BRAIN
ORIGINAL ARTICLE

Cerebral amyloid angiopathy interacts with neuritic amyloid plaques to promote tau and cognitive decline

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Accumulating data suggest that cerebrovascular disease contributes to Alzheimer's disease pathophysiology and progression toward dementia. Cerebral amyloid angiopathy is a form of cerebrovascular pathology that results from the build-up of β-amyloid in the vessel walls. Cerebral amyloid angiopathy commonly co-occurs with Alzheimer's disease pathology in the ageing brain and increases the risk of Alzheimer's disease dementia.

In the present study, we examined whether cerebral amyloid angiopathy influences tau deposition and cognitive decline independently or synergistically with parenchymal β-amyloid burden. Secondly, we examined whether tau burden mediates the association between cerebral amyloid angiopathy and cognitive decline. We included data from autopsied subjects recruited from one of three longitudinal clinical–pathological cohort studies: the Rush Memory and Aging Project, the Religious Orders Study and the Minority Aging Research Study. Participants completed annual clinical and cognitive evaluations and underwent brain autopsy. Cerebral amyloid angiopathy pathology was rated as none, mild, moderate or severe. Bielschowsky silver stain was used to visualize neuritic β-amyloid plaques and neurofibrillary tangles. We used linear regression and linear mixed models to test independent versus interactive associations of cerebral amyloid angiopathy and neuritic plaque burden with tau burden and longitudinal cognitive decline, respectively. We used causal mediation models to examine whether tau mediates the association between cerebral amyloid angiopathy and cognitive decline. The study sample included 1722 autopsied subjects (age at baseline = 80.2 ± 7.1 years; age at death = 89.5 ± 6.7 years; 68% females).

Cerebral amyloid angiopathy interacted with neuritic plaques to accelerate tau burden and cognitive decline. Specifically, those with more severe cerebral amyloid angiopathy pathology and higher levels of neuritic plaque burden had greater tau burden and faster cognitive decline. We also found that tau mediated the association between cerebral amyloid angiopathy and cognitive decline among participants with higher neuritic plaque burden. In summary, more severe levels of cerebral amyloid angiopathy and higher parenchymal β-amyloid burden interacted to promote cognitive decline indirectly via tau deposition. These results highlight the dynamic interplay between cerebral amyloid angiopathy and Alzheimer's disease pathology in accelerating progression toward dementia. These findings have implications for Alzheimer's disease clinical trials and therapeutic development.

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Received January 10, 2022. Revised April 25, 2022. Accepted April 27, 2022

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Keywords: cerebral amyloid angiopathy; β-amyloid; tau; cognitive decline; neuropathology

Abbreviations: Aβ = β-amyloid; CAA = cerebral amyloid angiopathy; CERAD = Consortium to Establish a Registry for Alzheimer's Disease

Introduction

Alzheimer's disease neuropathology is characterized by extracellular deposition of parenchymal β-amyloid (Aβ) and intracellular accumulation of tau as neurofibrillary tangles.[1] Vascular pathology frequently co-occurs with Alzheimer's disease neuropathology[2] and increases the risk of cognitive impairment and dementia.[3,4] While vascular contributions to the clinical syndrome of Alzheimer's disease have long been appreciated,[5] it remains unclear whether cerebrovascular pathology drives cognitive impairment through independent pathways, through Alzheimer's disease pathways (i.e. by directly promoting Alzheimer's disease pathology) or both.

A growing number of studies support an association between vascular burden (i.e. vascular risk factors and cerebrovascular pathology) and Alzheimer's disease neuropathology. For instance, there is evidence that greater vascular risk is associated with higher levels of parenchymal Aβ burden.[6,7] Studies also report positive associations between vascular risk factors and tau deposition, either independently or synergistically with Aβ burden.[7–10] In addition, cerebrovascular disease, as measured by white matter hyperintensities, has been associated with increased tau deposition[11–13] and atrophy patterns typical of Alzheimer's disease dementia.[14]

Cerebral amyloid angiopathy (CAA) is a form of cerebrovascular pathology that results from the build-up of Aβ in the small and medium-sized arteries of the cerebral cortex and leptomeninges. Vascular Aβ accumulation weakens the blood vessel wall, leading to infarcts, ischaemia and cerebral haemorrhages.[15,16] The apolipoprotein E ε4 (APOE4) allele is the strongest genetic risk factor for both CAA and late-onset Alzheimer's disease and is associated with a dose-dependent increase in the amount of vascular and parenchymal Aβ burden.[17–19] Although Aβ plays a central role in both CAA and Alzheimer's disease, the two entities are considered clinically and pathologically distinct.[20,21] Alzheimer's disease and CAA commonly co-occur in the ageing brain.[22] Advanced CAA is present in approximately 25–44% of adults with neuropathological Alzheimer's disease[18,23] and CAA increases the risk of Alzheimer's disease dementia.[24–26]

Previous studies report an association between CAA and increased tau deposition.[27–29] In the Honolulu–Asia Aging Study, individuals with CAA had more neuritic plaques and neurofibrillary tangles compared to those without CAA.[26] In a subsample from the Religious Orders Study categorized as either Braak stage 0–II or III, CAA was more common in those with Braak stage III compared with stage 0–II.[30] In another autopsy study, individuals with dominantly inherited prion protein CAA exhibited intraneuronal tau aggregates that were identical to the type of tau observed in Alzheimer's disease.[27,31,32]

Motivated by these prior findings, we examined whether CAA interacts with Alzheimer's disease pathology to accelerate clinical progression of dementia. Specifically, we examined whether CAA influences tau deposition and whether this occurs independently or synergistically with parenchymal Aβ burden. We next examined whether CAA contributes to cognitive decline, independently or synergistically with parenchymal Aβ burden, and finally whether tau burden mediates this association. To address these questions, we used clinical and pathological data from more than 1700 deceased participants enrolled in one of three longitudinal cohort studies of ageing from the Rush Alzheimer's Disease Center.

Materials and methods

Participants

We used clinical and neuropathological data from decedents enrolled in one of three community-based cohort studies as part of the Rush Alzheimer's Disease Center (radc.rush.edu): the Religious Orders Study,[33] the Rush Memory and Aging Project[34]

and the Minority Aging Research Study.[35] The Religious Orders Study began in 1994 and recruits older Catholic nuns, priests and brothers from over 40 sites across the US. The Memory and Aging Project began in 1997 and recruits older adults from the Chicago metropolitan area. The Minority Aging Research Study began in 2004 and recruits older African Americans from the Chicago metropolitan area. All three studies enrol participants without known dementia who agree to annual clinical and cognitive evaluations. Participants in the Religious Orders Study and the Memory and Aging Project consent to brain donation; it is not required for participants in the Minority Aging Research Study. The three cohort studies share nearly identical study designs, operations and protocols, which allow for combined analyses. Each study was approved by the Institutional Review Board of Rush University Medical Center, and all participants signed an informed consent form.

At the time of the analyses, 4459 participants were enrolled across the three cohorts and 2330 participants had died. Of the deceased, 1834 consented to brain donation and underwent autopsy (79%). Analyses were restricted to participants with complete neuropathological data ($n = 1789$) and complete data for relevant covariates (cross-sectional analyses: $n = 1728$; longitudinal analyses: $n = 1715$). We further excluded the small number of participants who self-identified as a race other than White or Black/African American ($n = 6$). Longitudinal analyses additionally excluded participants with fewer than two cognitive assessments ($n = 76$), resulting in a final analytic sample of 1722 for cross-sectional autopsy analyses and 1633 for longitudinal cognitive analyses. Additional details on the sample selection process are available in Supplementary Fig. 1.

Assessment of longitudinal cognition and clinical diagnosis

A battery of 19 cognitive tests was administered to each participant at baseline and at each follow-up visit. The battery assessed a broad range of cognitive abilities, including episodic memory, working memory, semantic memory, perceptual speed and visual perceptual ability/perceptual orientation.[36] As in previous studies,[24] raw test scores were converted to *z* scores using the mean and standard deviation (SD) of the baseline sample. Scores were then averaged to compute a measure of global cognition.

As previously described,[37] cognitive diagnosis proximate to death was based on a three-stage process, including standardized scoring of cognitive tests, clinical judgement by a neuropsychologist and diagnostic classification by a clinician. Based on this information, persons were diagnosed as either having no cognitive impairment, mild cognitive impairment or dementia.

Assessment of covariates

Depressive symptoms at baseline were assessed with the 10-item version of the Center for Epidemiological Studies Depression Scale.[38] Participants were asked to rate the frequency with which they experienced 10 depressive symptoms in the past week. Higher scores on this scale reflect greater depressive symptoms. Baseline vascular risk was assessed as the count of nine variables summarizing vascular risk factors or vascular conditions (diabetes, hypertension, smoking, obesity, high cholesterol, self-reported claudication, stroke, heart disease and congestive heart failure). Additional details on the construction of the vascular summary score are provided in the Supplementary material. Race was based on self-selection of one of seven racial categories. As mentioned above, analyses were restricted to participants who self-identified as White or Black/African American. Other variables used in the analyses included sex/gender (self-reported as male or female) and years of education (years of schooling completed).

Neuropathological assessment

The brains of deceased participants were removed and prepared following standard protocols.[39] Briefly, each brain hemisphere was cut into 1 cm coronal slabs. One hemisphere was fixed in 4% paraformaldehyde and then cut, while the other was immediately photographed and frozen. Regions of interest were dissected from the fixed slabs and embedded in paraffin; sections of the paraffin blocks were cut and stained to characterize pathologies. All measures were reviewed by a board-certified neuropathologist or by a neuropathologist-trained expert neuroscientist.

Cerebral amyloid angiopathy pathology

CAA pathology was assessed in four neocortical regions: midfrontal, midtemporal, parietal and calcarine cortices. Paraffin-embedded sections were immunostained for Aβ using one of three monoclonal anti-human antibodies: 4G8 (1:9000; Covance Labs, Madison, WI), 6F/3D (1:50; Dako North America Inc.) and 10D5 (1:600; Elan Pharmaceuticals).[24] For each region, meningeal and parenchymal vessels were assessed for Aβ deposition and scored on a semiquantitative scale (ranging from 0 to 4). The maximum of the meningeal and parenchymal CAA scores defined the CAA score for that region. The scores were then averaged across the four regions. The average score was further classified into a four-level semiquantitative measure, rated as none, mild, moderate or severe, using consistent cut-offs selected by the neuropathologist. Interrater consistency for CAA pathology across raters using a weighted kappa (0.9 for scores across two raters within one grade) was 0.6, which reflects good agreement between the raters.

Alzheimer's disease pathology

Bielschowsky silver stain was used to visualize neuritic Aβ plaques and neurofibrillary tangles in five cortical areas: hippocampus, entorhinal, midfrontal, middle temporal and inferior parietal.[39] Neuritic plaques and neurofibrillary tangles were counted in the region of highest density in a 1 mm^2 area. The interrater reliability of counts of neuritic plaques and neurofibrillary tangles ranged from $r = 0.89$ to $r = 0.93$.[40] As in prior work, a standardized summary score was created for each of the two pathologies in each region by dividing the raw count by the corresponding standard deviation.[39] The five scaled regional measures were then averaged together separately for each pathology. Counts were missing for some regions (e.g. due to damage from infarct); however, if data were present for at least two regions, summary measures were computed. Because the distributions of the neuritic plaque and neurofibrillary tangle measures were skewed, we used the square root of each measure of pathology in the correlation and regression analyses, and in causal mediation models. This approach is consistent with prior studies.[18,41,42] For some analyses, neuritic plaque burden was dichotomized into high *versus* low Aβ plaque levels using the mean of the study sample.

Immunohistochemistry and computer-assisted image analysis were used to measure Aβ load and paired helical filament tangle burden.[34] Aβ was measured in eight cortical regions of the brain: anterior cingulate cortex, superior frontal cortex, mid frontal cortex,

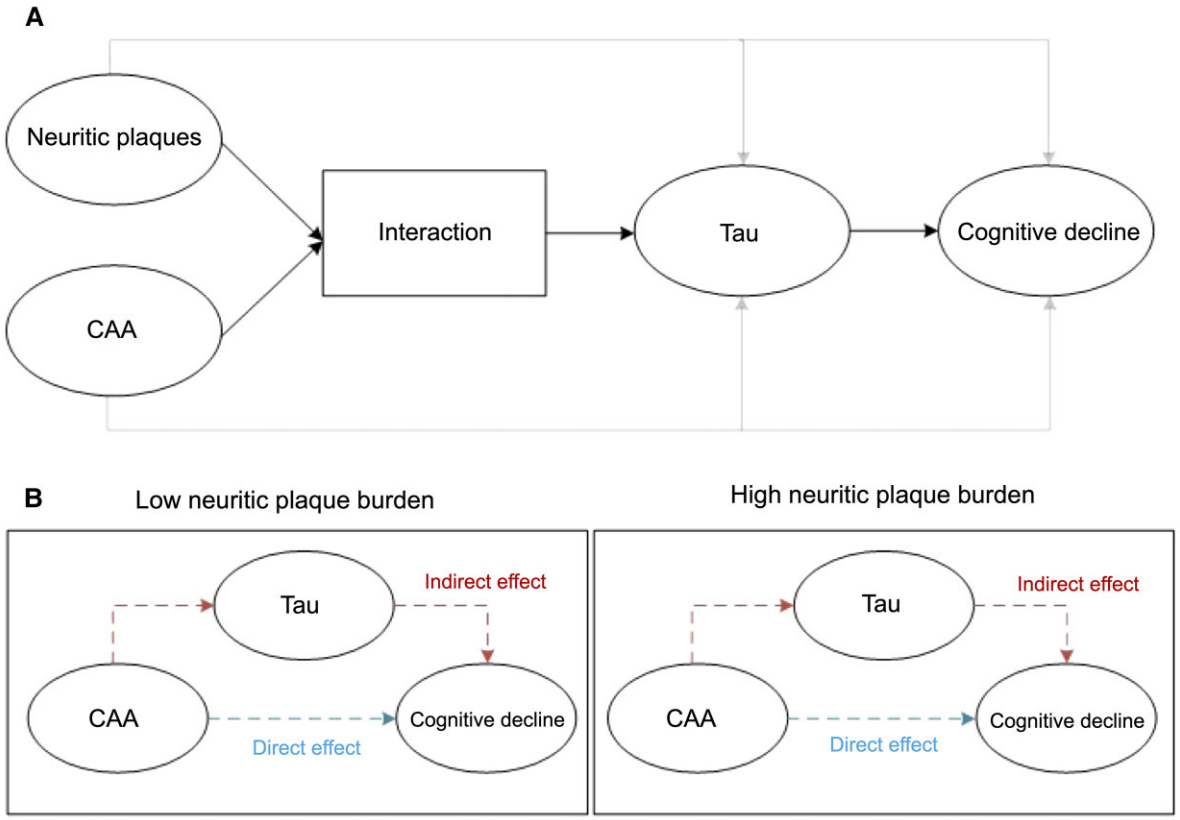

Figure 1 Illustration of the causal mediation analyses performed. (**A**) We used causal mediation analyses to assess whether tau mediates the interactive association of CAA and amyloid plaque burden on cognitive decline (depicted by the black arrows). Other potential pathways less central to our primary hypotheses are shown by the grey arrows. (**B**) To probe the interaction in a mediation framework, we performed two meditation analyses stratified by amyloid plaque burden. The natural indirect effect quantifies the size of the effect of CAA on cognitive decline that is mediated through tau. The natural direct effect quantifies the size of the effect of CAA on cognitive decline through other pathways.

inferior temporal cortex, hippocampus, entorhinal cortex, angular gyrus/supramarginal cortex and calcarine cortex. Tangle densities were assessed using levels of abnormally phosphorylated tau measured with AT8 antibody across the same eight brain regions. Separate summary scores were computed for Aβ load and tangle density by averaging the mean percentage area per region across all regions. The distributions of these Aβ and tau measures were skewed, and therefore the square root of each pathology measure was used in analyses.

The immunohistochemistry-based measure of Aβ includes both parenchymal and vascular Aβ burden. For this reason, we used the silver stain measures of Alzheimer's disease pathology in our primary analyses to ensure independence between measures of parenchymal Aβ and CAA. To assess the robustness of our findings, in sensitivity analyses we repeated the main models using the immunohistochemistry measures in place of the silver stain measures.

We also used the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque and Braak staging scores in our analyses. The CERAD score is a semiquantitative measure of neuritic plaques, classified as none, sparse, moderate and frequent. Braak stage is a semiquantitative measure reflecting the regional distribution of neurofibrillary tangle pathology, classified as Braak stage 0, I, II, III, IV, V and VI. Silver-stained slides from each case were reviewed by a clinical or research neuropathologist for a final determination of CERAD and Braak scores. Pathologic Alzheimer's disease diagnosis followed the National Institute on Aging (NIA) Reagan criteria.[43] The criteria rely on both CERAD and Braak staging scores. A pathologic diagnosis of Alzheimer's disease required either an intermediate likelihood of Alzheimer's disease (i.e. CERAD moderate plaques and at least Braak stage III or IV) or a high likelihood of Alzheimer's disease (i.e. CERAD frequent plaques and at least Braak stage V or VI).[44]

APOE genotyping

DNA was extracted from peripheral blood or frozen post-mortem brain tissue. The APOE genotypes were determined by sequencing codon 112 (position 3937) and codon 158 (position 4075) in exon 4 of the APOE gene on chromosome 19. Participants with one or two copies of the ϵ4 allele were considered ϵ4 carriers.

Statistical analyses

Analyses were performed with statistical software R version 4.1.1 (http://www.r-project.org/). We used descriptive statistics to characterize the sample overall, as well as stratified by CAA burden (none/mild versus moderate/severe). We used chi-squared tests and two-sample *t*-tests to assess differences between groups. Polyserial correlations, which are on the same scale as Pearson correlations, were used to assess the strength of the unadjusted correlations between CAA pathology (assessed on an ordinal scale) with neuritic plaque and tau burden. We also examined the associations

among neuritic plaques, tau and CAA using graphical displays of the data.

We used linear regression models to test independent versus interactive effects of CAA and neuritic plaques on tau burden. Analyses were adjusted for age at death, sex/gender, years of education, race and APOE4 status (carrier versus non-carrier). We then used linear mixed-effects models to assess independent versus interactive effects of CAA and neuritic plaque burden on cognitive decline. A random intercept was included for each participant. Time was operationalized as years from baseline, scaled to 5-year units to aid in the interpretability of coefficients. In this analysis, we were interested in controlling for both age at baseline, which affects cognitive trajectories, and age at death, which affects neuropathological burden. However, because of the inherent collinearity of the two age terms, we adjusted for the interaction between age at baseline and the number of follow-up visits for each participant. The model additionally adjusted for sex/gender, years of education, race, baseline depressive symptoms, baseline vascular risk burden, APOE4 status, the time interval between the last cognitive assessment and death, as well as each variable interacted with time.

Finally, we used causal mediation models to investigate whether tau mediates the association between CAA and cognitive decline. Because we found that CAA interacts with neuritic plaque burden to promote cognitive decline (see Results), we performed two meditation analyses stratified by mean neuritic plaque burden to probe the interaction (Fig. 1). The causal mediation analytic framework relies on counterfactual reasoning to define contrasts that quantify both the effect of an exposure that occurs through a mediating variable (the natural indirect effect) and the effect of an exposure that occurs independently of a mediating variable (the natural direct effect).[45–47] To evaluate these effects, we first defined M0 as the value that the mediator would take if the exposure was equal to 0 and M1 as the value the mediator would take if the exposure was equal to 1. We then defined the natural indirect effect as the difference in the counterfactual outcomes comparing: (i) a set of individuals who had an exposure of 1 and mediator of M1; and (ii) the same set of individuals who instead had an exposure of 1 and mediator of M0. The natural direct effect was the difference in the counterfactual outcomes between: (i) a set of individuals who had an exposure of 1 and mediator M0; and (ii) the same set of individuals who instead had an exposure of 0 and mediator M0.

We used regression modelling to estimate and predict counterfactual outcomes in our sample and to estimate the natural indirect and direct effects. We estimated uncertainty intervals for these effects using a nonparametric bootstrap and use the term 'confidence interval' to refer to all estimates of uncertainty. Additional details on the estimation of causal mediation models can be found in the Supplementary material.

We performed two sensitivity analyses to assess the robustness of the above findings: (i) we repeated the analyses controlling for clinical diagnosis at death; and (ii) we repeated the analyses using the immunohistochemistry measures of Aβ and tau in place of the measures derived by silver staining.

Data availability

The data from the present study are available upon request from the Rush Alzheimer's Disease Center Resource Sharing Hub (www.radc.rush.edu).

Results

Table 1 summarizes the baseline demographic information for the 1722 autopsied participants included in the cross-sectional analyses both overall and stratified by low CAA (none/mild) and high CAA (moderate/severe). The mean age at baseline was 80.2 years (SD: 7.1) and participants were followed for an average of 8.8 years (SD: 5.4). Compared to participants with moderate/severe CAA, those with none/mild CAA were slightly younger at baseline (0.9 years younger) and at death (1.5 years younger), but these differences were of small magnitude. Baseline global cognition did not differ between those with none/mild CAA versus moderate/severe CAA. However, proximate to death, relative to individuals with none/mild CAA, those with moderate/severe CAA showed worse cognitive performance ($P < 0.001$) and a greater proportion of participants were diagnosed with cognitive disorders ($P < 0.001$) (Table 1). According to NIA–Reagan criteria, 64.6% of all cases met criteria for pathological Alzheimer's disease. Pathological Alzheimer's disease was much more common in participants with moderate/severe CAA (82.0%) compared to none/mild CAA (54.9%, $P < 0.001$). Differences between those with moderate/severe *versus* none/mild CAA were also observed in the distribution of CERAD scores and Braak stages ($P < 0.001$ for both), such that a larger proportion of participants in the moderate/severe CAA group had higher CERAD scores and more advanced Braak stages.

Table 1 Characteristics of the Religious Orders Study/Rush Memory and Aging Project/Minority Aging Research Study (*n* = 1722) sample overall and by CAA pathological burden

	All	None/mild CAA	Moderate/severe CAA
Number of participants, *n*	1722	1101	621
Age at baseline in years, mean (SD)	80.2 (7.1)	79.9 (7.1)	80.8 (7.1)
Age at death in years, mean (SD)	89.5 (6.7)	89.0 (6.9)	90.5 (6.3)
Education in years, mean (SD)	16.2 (3.6)	16.2 (3.5)	16.3 (3.7)
Females, *n* (%)	1169 (67.9)	748 (67.9)	421 (67.8)
White participants, *n* (%)	1636 (95.0)	1043 (94.7)	593 (95.5)
APOE4 positive, *n* (%)	439 (25.5)	186 (16.9)	253 (40.7)
Baseline cognition, mean (SD)	−0.1 (0.7)	−0.1 (0.7)	−0.2 (0.7)
Cognition proximate to death, mean (SD)	−1.0 (1.2)	−0.9 (1.2)	−1.3 (1.2)
Final clinical diagnosis			
No cognitive impairment, *n* (%)	549 (31.9)	397 (36.1)	152 (24.5)
Mild cognitive impairment, *n* (%)	395 (22.9)	274 (24.9)	121 (19.5)
Dementia, *n* (%)	778 (45.2)	430 (39.1)	348 (56.0)
Pathological Alzheimer's disease, *n* (%)	1113 (64.6)	604 (54.9)	509 (82.0)
CERAD score			
None, *n* (%)	405 (23.5)	360 (32.7)	45 (7.2)
Mild, *n* (%)	138 (8.0)	91 (8.3)	47 (7.6)
Moderate, *n* (%)	605 (35.1)	367 (33.3)	238 (38.3)
Severe, *n* (%)	574 (33.3)	283 (25.7)	291 (46.9)
Braak stage			
Stage 0, *n* (%)	20 (1.2)	15 (1.4)	5 (0.8)
Stage I–II, *n* (%)	267 (15.5)	222 (20.2)	45 (7.2)
Stage III–IV, *n* (%)	965 (56.0)	659 (59.9)	306 (49.3)
Stage V–VI, *n* (%)	470 (27.3)	205 (18.6)	265 (42.7)

Cognition = general cognitive functioning.

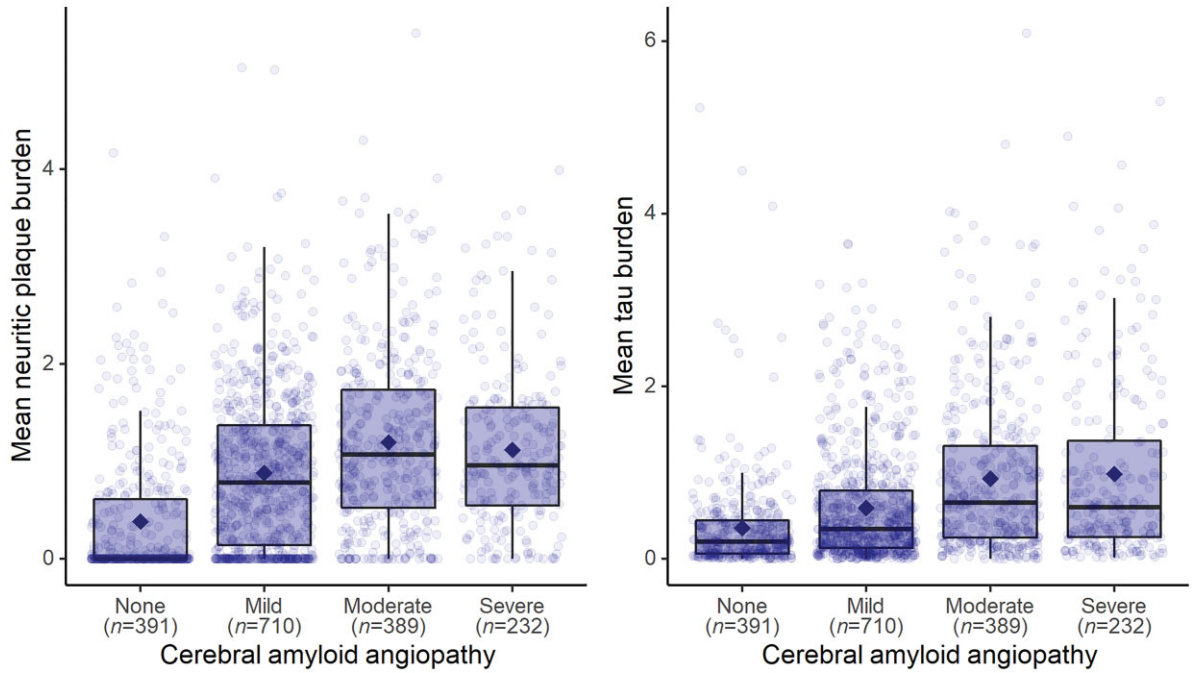

Figure 2 Mean neuritic plaque and tau levels by CAA severity. (*Left*) Nonmonotonic relationship between CAA severity and neuritic plaque burden. (*Right*) Monotonic association between CAA severity and tau burden. Error bars indicate 95% CIs for the sample means.

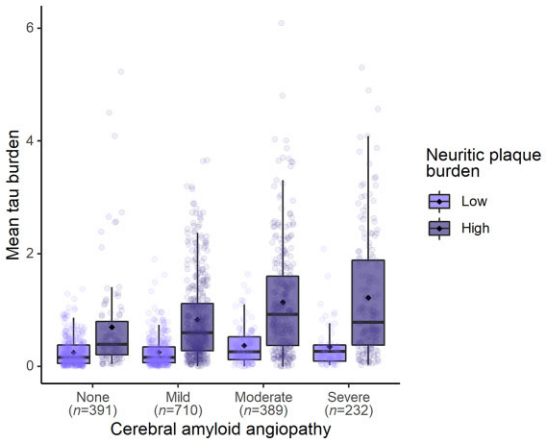

Figure 3 Mean tau burden by CAA severity stratified by low versus high neuritic plaque burden. Tau burden was highest in those with combined moderate or severe CAA and high neuritic plaque burden. Error bars indicate 95% CIs for the sample means.

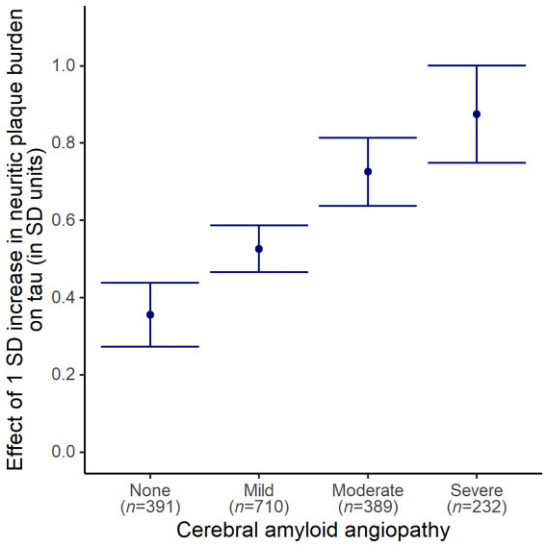

Figure 4 The association between neuritic plaque burden and tau burden stratified by CAA severity. The significant interaction between CAA and neuritic plaque burden on tau burden. The association of neuritic plaque burden with tau burden was stronger at more severe levels of CAA. Results are from a linear regression model controlling for age at death, sex/gender, race, years of education and APOE4 status.

CAA severity correlated with both neuritic plaque burden [correlation coefficient: 0.40; 95% confidence interval (CI): 0.36–0.44] and tau burden (correlation coefficient: 0.33; 95% CI: 0.28–0.37). Despite the close mechanistic relationship between CAA and neuritic plaque burden, CAA explained only 18% of the variance in neuritic plaque burden in a univariate linear regression model. Additionally, visual assessment of the relationship between CAA severity and neuritic plaque burden revealed a nonmonotonic relationship (Fig. 2), further indicating that the two variables assess distinct biological constructs. By contrast, we observed a positive monotonic association between CAA severity and tau burden (Fig. 2), and this association appeared to be influenced by neuritic plaque burden (Fig. 3).

An interaction between CAA and neuritic plaque burden on tau showed that the association of neuritic plaques with tau burden was stronger at more severe levels of CAA (Fig. 4; Supplementary Fig. 2). Among the group with no evidence of CAA, a 1 SD increase in neuritic plaque burden was associated with a 0.35 (95% CI: 0.27–0.43) SD unit greater increase in tau burden. By contrast, among the group with the most severe CAA burden, a 1 SD increase in neuritic

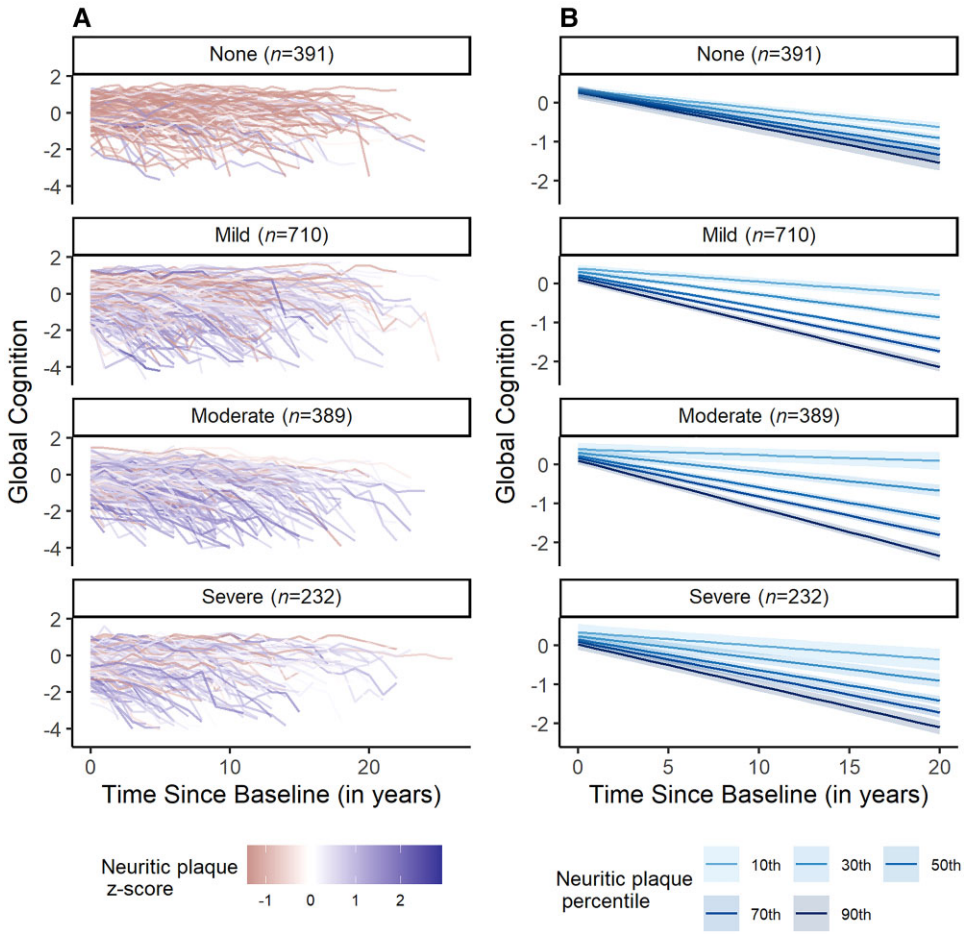

Figure 5 Cognitive trajectories by neuritic plaque burden and CAA severity. Both raw (**A**) and modelled (**B**) trajectories depict the significant interaction between neuritic plaque burden and CAA on cognitive decline. Cognitive decline was steepest in those with higher neuritic plaque burden and more severe CAA. Results are from a linear mixed-effects model controlling for age at baseline, gender, race, years of education, APOE4 status, baseline depressive symptoms, baseline vascular risk, number of visits and the interval between the last visit and death.

plaque burden was associated with a 0.88 (95% CI: 0.75–1.00) SD unit greater increase in tau burden. In sensitivity analyses, the results were similar when we adjusted for clinical diagnosis and when immunohistochemistry measures of Aβ and tau were used in place of the silver stain measures (Supplementary Fig. 3).

We observed a significant interaction between (mild, moderate and severe) CAA and neuritic plaque burden on cognitive decline in a linear mixed-effects model ($P < 0.001$, $P < 0.001$, $P = 0.003$ for mild, moderate and severe CAA, respectively). The groups with the steepest cognitive decline were those with greater levels of CAA pathology and higher neuritic plaque burden (Fig. 5, Supplementary Table 1, Supplementary Fig. 4). There was a strong independent association of neuritic plaque burden on cognitive decline ($P < 0.001$); however, there was no independent association of CAA on cognitive decline, ($P = 0.062$, $P = 0.548$, $P = 0.450$ for mild, moderate and severe CAA, respectively). In sensitivity analyses, results were similar when we additionally controlled for clinical diagnosis at death and when using immunohistochemistry variables for the quantification of Aβ and tau (Supplementary Fig. 5).

We found that tau mediated the association of CAA on cognitive decline among participants with high, but not low, levels of neuritic plaque burden (Fig. 6, Supplementary Table 2). In the high neuritic plaque burden group, there was evidence of a dose–response association by CAA severity, such that the mediating effect of tau was largest in the groups with greater levels of CAA pathology. Among those with high neuritic plaque burden, we estimated that increases in tau pathology mediated by the presence of severe CAA was associated with a 5-year decline in global cognition that was 0.10 (95% CI: 0.03–0.19) SD units greater than those with no CAA ($P < 0.001$). The estimated increased decline for moderate CAA in comparison to those with no CAA [increased decline in global cognition of 0.08 (95% CI 0.02–0.15) SD units] was similar to severe CAA ($P = 0.012$), whereas the estimated increased decline for mild CAA [increased decline in global cognition of 0.02 (95% CI –0.03–0.07) SD units] was smaller ($P = 0.407$). Across both the high and low neuritic plaque groups, we did not find evidence of a direct effect of CAA on cognitive decline (i.e. an association that was not mediated by tau). In sensitivity analyses, controlling for clinical diagnosis in the mediator and outcome models attenuated effect estimates, but the overall pattern remained the same. Effect estimates were stronger when we used immunohistochemistry measures of Aβ and tau in place of the silver stain measures (Supplementary Fig. 6).

Discussion

In a large, well-characterized autopsy sample, we found that greater CAA severity and higher parenchymal Aβ burden were synergistically associated with greater tau burden and faster cognitive decline.

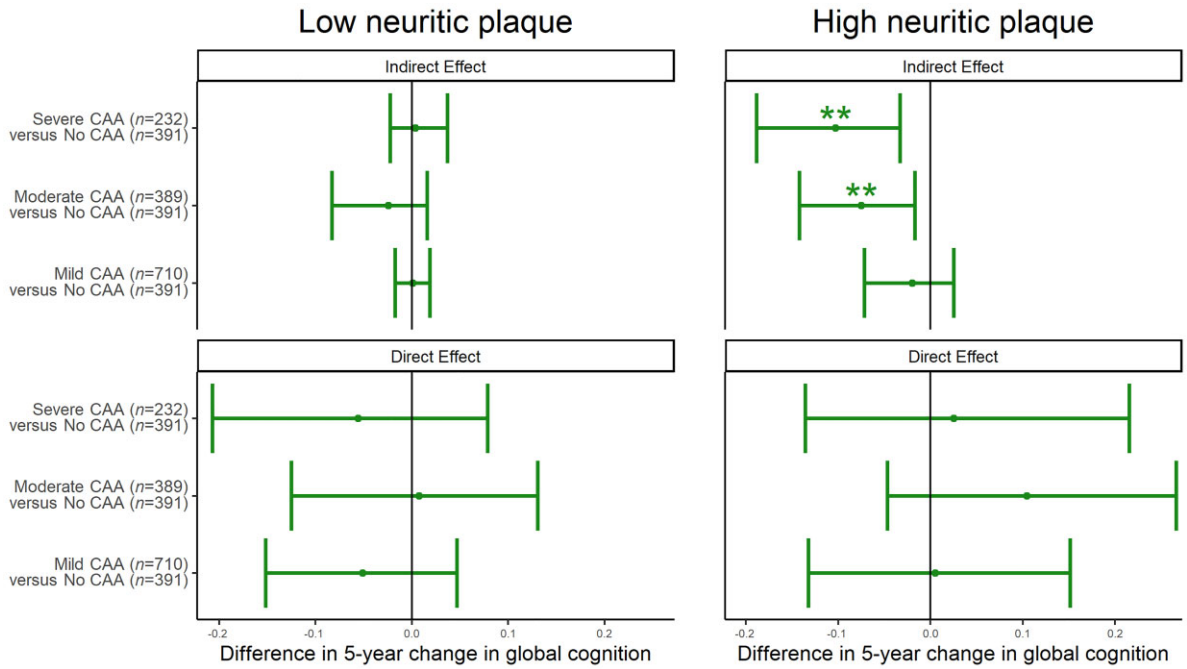

Figure 6 Mediating role of tau in the association between CAA and cognitive decline stratified by neuritic plaque burden. (*Left*) The results of the causal mediation analysis in those with low neuritic plaque burden, and (*right*) the results of the causal mediation in those with high neuritic plaque burden (stratified by mean neuritic plaque burden). Tau mediated the association of CAA on cognitive decline among participants with high neuritic plaque burden, such that the mediating effect of tau was largest in the groups with more severe CAA (*top right*). The mediation was not significant among participants with low neuritic plaque burden (*top left*). Across both the high and low neuritic plaque groups, the direct effect of CAA on cognitive decline was not significant (*bottom panels*). Cognition is represented in standard deviation units per 5 years.

We further observed that tau mediated the association of greater CAA severity and cognitive decline in those with higher parenchymal Aβ burden. These findings suggest that one route by which CAA drives cognitive impairment is through Alzheimer's disease pathways.

Despite a modest positive association between CAA severity and parenchymal Aβ burden, we found that these two neuropathologies interacted to promote tau pathology. Specifically, higher parenchymal Aβ burden accelerated tau burden in a dose dependent manner across mild, moderate and severe CAA groups. These findings are consistent with previous human and animal studies showing an association between CAA and increased Alzheimer's disease pathology burden. For example, in a pericyte-deficient mouse model of Alzheimer's disease, CAA and Aβ burden together influenced the development of tau burden.[48] In another study, Williams and colleagues reported that in patients with Alzheimer's disease, tau burden was higher around blood vessels with moderate to marked CAA compared to blood vessels with little or no CAA.[29] Similarly, in a cohort study of older Japanese-American men, autopsy cases with CAA had more neuritic plaques and neurofibrillary tangles compared to cases without CAA.[26] Together, these findings suggest that CAA, in the setting of elevated parenchymal Aβ burden, may accelerate tau accumulation.

The mechanism by which CAA and Aβ pathology interact to promote tau remains unclear. One possibility is that Aβ aggregation in the vessel walls (i.e. CAA) leads to reduced Aβ clearance via perivascular drainage pathways. Interference with perivascular clearance might increase vascular and parenchymal Aβ accumulation[21,49–51] and accelerate tau.[52–54] Tau pathology, in turn, might impact the brain's vasculature,[55] further exacerbating vascular and parenchymal Aβ accumulation.[56] Pericyte loss may also play a central role in this cascade. Pericytes are critical to the integrity of the blood–brain barrier and degenerate in the setting of CAA and Alzheimer's disease.[57] Animal work shows that pericyte loss not only accelerates the breakdown of the blood–brain barrier, but also accelerates parenchymal Aβ, CAA and tau accumulation.[48] Neuroinflammation may also be the link by which combined CAA and parenchymal Aβ leads to elevated tau burden. Chronic activation of microglia promotes parenchymal Aβ accumulation and leads to the development of tau tangles.[58–60] The presence of vascular Aβ might exacerbate this neuroinflammatory response, further amplifying tau accumulation and spreading.

Another major finding was that greater CAA severity and parenchymal Aβ burden synergistically influenced cognitive decline. Specifically, the fastest rates of cognitive decline were observed in those with combined moderate or severe CAA and higher parenchymal Aβ burden. However, even mild CAA (relative to cases with no CAA) was associated with accelerated cognitive decline in the presence of elevated parenchymal Aβ burden. Several prior studies report an association between more severe levels of CAA and worse cognition[24,26,61]; however, those studies did not consider the interaction of CAA with parenchymal Aβ burden in their models. Our findings add to the literature by showing that Alzheimer's disease clinical progression is accelerated in a synergistic manner when there is co-occurring CAA.

An important goal of the present study was to determine the mechanism by which combined CAA and parenchymal Aβ burden accelerate cognitive decline. Here, we examined the possibility that tau plays an intermediary role in this association. This hypothesis was motivated by a large body of work suggesting that neocortical tau accumulation occurs downstream of Aβ burden[62–64] and is

closely tied to cognitive impairment.[39,65,66] Our causal mediation analysis supported this view. Specifically, in the high parenchymal Aβ subgroup, tau mediated the association between moderate to severe CAA and cognitive decline, suggesting that tau plays a critical role in the chain of events that ultimately leads to dementia.

It was somewhat surprising that we did not observe a direct effect of CAA on cognitive decline (that was not mediated by tau burden) given that CAA triggers a host of vascular changes that are known to affect cognition.[25,67] However, this observation may partly be explained by the sample composition. It is possible that the sample underrepresents individuals with severe symptomatic CAA as a result of the study inclusion criteria (i.e. no known dementia at baseline in participants who are on average 80 years old).[68] In severe symptomatic cases of CAA, brain lesions, such as lobar haemorrhages, microbleeds and superficial siderosis, might be more likely to directly affect cognition[69,70] (i.e. independent of tau).

The present findings have implications for clinical trials and therapeutic development. First and foremost, our results suggest that when there is co-occurring parenchymal and vascular Aβ, both pathologies could be targeted to slow the progression of Alzheimer's disease dementia. Recent efforts targeting vascular Aβ have not been successful,[71] and therefore there is a need for additional research focused on effective therapies for CAA. Second, our results have implications for anti-Aβ therapies, which have been at the forefront of disease-modifying treatments for Alzheimer's disease. Successful removal of Aβ from the brain has been associated with amyloid-related imaging abnormalities (ARIA).[72] It is not fully understood why ARIA develops; however, current evidence suggests that anti-Aβ therapies release Aβ into the vessels, which may exacerbate CAA, perivascular inflammation and/or impair perivascular clearance.[21] As suggested previously[21,73] and in line with the present findings, these secondary effects may ultimately promote (rather than hinder) the progression of neurodegeneration and dementia. Currently, anti-Aβ trials exclude individuals with imaging evidence of CAA (due to concerns of ARIA).[74] While this makes sense from a safety perspective, it may result in trials excluding patients who are expected to progress more quickly.

Strengths of this study include the large sample size, annual cognitive testing over an average of 8.8 years, high autopsy rates, uniform neuropathological evaluations across the three Rush cohorts and consistency of findings across sensitivity analyses. However, limitations to this study also warrant consideration. First, the study sample was highly educated and predominantly White. Therefore, our findings might not generalize to more diverse populations. Second, the three Rush cohorts enrol older adults without known dementia who are on average 80 years old.[68] This might lead to a healthy volunteer effect to some degree, whereby study participants are healthier than the general population.[75] Third, neuropathology analyses are inherently cross-sectional and therefore we made assumptions about the temporal sequencing of the processes studied (e.g. that cognitive decline results from neuropathology even though pathological changes were measured after cognition was assessed).

In summary, our findings suggest that more severe levels of CAA pathology and higher parenchymal Aβ burden are synergistically associated with cognitive decline indirectly via tau burden. These findings highlight the dynamic interplay between CAA and Alzheimer's disease pathology in accelerating the clinical and pathological progression of Alzheimer's disease. These results have important implications for Alzheimer's disease clinical trials and therapeutic development.

Acknowledgements

This manuscript resulted from a conference that was funded in part by a grant from the National Institute on Aging to the University of California, Davis (R13 AG030995, Dan Mungas PI).

Funding

J.S.R. receives support from the Harquail Centre for Neuromodulation, the Dr. Sandra Black Centre for Brain Resilience & Recovery and Canadian Institutes of Health Research (173253, 438475). E.N. receives support from T32AG000247. R.L. receives support from K99AG065501. K.B.C. receives support from R01AG072475. C.L.S. receives support from the Texas Alzheimer's Research and Care Consortium (2020-58-81-CR) and R01 AG059727, UF1 NS125513 and P30 AG066546. J.A.S. receives support from P30AG010161/P30AG072975, R01AG015819, R01AG17917, R01AG022018. J.P. receives support from RF1AG054617.

Competing interests

J.A.S.: Scientific Advisory Board/Consultant: AVID radiopharmaceuticals (subsidiary of Lilly), Alnylam Pharmaceuticals, Apellis Pharmaceuticals, Takeda Pharmaceuticals, National Hockey League.

Supplementary material

Supplementary material is available at *Brain* online.

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