios (SUVRs) but not on inferior temporal tau SUVRs and results from the voxel-wise analyses showing an interaction between stress coping ability and amyloid status

(A) Results from the regional analyses show an interaction between stress coping scale and amyloid status on entorhinal tau SUVRs (left) but not on inferior temporal tau SUVRs (right). (B) Results from the voxel-wise analyses show an interaction between stress coping ability and amyloid status. Maps were thresholded at $p < 0.005$ at voxel level. Medial temporal results are shown as a binary mask overlaid on a T1 structural image. Both analyses were adjusted for age, sex, and years of education.

To our knowledge, this is the first study to investigate associations between stress responses and in vivo tau measurements using flortaucipir PET. We found that greater stress coping ability was associated with lower tau. The results show a specific association of tau with stress—and not with amyloid or neurodegeneration—thus suggesting an early mechanistic link between tau and stress. This association was not restricted to areas of early tau deposition but included the inferior and medial temporal lobes, occipito-temporal (fusiform and lingual gyri), and cuneal/precuneus cortices. A previous study in MCSA participants suggested that tau-PET signal is not confined to medial temporal regions in cognitively unimpaired individuals (A+ or A–).^{e4}

The present study was cross-sectional and, as a result, causal relationships cannot be established. Further, the association between stress coping ability and the biological stress response is speculative. Our results can be interpreted using 2 distinct arguments as discussed further below: (1)

a maintained stress response (lower ability to cope or recover from stress) may trigger or exacerbate tau pathology; or (2) lower stress coping ability may be an early sign of accumulating tau pathology.

Studies in mice have reported associations between elevated glucocorticoid levels and increased tau accumulation suggesting a modulation of glucocorticoids on tau deposition.^{19–21} In this study, stress coping ability was measured as the ability to bounce back and recover from stress.⁴³ This assessment likely captures more of a stable personality trait. Higher stress coping ability implies a faster recovery after stressor exposure and thus may imply a faster termination of the stress response, which involves the HPA axis and leads to glucocorticoid secretion.^{17,18} Thus, a tentative mechanistic explanation for our results is that a faster termination of the stress response may limit the negative effects that elevated levels of glucocorticoids may have on tau deposition. Measuring glucocorticoids in the future may further help clarify

the causal mechanisms through which stress response and tau deposition are related.

Stress coping strategies did not differ by amyloid status. This suggests that amyloid did not disrupt the ability to cope with stress. However, the association between stress and tau was stronger in A+ than A− CU older adults. A+ CU older adults with lower stress coping ability had increased medial temporal tau, mainly the ERC and parahippocampal cortex, but not in other areas of early accumulation. This result could be explained by the fact that A+ have a wider range of tau values to detect these associations. Previous studies in animals suggest that stress may play a role in the development and progression of AD pathologies^{20,21,e6–8} with tau hyperphosphorylation mediating the effects of stress on neurodegeneration²² and cognition¹⁹ even in the absence of amyloid. The present results thus suggest the hypothesis that stress may play a double role as a trigger of tau in aging independently of amyloid and as an accelerator of the biomarker cascade in older adults with AD pathologic change, promoting medial temporal lobe tau in the presence of amyloid. Previous studies showed that high cortisol levels were associated with accelerated cognitive decline in cognitively impaired—but not unimpaired—participants^{30,31} and suggested that cortisol dysregulation modulates the downstream clinical expression of AD pathology.³³ High cortisol levels may also accelerate the effect of amyloid positivity on cognitive decline in cognitively unimpaired participants.³⁵ Further studies are needed to understand the role that tau pathology plays on the described effects.

The topography of the association between stress coping ability and tau deposition included brain regions involved in the stress response such as the amygdala.^{e9} Thus, it is possible that tau deposition influences stress-related brain mechanisms and lowers the ability to cope with stress.^{e10} This argument is supported by the literature showing HPA axis dysregulation in MCI and AD.^{31,33,34} Further, neuropsychiatric symptoms are present early in AD,^{e11} and are associated with faster cognitive decline.^{e12} Indeed, previous studies showed that prolonged stress exposure was associated with depression,^{37,38} which often co-occurs with anxiety, both associated with increased risk of AD clinical syndrome.^{e13,e14} The cognitive debt hypothesis^{e15} proposes a framework where a cognitive process—repetitive negative thinking—may activate the stress response and underlie the risk associated with several neuropsychiatric symptoms. In line with this, the present findings add to recent preliminary evidence linking depression to in vivo tau measurements.^{e16} The association between stress coping and tau, however, remained significant after adjusting for depression and anxiety scores, and thus low stress coping ability may represent an earlier manifestation or have an independent role.

In the present study, we did not find a significant association between stress-coping ability and neurodegeneration in AD regions. This result suggests that the association between tau

and stress precedes neurodegeneration in these areas. In previous studies, tau deposition in the ERC has been associated with episodic memory and subjective cognitive decline independent of amyloid.^{e17,e18} An important avenue of future research therefore will be to understand the role that stress may play in primary age-related tauopathy.^{e19}

A recent study in CU women reported an association between midlife stress and total CSF tau suggesting an association between stress and nonspecific neurodegenerative processes but not the core biomarkers of AD.^{e20} While differences with the present results may be partly explained by the use of fluid vs imaging markers, which capture different aspects of tau pathology,^{e21} and midlife vs late life assessments, these results may also highlight different paths through which stress may affect brain health, including disease-independent pathways.

Resilience to stress and stress coping ability depends upon demographic factors such as age, sex, and education.^{e22} In this study, stress coping ability was not associated with age or sex, as reported previously. Although some studies suggest differences in tau burden by sex,^{e23} there was no interaction between sex and stress coping ability on tau. This question, however, needs further assessment in future studies using gender-sensitive tools. Aside from age and sex, lifestyle habits may be associated with stress and warrant further investigation in future studies. Further, future studies may also benefit from measuring stressful life events and social support, both important for stress resilience. Finally, unraveling the mechanism through which stress plays a role in AD clinical syndrome will be fundamental to designing successful interventions. If stress increases tau accumulation in aging, stress resilience could be an area for intervention earlier in life. In addition, stress may accelerate the AD biomarker cascade, in which case stress regulation could be a potential target for interventions in participants with AD pathologic change. On the other hand, if the stress response is altered early in the disease process, then stress assessment can be used for early detection and treatment. Future studies are warranted to assess the associations between stress resilience and tau in cognitively impaired participants.

The main limitation of the present study is that its cross-sectional design does not allow assessing causality. The association between stress and tau needs further assessment using other measurements of stress such as cortisol levels. However, it is important to highlight that stress responses depend upon different variables including resilience resources and objective exposure to stressors that may influence stress coping ability and were not measured in the present study. Our results highlight that measuring the ability to cope or bounce back from stress may be clinically relevant and important to study stress in the context of aging.

Higher stress coping ability was associated with lower tau in aging and amyloid-positive CU older adults. Further studies are warranted to understand the role of stress in AD: stress may

play a role in the development or promotion of tau pathology, or alternatively, lower stress coping ability may represent an early manifestation of accumulating tau pathology.

Author contributions

Dr. Arenaza-Urquijo: study concept and design, analysis and interpretation. Dr. Machulda: interpretation, critical revision of the manuscript for important content. Dr. Knopman: interpretation, critical revision of the manuscript for important intellectual content. Dr. Lowe: interpretation, critical revision of the manuscript for important intellectual content. Dr. Mielke: critical revision of the manuscript for important intellectual content. A.L. Reddy: acquisition of data and analysis. Dr. Geda: critical revision of the manuscript for important intellectual content. Dr. Jack Jr: study design, interpretation, critical revision of the manuscript for important intellectual content. Dr. Petersen: study design, interpretation, critical revision of the manuscript for important intellectual content. Dr. Vemuri study concept and design, interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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