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Tau-PET pathology in the subregions of the amygdala and its associations with cognitive performance and neuropsychiatric symptoms in autosomal dominant Alzheimer's disease

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Abstract

Background The amygdala plays a role in behavior and emotional response and is vulnerable to Alzheimer's disease (AD) pathology, yet little is known about amygdala tau accumulation before clinical symptom onset. To investigate whether certain amygdala nuclei are particularly vulnerable to degeneration and might underlie early neuropsychiatric symptoms in AD, we aimed to characterize subregional amygdala tau pathology and its correlates associations with established biomarkers of early AD and cognitive-behavioral measures in Presenilin-1 E280A mutation carriers of autosomal dominant AD.

Methods Participants included 25 cognitively unimpaired mutation carriers and 37 non-carrier family members from the Colombia-Boston (COLBOS) Biomarker Study. Measures included 18F-flortaucipir, 11C-Pittsburgh compound B, Consortium to Establish a Registry for Alzheimer's Disease Word List Learning, Trail Making Test, Geriatric Depression Scale, and Geriatric Anxiety Inventory. We examined group differences in amygdala tau levels (whole amygdala, lateral nucleus and basal nucleus) and analyzed tau associations with disease markers and clinical measures.

Results Amygdala tau levels were higher in unimpaired carriers compared to non-carriers. Among carriers, the basal nucleus showed a greater tau burden than the lateral nucleus, and tau accumulation correlated with closer estimated age to clinical onset and increased cortical amyloid. Additionally, tau in both the basal and lateral amygdala was associated with poorer working memory, lower executive function and greater depressive symptoms. However, amygdala tau did not correlate with symptoms of anxiety. Notably, tau levels in the basal amygdala differentiated carriers from non-carriers, with higher predictive accuracy when neuropsychiatric measures were included.

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Conclusions These findings suggest that in autosomal dominant AD, tau accumulation in the amygdala begins early in the basal nucleus, while both the basal and the lateral nuclei are associated with early cognitive deficits and depressive symptoms. The nuclei's differential vulnerability to pathology underscores the importance of investigating tau spread within amygdala-associated networks, relative to the early clinical manifestations of AD. This study reinforces the potential of amygdala tau burden as a valuable biomarker for preclinical AD.

Keywords Autosomal-dominant Alzheimer's disease, Neuropsychiatric symptoms, Tau pathology, Amygdala, PET imaging

Background

Alzheimer's disease (AD) consists of a long preclinical phase during which amyloid-β (Aβ) plaques and neurofibrillary tau tangles accumulate before the onset of clinical symptoms [1]. The amygdala, a collection of nuclei in the medial temporal lobe, is one of the regions vulnerable to AD early in the disease progression [2] and is theorized to be a site vulnerable to pathology that results in accelerated cognitive decline and neuropsychiatric symptoms [3]. While the amygdala is considered a reservoir of Aβ pathology in later stages of disease [4], there is growing evidence for amygdala tau accumulation to be an earlier event in AD patients [5] and in cognitively unimpaired older adults with high levels of cortical Aβ [6–8]. Notably, tau accumulation in the amygdala has been proposed to start prior to other medial temporal regions [9, 10].

Amygdala nuclei have differential vulnerability to dementia pathology likely due to their functionality and associated networks [3]. Post-mortem investigations of neurofibrillary tau tangles in AD patients report higher intracellular tangle concentrations in the basal nucleus compared to the lateral nucleus [11, 12]. These areas of high tangle burden co-localize with greater amygdala atrophy observed in vivo in cognitively unimpaired older adults who subsequently progressed to mild cognitive impairment or dementia [11, 12]. Thus, tau accumulation in amygdala subregions may be differentially associated with clinical onset and progression and may provide additional insight into early disease detection. Characterizing these differences could have important implications in understanding cognitive-behavioral symptoms of early AD.

The amygdala is critically involved in memory function and emotion processing and regulation [13, 14], and early tau accumulation in amygdala subregions may explain neuropsychiatric symptoms in AD [3]. Mild behavioral impairment is characterized by apathy, depression, anxiety, agitation and psychosis, among other symptoms [15]. Such symptoms are prevalent in 60–90% of patients living with dementia [16] and up to 15% of cognitively unimpaired older adults at increased risk for AD [17], being increasingly recognized as one of the earliest manifestations of the disease [1]. In particular, in cognitively normal adults, depressive symptoms have been associated with cognitive decline [18] and with faster progression to dementia [19]. Depression and other neuropsychiatric symptoms have been shown to correlate with tau accumulation, however, existing studies have mainly focused on medial temporal lobe structures [20–22].

Despite the clinical significance of identifying early sites of pathological burden for future intervention studies, amygdala tau pathology and its cognitive and neuropsychiatric correlates are critically understudied in preclinical AD and autosomal dominant AD (ADAD). To address this gap, we examined amygdala tau pathology in cognitively unimpaired members of a Colombian kindred with a high prevalence of individuals who carry the E280A mutation on the Presenilin-1 (*PSEN1*) gene. Carriers of the *PSEN1* E280A mutation develop mild cognitive impairment at a median age of 44 years and dementia at 49 years [23], providing the ability to examine preclinical pathology in adults who are genetically determined to develop AD dementia with high certainty. Here, we sought to determine whether amygdala tau pathology is evident in *PSEN1* E280A mutation carriers prior to dementia onset and to characterize tau accumulation relative to known AD risk factors (i.e., estimated age from clinical onset and cortical Aβ) and cognitive-behavioral symptoms. We specifically focused on working memory and executive function domains, initial cognitive deficits often observed in early AD [24], as well as depressive and anxious symptoms, which may serve as behavioral indicators of early stage AD. Secondarily, we explored the vulnerability of basal and lateral amygdala nuclei to tau pathology, with the hypothesis that the basal nucleus would be primarily affected. Subregional amygdala volumes were additionally compared between groups and characterized in terms of clinical outcomes. Finally, we investigated whether tau accumulation in different amygdala nuclei, combined with cognitive-behavioral measures, could differentiate carriers from non-carriers compared to other medial temporal lobe structures.

Materials and methods

Participants

This study included participants from the Colombia-Boston (COLBOS) Biomarker Study, conducted by the Massachusetts General Hospital (Boston, USA) in collaboration with the Neuroscience Group of Antioquia at the University of Antioquia (Medellin, Colombia), which recruits members of a kindred with a high prevalence of the *PSEN1* E280A mutation for ADAD. In this study, participants were excluded if they met a diagnosis of dementia or mild cognitive impairment, had a significant medical, psychiatric, or neurological disorder, or a history of stroke, seizures, or substance abuse. All participants who met eligibility criteria and had available neuroimaging and neuropsychological evaluations were included in this study. Cognitive impairment was determined via the Functional Assessment Staging Tool (FAST; range: 1–7), with a score ≤ 2 indicating no objective impairment [25]. The final sample included 25 cognitively unimpaired carriers and 37 non-carrier family members. All participants provided written informed consent before participating and were compensated. The study was approved by the University of Antioquia and the Massachusetts General Hospital local institutional review boards. Researchers and participants were blind to genetic status.

Neuropsychological tasks and clinical measures

Neuropsychological testing was conducted in Spanish at the University of Antioquia within six months of neuroimaging data collection. Global objective cognition was assessed via Mini Mental State Examination (MMSE; range: 0–30) scores [26]. Working memory was assessed using the Colombian version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning in Spanish and executive function using the Trail Making Test Part B (TMB-T) [27]. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS; range: 0–15) [28, 29], a self-reported measure of depressive symptoms consisting of 15 yes/no questions. Anxious symptoms were assessed using the Geriatric Anxiety Inventory (GAI; range: 0–20), a self-reported measure of 20 agree/disagree items [30].

Image acquisition and processing

Magnetic resonance imaging (MRI) and positron emission tomography (PET) were conducted at Massachusetts General Hospital. Structural T1-weighted MRI data were acquired using a Siemens 3 Tesla Tim Trio scanner (repetition time = 2300 ms, echo time = 2.95 ms, flip angle = 9 degrees, voxel size = $1.05 \times 1.05 \times 1.2$ mm). Images were processed using FreeSurfer v6 [31] to identify white and pial surfaces, along with regions of interest (ROIs) from the Desikan atlas for PET sampling [32] and segmentation of amygdala nuclei (available as an add-on to version 6) [33]. Outputs were quality checked for accuracy, and manual edits were made when necessary to ensure accurate segmentation and surface identification.

PET data were acquired on a Siemens ECAT HR + scanner (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; 2.4 mm slice interval). Tau data were acquired using the 18F-flortaucipir (FTP) tracer from 80–100 min post-injection in 4×5-min frames. Aβ data were acquired using the 11C-Pittsburgh compound B (PiB) tracer using a 60-min dynamic protocol and analyzed by the Logan reference method [34]. Outcome measures were standardized uptake value ratio (SUVr) for FTP and distribution volume ratio (DVR) for PiB, using cerebellar gray matter as the reference region for both outcomes. The cut-off point for PiB positivity was DVR = 1.2, as previously defined [35]. Co-registration between PET and T1 images was performed using affine transformation, and all PET data were sampled using FreeSurfer-derived ROIs. A composite region comprising frontal, lateral temporal, parietal, and retrosplenial cortices was used to represent PiB DVR [36]. Because we had no hypotheses about lateralization, and there were no hemispheric differences in amygdala tau accumulation in any group ($ps > 0.312$), the left and right hemispheres were averaged for each FTP ROI. Due to the spatial resolution of the images, a composite "basal" region was created from the basal and accessory basal amygdala nuclei using in-house scripts to combine SUVr uptake in each nucleus, adjusting for the voxel size of each region. The whole amygdala, composite basal region, and lateral nucleus were identified as a priori ROIs (Supplementary Fig. 1). SUVr uptake was additionally averaged in the entorhinal cortex and the inferior temporal lobe as ROIs of the medial temporal lobe. For voxel-wise analyses, tau-PET images were normalized to standard space.

Statistical analysis

Analyses were ran in R (v4.1.1) using two-sided tests and an alpha level of 0.05 to determine statistical significance. Demographic characteristics were compared across groups using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Amygdala tau uptake and volumes were compared between groups using the Wilcoxon rank sum test and within-subjects subregional tau uptake in the basal and lateral nuclei was compared using the Wilcoxon signed-rank test. Voxel-wise amygdala tau uptake was compared between carriers and non-carriers within bilateral amygdala ROIs using two-tailed t-tests with false discovery rate (FDR) correction for multiple comparisons. Spearman rank correlation was used to examine associations of tau and volumes with

estimated years from clinical onset, Aβ, and neuropsychological measures (CERAD Word List Learning, TMT-B time, GDS and GAI). To study the predictive performance of subregional amygdala tau in differentiating *PSEN1* mutation carriers from non-carriers, logistic regression models were fitted using carriership as the outcome and SUVr in the basal, lateral or whole amygdala as individual predictors. In combination with tau, secondary models additionally included cognitive and neuropsychological measures as predictors (CERAD Word List Learning, TMT-B time, GDS and GAI). Fitted values were used in the receiver operating characteristic analysis to obtain the corresponding areas under the curve (AUCs), which were compared using DeLong's test. All analyses were repeated using entorhinal and inferior temporal tau.

Results

Participant characteristics

Demographic characteristics are shown in Table 1. Cognitively unimpaired carriers and non-carriers did not differ in age ($p=0.763$), years of education ($p=0.181$) or sex distribution ($p>0.999$). Cognitively unimpaired carriers had lower MMSE scores ($p=0.018$) and lower memory performance ($p=0.023$) than non-carriers. Groups did not differ in FAST score ($p=0.052$), executive function ($p=0.166$), depressive ($p=0.719$) or anxious ($p=0.411$) symptoms.

Group differences in amygdala and subregional tau burden

Group comparisons indicated higher tau uptake in cognitively unimpaired carriers compared to non-carriers in the amygdala ($W=210$, $r=0.46$, $p<0.001$), as well as in basal ($W=181$, $r=0.51$, $p<0.001$) and lateral ($W=255$, $r=0.38$, $p=0.003$) amygdala subregions (Fig. 1A).

We further probed whether basal or lateral amygdala nuclei were particularly affected by tau accumulation, finding higher tau SUVr in the basal compared to the lateral region in cognitively unimpaired carriers ($W=309$, $r=0.79$, $p<0.001$, Fig. 1B). There was no difference in non-carriers ($W=344$, $r=0.02$, $p=0.917$). We also performed a voxel-wise comparison of tau SUVr within the amygdala and the greatest differences in uptake between carriers and non-carriers were observed in the medial portions, consistent with the results from ROI analyses (Fig. 2).

Tau uptake in the entorhinal was also higher in cognitively unimpaired carriers than non-carriers ($W=225$, $r=0.43$, $p<0.001$) but not in the inferior temporal ($W=336$, $r=0.23$, $p=0.076$, Supplementary Fig. 2A).

Associations between amygdala tau and markers of disease progression

Next, we sought to characterize subregional amygdala tau accumulation in the context of two known risk factors in ADAD: estimated years from clinical onset, since the disease time course of ADAD due to the *PSEN1* E280A mutation is known with relative

Table 1 Participant demographics by group

	Non-Carriers ($n=37$)	Unimpaired Carriers ($n=25$)	*P*-value
Age (years)	35.8 [31.3 – 38.8]	35.8 [31.8 – 40.3]	0.763
Education (years)	11.0 [8.0 – 14.0]	11.0 [6.0 – 12.0]	0.181
Sex			1.000
Female	20 (54%)	14 (56%)	
Male	17 (46%)	11 (44%)	
Amyloid status			**<0.001**
PiB-	37 (100%)	8 (32%)	
PiB+	0	17 (68%)	
MMSE	29.0 [28.0 – 30.0]	28.0 [28.0 – 29.0]	**0.018**
FAST			0.052
1	35 (95%)	19 (76%)	
2	2 (5%)	6 (24%)	
CERAD Word List Learning	20.0 [19.0 – 23.0]	19.0 [16.0 – 21.0]	**0.023**
CERAD TMT-B Time	78.0 [56.0 – 103.0]	99.0 [54.0 – 138.0]	0.166
GDS-15	0.0 [0.0 – 2.0]	0.0 [0.0 – 2.0]	0.719
GAI-30	1.0 [0.0 – 3.0]	1.0 [0.0 – 6.0]	0.411

Continuous variables represented as median [interquartile range] and compared across groups using Wilcoxon rank sum tests; and categorical variables represented as n (%) and compared across groups using Fisher's exact tests

CERAD Consortium to Establish a Registry for Alzheimer's Disease, *FAST* Functional Assessment Staging Tool, *GAI* Geriatric Anxiety Inventory, *GDS* Geriatric Depression Scale, *MMSE* Mini Mental State Examination, *PiB* 11C-Pittsburgh compound B, *TMT-B* Trail Making Test Part B

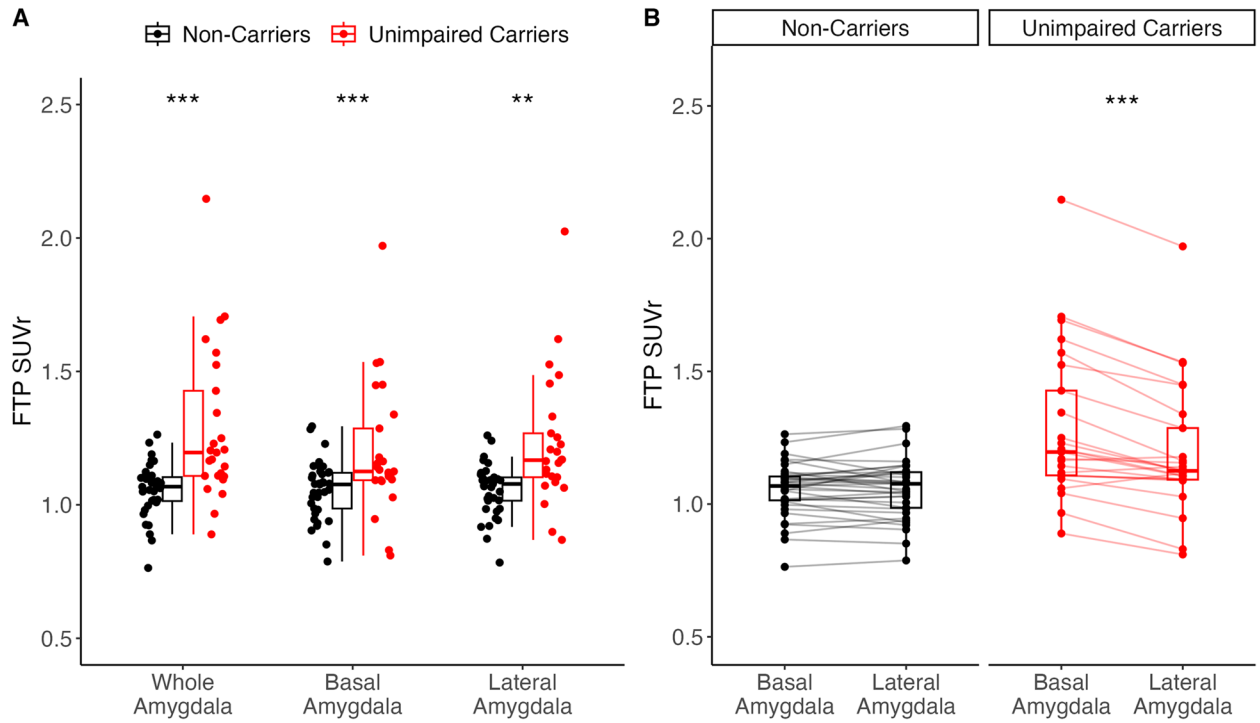

Fig. 1 Regional tau-PET accumulation in *PSEN1* E280A carriers and non-carriers. Differences in FTP SUVr in the whole amygdala and basal and lateral subregions between non-carriers (black) and cognitively unimpaired carriers (red) (**A**). Within-subject differences in subregional amygdala FTP SUVr (**B**). Each line connects an individual. Boxplots indicate median (bold line), first and third quartiles (box limits) and ± 1.5 times the interquartile range (whiskers). Between-group and within-group differences were assessed using Wilcoxon rank sum and Wilcoxon signed-rank tests, respectively. $^{**}p < .01$, $^{***}p < .001$; FTP = flortaucipir, SUVr = standardized uptake value ratio

certainty [23], and cortical Aβ. Proximity to clinical onset was associated with higher tau in the basal amygdala ($\rho = 0.61$, $p = 0.001$) and in the lateral amygdala ($\rho = 0.66$, $p < 0.001$) in cognitively unimpaired carriers but not in non-carriers (basal: $\rho = 0.06$, $p = 0.730$; lateral: $\rho = 0.22$, $p = 0.187$, Fig. 3A-B).

Higher cortical Aβ was associated with higher tau accumulation in cognitively unimpaired carriers (basal: $\rho = 0.51$, $p = 0.010$; lateral: $\rho = 0.50$, $p = 0.012$), however, there was no association in non-carriers (basal: $\rho = -0.04$, $p = 0.811$; lateral: $\rho = -0.02$, $p = 0.927$, Fig. 3C-D). In the whole amygdala, tau correlations with estimated years from onset and cortical Aβ were similar to those in the amygdala nuclei, for carriers and non-carriers (Supplementary Fig. 3).

The correlations of entorhinal and inferior temporal tau SUVr with estimated years from onset and cortical Aβ were similar in magnitude to those observed in the amygdala nuclei for carriers and non-carriers (Supplementary Fig. 2B-E).

Associations among amygdala tau, cognitive and neuropsychiatric measures

Next, we examined the associations among working memory, executive function, depressive, anxious symptoms and tau in the amygdala. In cognitively unimpaired carriers, lower Word List Learning was associated with higher tau in the basal nucleus ($\rho = -0.51$, $p = 0.010$), lateral amygdala ($\rho = -0.51$, $p = 0.010$, Fig. 4A-B) and whole amygdala ($\rho = -0.49$, $p = 0.013$, Supplementary Fig. 4A). There was no relationship between tau and working memory in non-carriers (basal: $\rho = 0.12$, $p = 0.483$; lateral: $\rho = 0.10$, $p = 0.565$; whole amygdala: $\rho = -0.10$, $p = 0.553$). Similarly, higher TMT-B time was associated with higher basal ($\rho = 0.41$, $p = 0.041$) and lateral ($\rho = 0.45$, $p = 0.023$) amygdala tau in carriers but not in non-carriers (basal: $\rho = 0.04$, $p = 0.796$; lateral: $\rho = 0.05$, $p = 0.769$, Fig. 4C-D). This correlation did not reach significance in the whole amygdala in carriers ($\rho = 0.39$, $p = 0.055$) nor in non-carriers ($\rho = 0.05$, $p = 0.786$, Supplementary Fig. 4B).

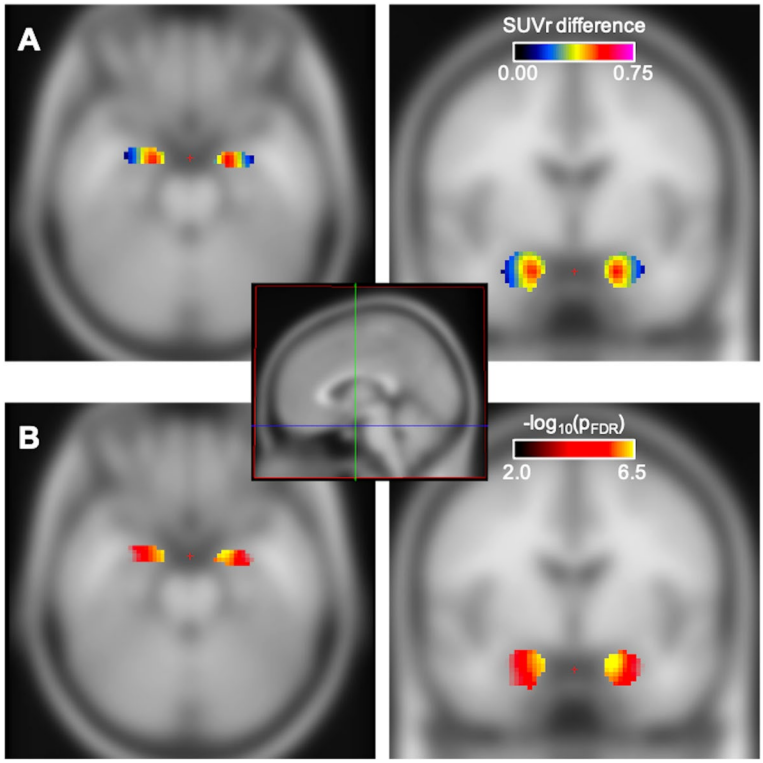

Fig. 2 Voxel-wise amygdala tau-PET accumulation in *PSEN1* E280A carriers and non-carriers. Tau-PET uptake was compared between carriers ($n=25$) and non-carriers ($n=37$) in voxels within the amygdala. Mean SUVr difference between carriers and non-carriers, with positive values indicating higher SUVr in carriers, according to the color scale (**A**). Significance of two-sample two-tailed t-tests at each voxel, displayed as $-\log_{10}(p)$ after FDR correction for multiple comparisons (**B**). FDR = false discovery rate; SUVr = standardized uptake value ratio

In cognitively unimpaired carriers, greater depressive symptoms were associated with higher tau burden in the basal nucleus ($\rho=0.47$, $p=0.019$) and lateral nucleus ($\rho=0.53$, $p=0.007$, Fig. 4E-F) as well as in the whole amygdala ($\rho=0.42$, $p=0.037$, Supplementary Fig. 4C). Subregional tau accumulation was not associated with depressive symptoms in non-carriers (basal: $\rho=-0.15$, $p=0.373$; lateral: $\rho=-0.09$, $p=0.603$; whole amygdala: $\rho=-0.10$, $p=0.555$). Additionally, there were no associations with anxious symptoms in amygdala nuclei (basal: $\rho=0.21$, $p=0.309$; lateral: $\rho=0.16$, $p=0.451$; Fig. 4G-H) or in the whole amygdala ($\rho=0.17$, $p=0.405$, Supplementary Fig. 4D) for cognitively unimpaired carriers nor for non-carriers (basal: $\rho=0.16$, $p=0.342$; lateral: $\rho=0.22$, $p=0.186$; whole amygdala: $\rho=0.21$, $p=0.204$).

Entorhinal tau was negatively correlated with working memory and positively correlated with TMT-B time in carriers, while no correlations were observed with GDS or GAI (Supplementary Fig. 5A-D). In the inferior temporal, higher tau was only correlated with increased TMT-B time (Supplementary Fig. 5E-H).

The sensitivity analysis showed that working memory was mildly associated with depressive and anxious symptoms in cognitively unimpaired carriers (Supplementary Table 1). Those correlations were not significant in non-carriers. Additionally, executive function was not associated with any neuropsychiatric symptoms in either group.

Discrimination between preclinical PSEN1 mutation carriers using subregional amygdala tau and neuropsychiatric measures

The receiver operating characteristic analysis was computed to test the performance of subregional amygdala tau in differentiating preclinical *PSEN1* mutation carriers vs non-carriers. The basal nucleus was the amygdala subregion with the highest AUC, with a better predictive performance than the lateral nucleus ($Z=-2.20$, $p=0.028$ [95% CI -0.15 – -0.01]) and nearly the whole amygdala ($Z=-1.93$, $p=0.054$ [95% CI -0.06 – 0.00]) (basal: AUC = 0.804 [95% CI 0.684 – 0.924], lateral: AUC = 0.724 [95% CI 0.588 – 0.861], whole amygdala: AUC = 0.773 [95% CI 0.642 – 0.904], Fig. 5). When including cognitive and neuropsychiatric symptoms to the previous models as additional predictors, the basal amygdala prevailed as the tau region with the highest AUC (AUC = 0.814 [95%

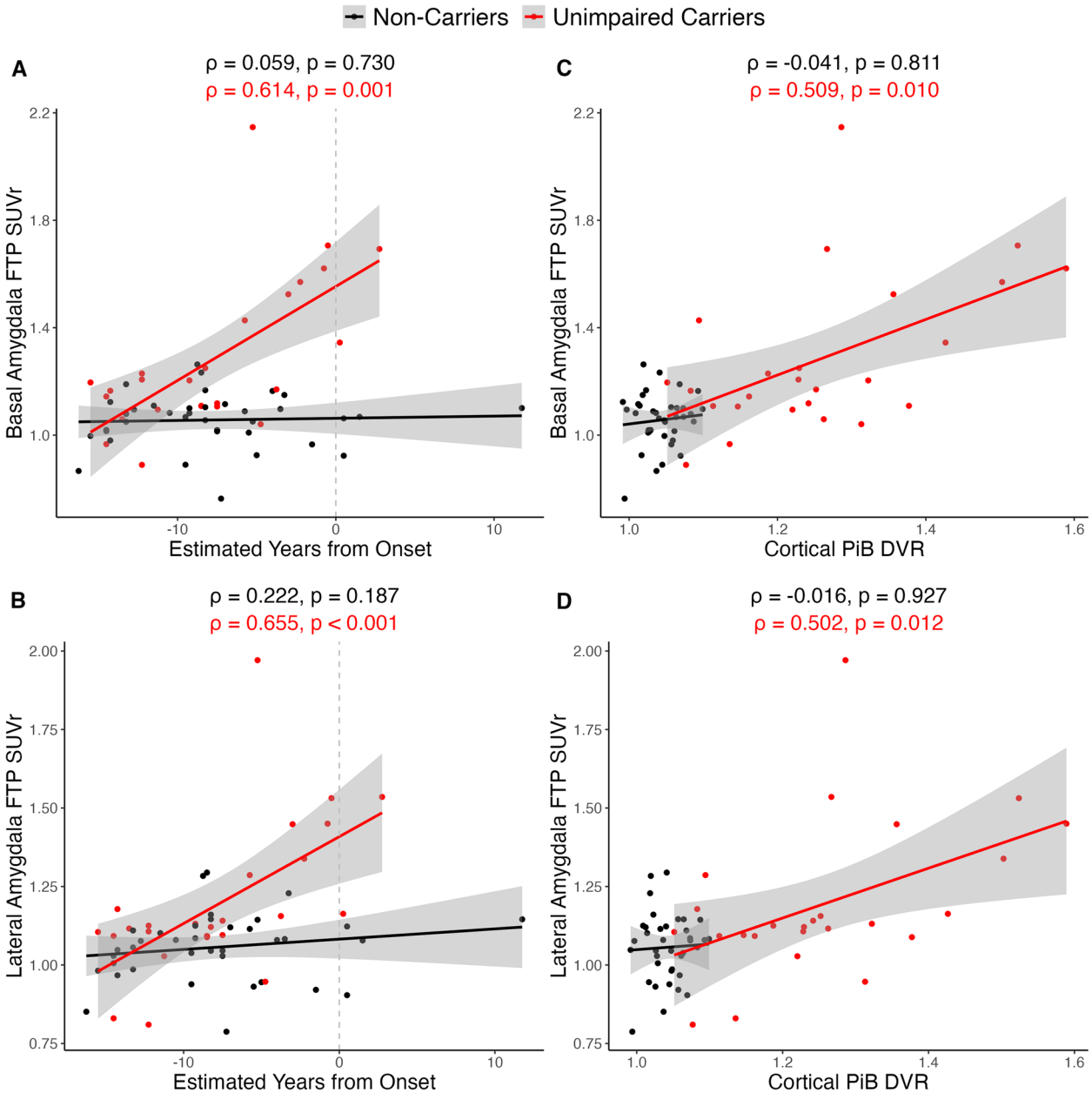

Fig. 3 Subregional amygdala tau associations with estimated years from clinical onset and cortical Aβ. Scatterplots showing the association between basal and lateral amygdala FTP SUVr and estimated years from onset (**A**, **B**) and cortical Aβ (**C**, **D**), respectively, in non-carriers (black) and cognitively unimpaired carriers (red). Color lines show estimated regression slopes and gray shadows represent 95% confidence intervals. Associations were derived from Spearman rank correlations. DVR = distribution volume ratio, FTP = flortaucipir, PiB = 11C-Pittsburgh compound B, SUVr = standardized uptake value ratio

CI 0.705 – 0.923], lateral: AUC = 0.729 [95% CI 0.599 – 0.858], whole amygdala: AUC = 0.800 [95% CI 0.688 – 0.912]).

Tau in the entorhinal cortex and inferior temporal lobe had lower AUC compared to tau in amygdala subregions. Compared to the basal amygdala, predictive performance was significantly worse in the inferior temporal lobe (Z = -2.73, $p = 0.006$ [95% CI -0.29 – -0.05]), but was considered statistically similar to that in the entorhinal cortex (Z = -0.70, $p = 0.487$ [95% CI -0.18 – 0.09], Supplementary Table 2).

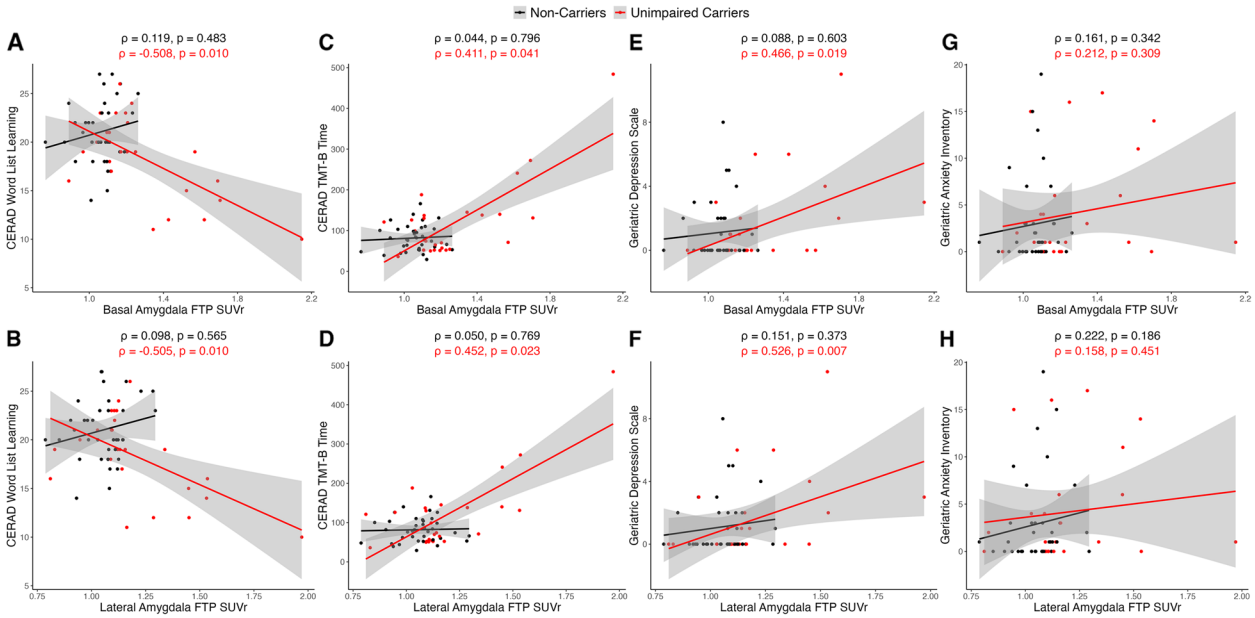

Fig. 4 Subregional amygdala tau associations with cognitive and neuropsychiatric measures. Scatterplots showing the association between basal and lateral amygdala FTP SUVr and CERAD Word List Learning (**A**, **B**), CERAD TMT-B time (**C**, **D**) depressive symptoms (**E**, **F**) and anxious symptoms (**G**, **H**), respectively, in non-carriers (black) and cognitively unimpaired carriers (red). Color lines show estimated regression slopes and gray shadows represent 95% confidence intervals. Associations were derived from Spearman rank correlations. CERAD = Consortium to Establish a Registry for Alzheimer's disease, FTP = flortaucipir, SUVr = standardized uptake value ratio, TMT-B = Trail Making Test Part B

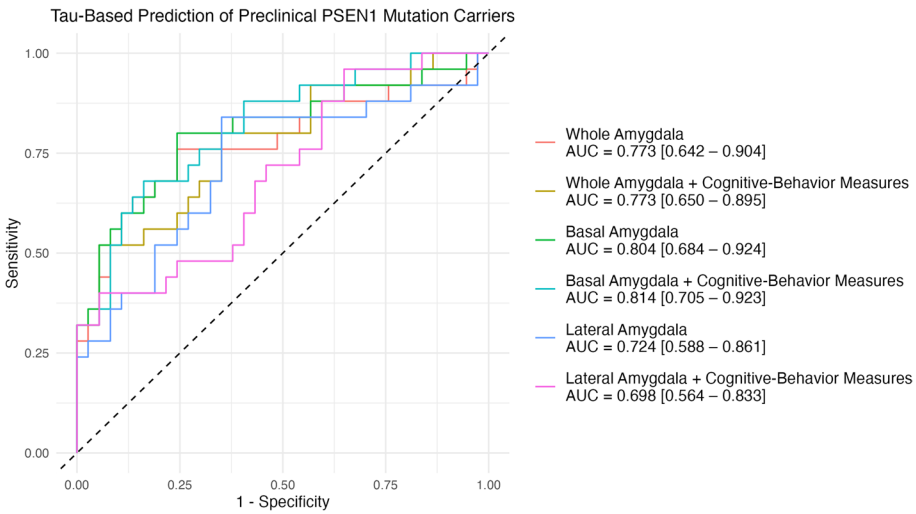

Fig. 5 Prediction of preclinical *PSEN1* mutation carriers using amygdala tau and cognitive-behavioral measures. Receiver operating characteristic analysis output of 6 models comparing the predictive performance of *PSEN1* carriership using tau pathology in the basal, lateral and whole amygdala with and without cognitive (CERAD Word List Learning and TMT-B time) and neuropsychiatric (GDS and GAI) measures as additional predictors. AUC = Area under the curve, CERAD = Consortium to Establish a Registry for Alzheimer's disease, GAI = Geriatric Anxiety Inventory, GDS = Geriatric Depression Scale, TMT-B = Trail Making Test Part B

Subregional amygdala volumes among groups and association with tau and clinical outcomes

Finally, we aimed to characterize subregional amygdala volumes in the context of preclinical ADAD. There were no differences in volume between cognitively unimpaired carriers and non-carriers in the whole amygdala or amygdala nuclei and subregional volumes were not associated with tau accumulation (Supplementary Fig. 6).

Subregional amygdala volumes were not correlated with cognitive or neuropsychiatric symptoms in carriers, except for the association between lower whole amygdala volume and greater depressive symptoms (Supplementary Fig. 7).

Discussion

The amygdala underlies cognitive and emotional processes [13, 14] and is theorized to play a critical role in the progression of AD pathology [3, 4]. To address the limited research on preclinical amygdala tau and its cognitive-behavioral associations, we leveraged a unique cohort of *PSEN1* E280A mutation carriers to characterize early subregional amygdala tau accumulation in ADAD, focusing on its associations with known biomarkers of AD progression, cognition, and neuropsychiatric symptoms. We found that amygdala tau is elevated in preclinical *PSEN1* E280A mutation carriers, with the basal nucleus showing higher tau accumulation than the lateral nucleus. Amygdala tau was also associated with closer estimated age to clinical onset and higher cortical Aβ burden. Worse memory performance and executive function as well as greater depressive symptoms were associated with higher tau burden in both basal and lateral amygdala nuclei. Further, tau accumulation in the basal nucleus showed better differentiation of mutation carriers vs non-carriers compared to the lateral nucleus, and this prediction improved when considering cognitive-behavioral measures. Our findings suggest that subregional amygdala tau quantification may provide additional insight into preclinical pathological changes in AD.

Prior work in *PSEN1* E280A carriers has identified the earliest observed tau-PET accumulation approximately a decade before estimated clinical onset in the medial temporal lobe [37, 38]. Our results highlight the amygdala as an important early site of tau pathology accumulation in this Colombian kindred. Consistent with our findings, elevated amygdala tau accumulation in sporadic AD has been documented in cognitively unimpaired older adults with high Aβ [6–8, 39], and possibly prior to entorhinal cortex or inferior temporal lobe [9, 10]. We found that greater amygdala tau burden is associated with closer estimated age to clinical onset and greater cortical Aβ in cognitively unimpaired *PSEN1* mutation carriers, in line with previous reports in older adults [8, 40]. Yet, Aβ is thought to accumulate in the amygdala at later stages, following tau accumulation in Braak stage I-II, as shown in autopsy data [11, 12]. Together, these findings highlight the importance of characterizing early amygdala tau accumulation. It has been previously demonstrated that tau-PET is superior over Aβ-PET or 18F-fluorodeoxyglucose-PET in identifying cognitive impairment in preclinical AD [41, 42] and its increasing availability positions amygdala imaging as a promising biomarker for enrichment in clinical trials and monitoring disease progression in ADAD.

Our subregional and voxel-wise analyses revealed important distinctions in basal and lateral tau accumulation. According to our hypothesis, the basal nucleus was the amygdala subregion with the largest tau difference between cognitively unimpaired carriers and non-carriers and had higher tau burden than the lateral nucleus among those carrying the *PSEN1* mutation. To our knowledge, this is the first report demonstrating amygdala subregional differences in preclinical ADAD. Our results are consistent with post-mortem neuropathological studies indicating high densities of neurofibrillary tangles in basal nuclei along with a high degree of basal nuclei atrophy in sporadic AD [11, 12]. In fact, amygdala volume loss has been identified as an independent predictor of cognitive performance and conversion to dementia, compared to other regional volumes [12, 43, 44]. In this preclinical population, we did not corroborate those findings, as amygdala volume did not differ between carriers and non-carriers and was not correlated with tau accumulation. This suggests that the basal amygdala nuclei may have a specific early predisposition to tauopathy before neurodegeneration.

Despite the differential functionality of amygdala nuclei, tau accumulation in the whole amygdala and in both the basal and lateral nuclei was associated with lower memory performance and executive function. Multiple reports have suggested that Aβ alone is insufficient to produce cognitive impairment, pointing to tau pathology as a greater contributor to clinical symptoms [1, 45]. Aligning with our study, medial temporal lobe tau has been reported to correlate with the largest changes in episodic memory and executive functioning [46]. Specifically, greater amygdala tau shows associations with memory deficits across the AD spectrum [45, 47], suggesting a central role in the progression of AD. Notably, we also found that basal and lateral amygdala tau accumulation correlate with greater depressive symptoms, evidencing its additional role in emotion processing and regulation [13, 14]. Previous PET studies have similarly shown that different neuropsychiatric scores correlate with greater tau burden across Braak stages in the AD continuum [20, 48, 49]. Different emotional domains might be associated with distinct patterns of tau uptake in AD [21], with depression and affective symptoms being reported to correlate with tau accumulation in the entorhinal cortex, transentorhinal region and inferior temporal lobe [22, 50]. In line with a study showing that tau accumulation in the medial temporal lobe was more strongly linked to depression than anxiety [51], anxious symptoms were

not associated with tau in any amygdala subregion investigated in our cohort, possibly indicating that anxiety may manifest later in the disease or is regulated by other amygdala nuclei, such as the medial nucleus [52]. Based on our findings, we could hypothesize that, in a preclinical population, the amygdala may be an epicenter of tau pathology linked to the onset of treatable neuropsychiatric symptoms, which have been increasingly considered as early predictors of AD [18, 51, 53], possibly preceding cognitive impairment [14, 19, 54]. However, it remains unclear whether the presence of Aβ is needed to accelerate the progression of neuropsychiatric symptoms [48, 55] or whether these symptoms are risk factors for the progression to cognitive impairment independently of AD biomarkers [54].

Our prediction analysis further suggested that subregional amygdala tau quantification could be useful for disease diagnosis and staging of preclinical populations. The basal nucleus showed higher accuracy in differentiating preclinical *PSEN1* mutation carriers from non-carriers compared to the lateral nucleus and to a lesser extent the whole amygdala. Although discrimination accuracy was not statistically different, we found a trend for improved predictive performance of tau accumulation in the basal amygdala when accounting for cognition and neuropsychiatric measures, underscoring the importance of neuropsychiatric assessment in preclinical AD as a potential screening tool to identify individuals at high-risk who could benefit from prevention strategies. The reasoning behind the different basal versus lateral nuclei involvement may lie in the spatio-temporal spread of tau across amygdala-associated networks, since heterogeneity in the order tau pathology affects the medial temporal lobe is presumed to explain differences in AD clinical manifestation [56, 57]. Yet, the clinical correlates of subregional amygdala tau and its functional connections warrant further investigation. While the treatment of neuropsychiatric symptoms in preclinical AD may offer an alternative target for therapeutics, future work should further probe the accumulation of tau pathology across amygdala nuclei, along with the associated longitudinal cognitive and neuropsychiatric changes [58].

The difference in tau accumulation between carriers and non-carriers in the amygdala was similar in magnitude to that in the entorhinal cortex. Tau burden in carriers starts to deviate from non-carriers 10–15 years prior to the estimated age of clinical onset in these regions, as reported previously [38]. Moreover, tau correlations with markers of disease progression and cognition were also comparable in the amygdala, entorhinal and inferior temporal regions. However, entorhinal or inferior temporal tau did not correlate with depressive symptoms in carriers, which may be specific to the amygdala and its nuclei, emphasizing amygdala's unique involvement in disease progression. Additionally, amygdala subregions outperformed other structures of the medial temporal lobe in discriminating mutation carriers from non-carriers, suggesting that amygdala tau quantification may offer an added value to PET studies and is worth exploring in the context of tau spread through the medial temporal lobe [59].

This is the first study considering subregional amygdala tau-PET pathology in ADAD. A primary strength of this study is the unique cohort of carriers of a single mutation for ADAD on the *PSEN1* gene. Due to the early age of onset (median age: 44 years [23]), we were able to examine tau pathology without the confounds of normal aging. This is critical in studies of tau pathology because aging individuals can develop tau neurofibrillary tangles in medial temporal lobe regions, including the amygdala, in the absence of dementia [60]. Additionally, *PSEN1* E280A mutation carriers follow a well-characterized trajectory of pathological and clinical decline [23, 40]. Therefore, although data are cross-sectional, we know with certainty which participants will develop dementia and with relative certainty the estimated years until dementia onset. This study also has several limitations. While investigating a kindred with a single ADAD mutation provides methodological and conceptual benefits, the current sample is limited in size. Also, this cognitively unimpaired population is well-preserved in terms of neuropsychiatric symptoms and does not offer much variability in terms of depressive and anxious symptoms, which were not clinically significant resulting in a floor-effect in GDS and GAI metrics. This limitation will be addressed in the future using other metrics that may be more robust and sensitive to early neuropsychiatric changes, such as the mild behavioral impairment checklist. Secondly, there is considerable overlap between in vivo pathology in ADAD and sporadic AD [61], but whether these results are generalizable to sporadic AD and other dementias is currently unknown. Moreover, tau PET has limited spatial resolution and this study investigates small brain regions in the medial temporal lobe, which could be impacted by partial volume effect. Finally, this study examines cross-sectional relationships, but longitudinal studies are needed to clarify the progression of tau pathology and its causal relationships with clinical, cognitive and neuropsychiatric measures.

Conclusions

In sum, amygdala tau accumulation is evident in preclinical ADAD and is associated with worse memory performance and executive function and greater depressive symptoms. Amygdala tau is higher in *PSEN1* E280A mutation carriers who are approaching clinical

symptom onset and have higher cortical Aβ. Further, subregional differences between basal and lateral amygdala nuclei suggest that fine-grained analyses may aid in the early detection of pathology. Together, these data highlight the importance of amygdala tau accumulation as a potential novel biomarker for preclinical AD.

Abbreviations

Aβ	Amyloid-β
AD	Alzheimer's disease
ADAD	Autosomal-dominant Alzheimer's disease
AUC	Area under the curve
CERAD	Consortium to Establish a Registry for Alzheimer's disease
COLBOS	Colombia-Boston Biomarker Study
DVR	Distribution volume ratio
FAST	Functional assessment staging tool
FDR	False discovery rate
FTP	18F-Flortaucipir
GAI	Geriatric anxiety inventory
GDS	Geriatric depression scale
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PiB	11C-Pittsburgh compound B
PSEN1	Presenilin-1 gene
ROI	Region of interest
SUVr	Standardized uptake value ratio
TMT-B	Trail Making Test Part B

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Y.T.Q., R.A.S., K.J., and J.R.G initiated this work. Y.T.Q. and K.J. directed and supervised conduction of the study. C.T.P. and S.L. drafted the manuscript. Clinical information was collected and analyzed by D.A., D.V., A.B., C.R., C.V.-C., J.A., J.M., A.G. PET scans were collected and analyzed by Z.R., V.M., B.H., J.S.S. Statistical analyses were conducted by C.T.P. J.S.S., and S.L. All authors revised and contributed to finalize the manuscript.

Data availability

Anonymized clinical, genetic and imaging data are available upon request, subject to an internal review by Y.T.Q. to ensure that the participants' anonymity, confidentiality, and PSEN1 E280A carrier or non-carrier status are protected. Data requests will be considered based on a proposal review, and completion of a data sharing agreement, in accordance with the University of Antioquia and Mass General Brigham institutional guidelines. Please submit data requests to Y.T.Q.

Declarations

Ethics approval and consent to participate

All participants provided written informed consent before participating and were compensated. The study was approved by the University of Antioquia (Medellin, Colombia) and the Massachusetts General Hospital (Boston, USA) local institutional review boards. Researchers and participants were blind to genetic status.

Competing interests

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