Supplementary materials

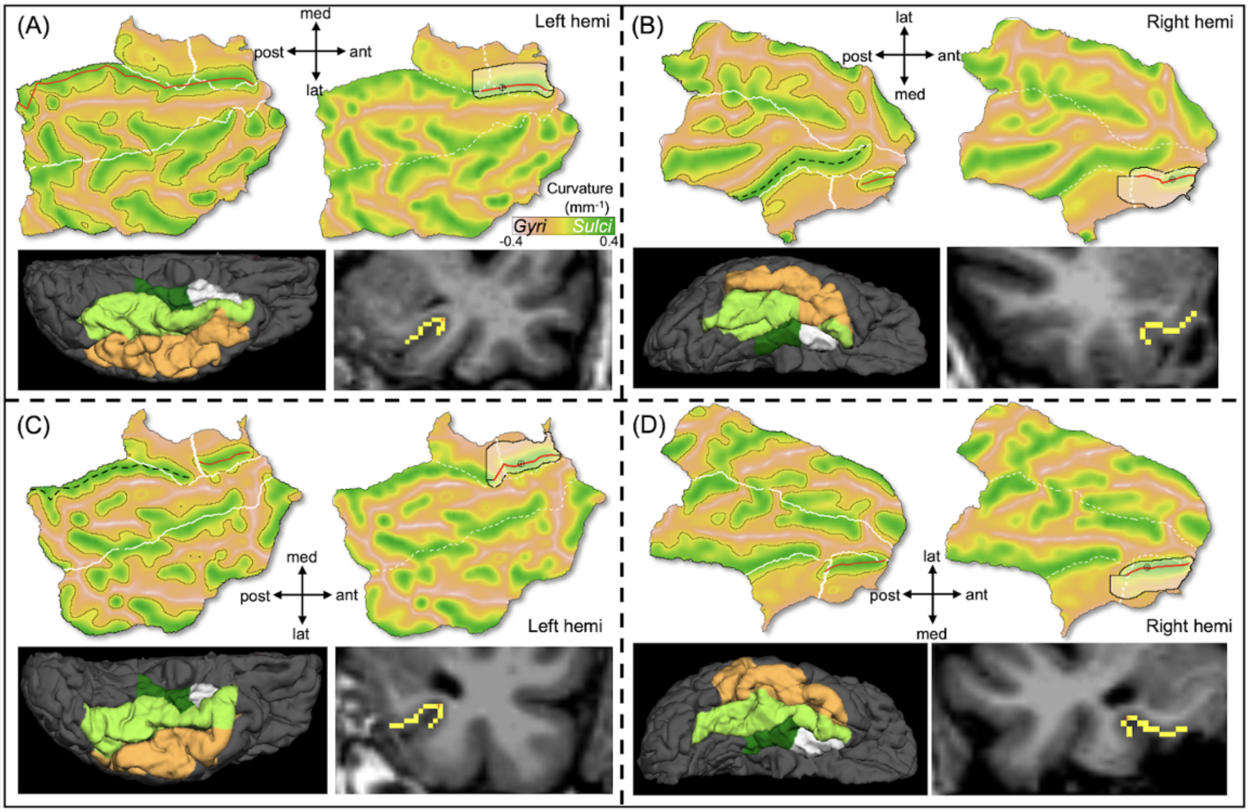


Fig. S1. Examples of collateral sulcus variations.

Method: Collateral sulcus (CS) identification procedure was optimized to account for the expected normal anatomic variability in CS as either continuous or discontinuous, as follows. For continuous CS cases, anterior CS was defined by truncating the CS from the posterior end to be within the target dimensions, as defined in *Methods* (main text). For discontinuous CS cases, an approximated continuous CS fundus was drawn by connecting discontinuous CS segments along points of maximal curvature, and this approximated CS was then truncated to be within the target dimensions. All geodesic distances relevant to this process were computed in R using package rgeos, version 0.3-23, (https://www.rdocumentation.org/packages/rgeos).

Figure: Temporal lobe data from the left (A,C) or right (B,D) hemispheres of 4 participants are shown in panels A-D (one individual per panel). Each panel shows flattened temporal surfaces (top), pial surface projection of temporal lobe regions (bottom left), and MP-RAGE coronal slice with projected rhinal cortex label (bottom right). Flat maps are color-encoded by white-pial average surface curvature, according to the scale in (A): sulcal fundi, shown in green, correspond to curvature maxima; gyral crests, in light brown, correspond to curvature minima. White lines (solid on left, dotted on right) on flat maps indicate region of interest (ROI) boundaries, for the four temporal ROIs shown on the corresponding pial surface (inferior) view in bottom left. Red solid line on flat maps indicates the anterior collateral / rhinal fundus, as identified automatically by local curvature maxima and anatomical landmarks; in cases of a discontinuous collateral sulcus (B-C), dotted black line indicates the posterior portion of collateral sulcus. Flat map in top right in each panel shows the result of automatically truncating (A) or extending (B-C) the rhinal sulcus to be within the target dimensions as described in Methods; white shaded region within black boundary indicates rhinal cortex. Case D required no rhinal sulcus adjustments. In bottom left of each panel is shown MP-RAGE coronal slice with projected rhinal cortex label shown in yellow; cursor (red cross) corresponds to cursor location on flat map above (black circle with cross).

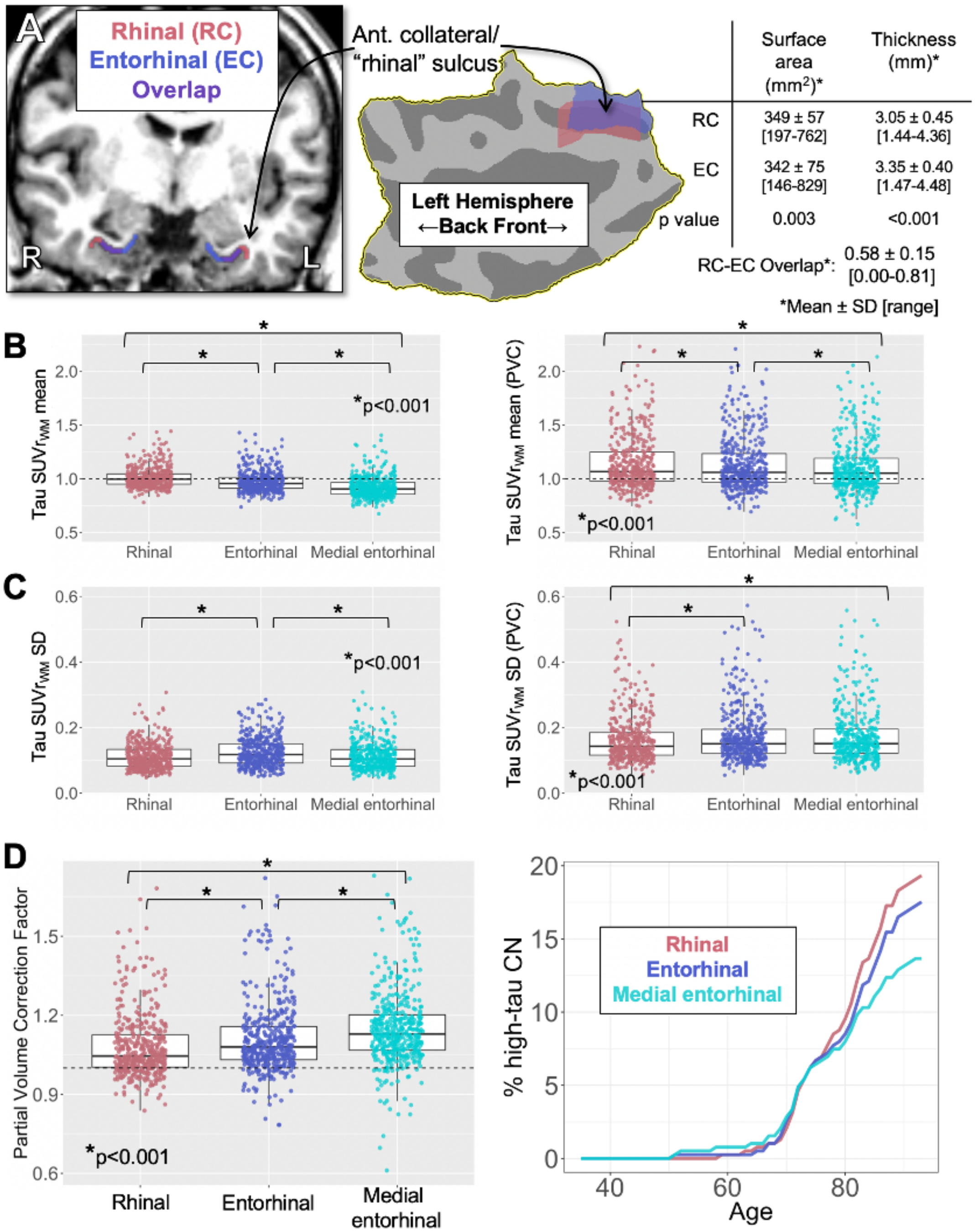


Fig. S2. Comparison of rhinal, FreeSurfer entorhinal, and non-overlapping region.

(A) Rhinal cortex (RC, red) and FreeSurfer-defined (Desikan) entorhinal (EC, blue) ROIs with overlap (purple) shown projected onto source T1-weighted MP-RAGE slice data (*left*) and on flattened left hemisphere temporal surface (*middle*), with dark grey indicating sulci and light grey indicating gyri, of an example 36 year-old clinically normal participant. *Right*, comparison of structural features of RC and EC: surface area (mm^2), cortical thickness (mm), Overlap=Dice coefficient between the regions, defined as twice the area of the overlapping region divided by the sum of the areas of the two individual regions.

(B) Comparison of mean TAU PET SUVr normalized to cerebral white matter (WM) in RC, EC, and "medial entorhinal" (mEC) cortex, where mEC was defined as the portion of EC in each subject that did not overlap with RC. *Left*, uncorrected SUVr; *right*, partial volume-corrected (PVC) SUVr. RC showed the highest mean SUVr of these medial temporal lobe (MTL) regions with and without PVC.

(C) Comparison of TAU PET SUVr standard deviation (SD) within ROI for RC, EC, mEC, uncorrected (*left*) and PVC (*right*) SUVr. RC showed the lowest within-ROI SD of these MTL regions, although this difference between RC and mEC was not significant for uncorrected data.

(D) *Left,* Comparison of partial volume correction (PVC) factor, defined as the ratio between PVC and uncorrected SUVr, in RC, EC, and mEC. RC had the lowest mean PVC factor of these three ROIs, suggesting that it may be less vulnerable to partial volume effects than the more medial portions of EC. *Right,* Cumulative percentage of clinically normal (CN) participants age 21-93 (N=388), including both low- and high-Aβ, classified as high-TAU on the basis of SUVr thresholds derived from Gaussian mixture modeling in RC, EC, and mEC (RC: 1.21, EC: 1.22, mEC: 1.21) as indicated by line color. In total, RC classified the highest number of CN participants as high-TAU (RC: 75 (19.3%); EC:

68 (17.5%); mEC: 53 (13.7%)), suggesting it may be a more sensitive marker of early tauopathy.

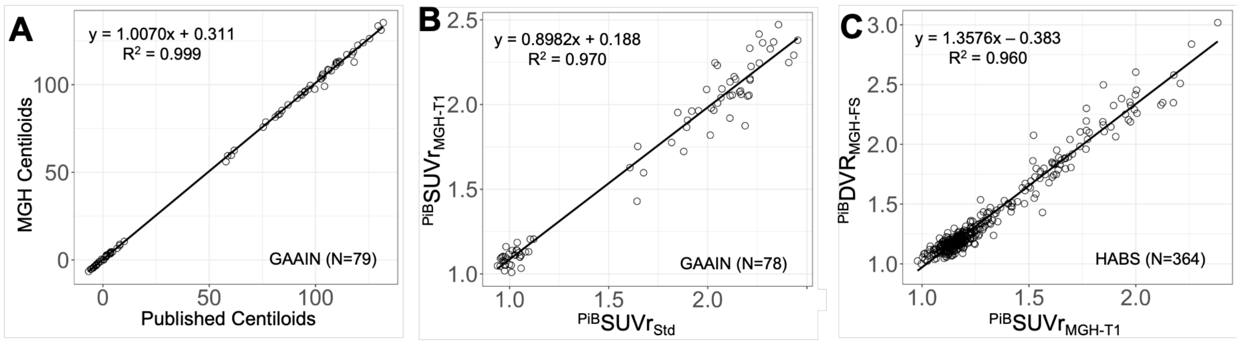


Fig. S3. Centiloid approximation method.

We standardized the ^{PiB}DVR values reported herein to the Centiloid (CL) scale in order to facilitate comparison across studies. After replication of the level-1 CL results (*26*, 2.2.2.1), the scaling was accomplished using an approximate CL method that was implemented in two steps: first, a regression was performed between ^{PiB}SUVr values we computed with the standard SUVr method described in the CL paper (*26*, 2.1) and ^{PiB}SUVr values computed with our in-house "MGH-T1" method, described below; second, a regression was performed between ^{PiB}SUVr values computed with the MGH-T1 method and ^{PiB}DVR values computed with our in-house "MGH-FreeSurfer (FS)" method, as reported in this paper and described previously (*12*). This approach was chosen to minimize the total number of transformations given the limitations of available datasets.

First, we replicated the level-1 CL analysis, per reference *26*, 2.2.2.1, using the GAAIN dataset (http://www.gaain.org). (**A**) shows the correlation between published CL values (CL CTX volume of interest (VOI), whole cerebellum reference) and the CL values obtained at our site (MGH) using the same method; this correlation fell within suggested thresholds (R^2>0.98, slope: 0.98-1.02, intercept: between -2 and 2 CL).

Having successfully replicated the expression of the level-1 PiB data on the CL scale, we next calibrated our MGH-T1 processing method (40-60min SUVr, details below) to the standard PiB 50-70min SUVr ("Std") method (*26*, 2.1.2-2.1.3). As our site does not acquire PiB data up to 70 minutes, this calibration was performed on the GAAIN dataset (N=78, subject AD01 not included) rather than site-acquired data to enable the calculation of 50-70min SUVrs with the standard method. (**B**) shows the correlation between ${}^{PiB}SUVr_{MGH\text{-}T1}$ and ${}^{PiB}SUVr_{Std}$ values. We observed a high correlation (R^2=0.97) and a relative variance near 1 (1.02, determined by the ratio of the SD of the young controls' (YC) ${}^{PiB}SUVr_{MGH\text{-}T1}$ values (0.049 SUVr) to the SD of the YC ${}^{PiB}SUVr_{Std}$ values (0.048 SUVr)); both of these reliability measures were well within suggested thresholds (*26*, 2.2.3.1-2.2.3.2).

Finally, we performed a regression between PiB values obtained from our two in-house processing methods (${}^{PiB}DVR_{MGH\text{-}FS}$ and ${}^{PiB}SUVr_{MGH\text{-}T1}$). We performed this step using a large dataset from HABS (N=364) in order to increase the validity of regression outcome measures (slope, intercept, R^2). (**C**) shows the relationship between ${}^{PiB}DVR_{MGH\text{-}FS}$ and ${}^{PiB}SUVr_{MGH\text{-}T1}$ values in HABS, which were highly correlated (R^2=0.96).

These two linear transformations were combined to yield a conversion from ${}^{PiB}DVR_{MGH\text{-}FS}$ to ${}^{PiB}SUVr_{Std}$, and ${}^{PiB}SUVr_{Std}$ values were converted to CL using the published CL equation (*26*, Eq. 1.3b)

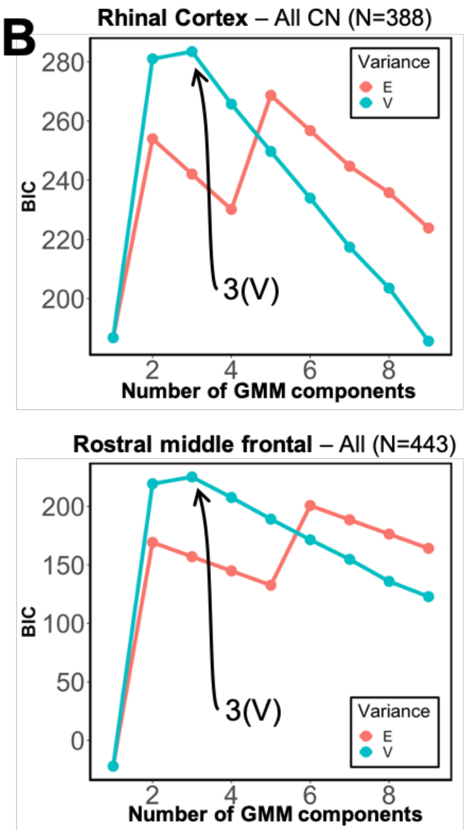
MGH-T1 method details

This method was developed for the purpose of sampling PET data in FS VOIs where a corresponding T1 image is available but has not been processed with FS. First, a mean counts-per-second image (meanCPS) is generated from PiB PET data 40-60min postinjection. The meanCPS is co-registered to T1, and T1 is normalized to MNI space (SPM12). Transformation parameters obtained from T1-to-MNI normalization are applied to the co-registered meanCPS, which is then sampled using a probabilistic MNI-space version of the FS Desikan atlas. SUVrs are calculated for a large cortical summary VOI (FLR region) (*12*) and cerebellar cortex reference.

A

Best-fit GMM to tau PET distribution
\# of components [1-9]
Variance – Equal (E) or Unequal (V), (X)=unimodal

Region	Lo-aβ CN N=327	Hi-aβ CN N=61	MCI-AD N=55	All CN N=388	All N=443
Rhinal Cortex	2(E)	2(E)	1(X)	3(V)*	2(V)
Entorhinal	2(E)	2(E)	1(X)	2(V)	2(V)
Parahippocampal	1(X)	2(E)	1(X)	2(E)	2(V)
Fusiform	1(X)	2(E)	2(V)	2(E)	2(V)
Inferiortemporal	1(X)	2(E)	2(V)	2(E)	2(V)
Middletemporal	1(X)	1(X)	2(E)	2(E)	2(V)
Superiortemporal	1(X)	1(X)	1(X)	1(X)	2(V)
Cuneus	1(X)	2(E)	2(V)	2(E)	2(V)
Isthmuscingulate	1(X)	1(X)	2(V)	1(X)	2(V)
Precuneus	1(X)	1(X)	2(V)	1(X)	2(V)
Inferiorparietal	1(X)	1(X)	2(V)	1(X)	2(V)
Superiorparietal	1(X)	1(X)	2(V)	1(X)	2(V)
Caudalmiddlefrontal	1(X)	2(E)	2(V)	1(X)	2(V)
Rostralmiddlefrontal	1(X)	2(E)	3(E)*	2(E)	3(V)*



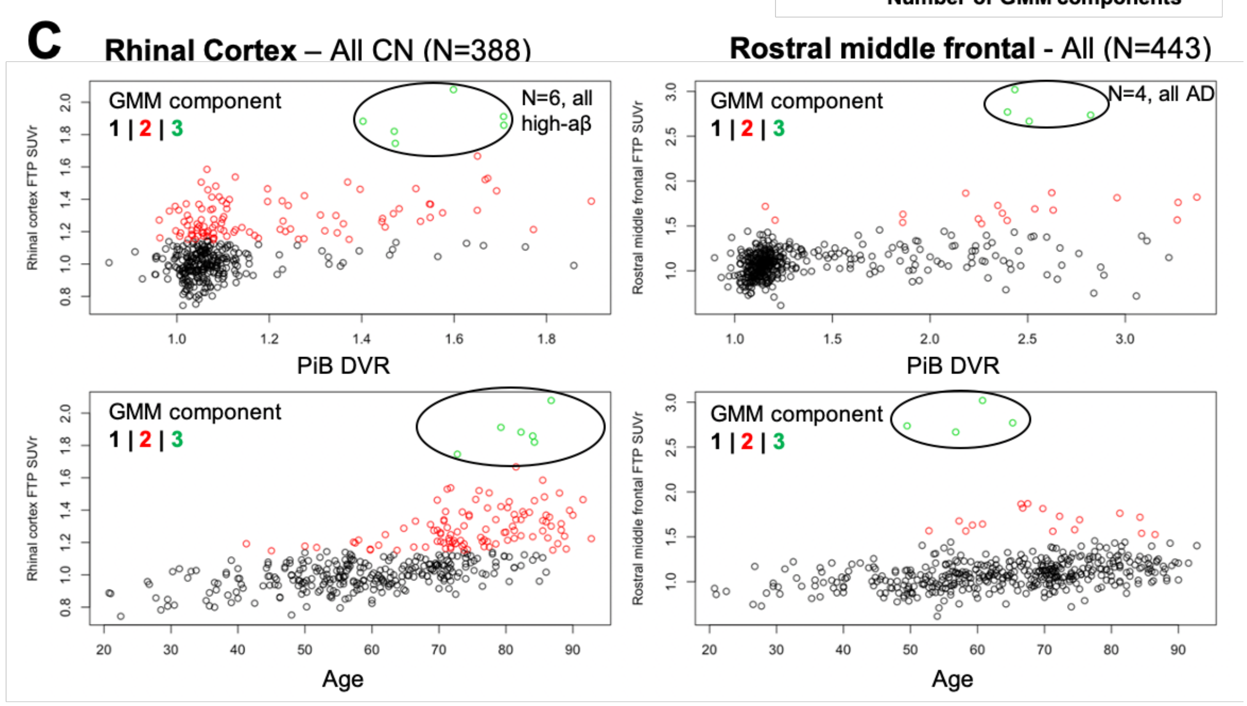


Fig. S4. Assessment of >2 modes in Gaussian mixture models (GMM).

(A) GMM with 1-9 mixture components, allowing for equal (E) or unequal (V) variance, were fit to regional TAU PET (Flortaucipir (FTP) SUVr, cerebral white matter-reference, partial volume corrected) distributions in subgroups defined by Aβ status (determined by PiB PET; high Aβ threshold ~20Centiloids) and clinical diagnosis (CN=clinically normal; MCI-AD=clinical diagnosis of mild cognitive impairment or Alzheimer's dementia). GMM fits were compared using Bayesian information criteria (BIC) to determine best-fit GMM for each ROI, shown in table. Most TAU PET distributions (96%) evaluated were either unimodal (1(X)) or bimodal (2(E) or 2(V)), with several trimodal distributions, indicated by * and described in detail in (B) and (C).

(B) BIC for all GMM fits tested for rhinal cortex TAU within all CN (top) and rostral middle frontal in the full sample (bottom): number of components indicated on the X-axis, and equal (E) or unequal (V) variance indicated by dot and line color according to inset legend. 2(V) and 3(V) had similar BIC in both cases, with 3(V) being higher.

(C) Distribution of FTP SUVr values vs PiB DVR (*upper*) and Age (*lower*) for trimodal FTP distributions - rhinal cortex (RC), all CN (*left*) and rostral middle frontal (rMF), full sample (*right*). In both cases, trimodal GMM fits were significantly more likely than bimodal fits based on LRT (RC: LRT=20, rMF: LRT=24, both bootstrap $p<0.001$). In rhinal cortex, 3rd TAU component (green, circled) was composed of 6 high-Aβ CN participants, who had RC FTP SUVrs comparable to MCI-AD participants (1.7-2.1). In rostral middle frontal, 3rd TAU component (green, circled) was comprised of four AD patients with markedly elevated middle frontal TAU PET signal – these four participants were relatively younger (age 49-65), suggesting that they may be cases of atypical AD, although available clinical and neuropsychological data did not allow us to confirm this.

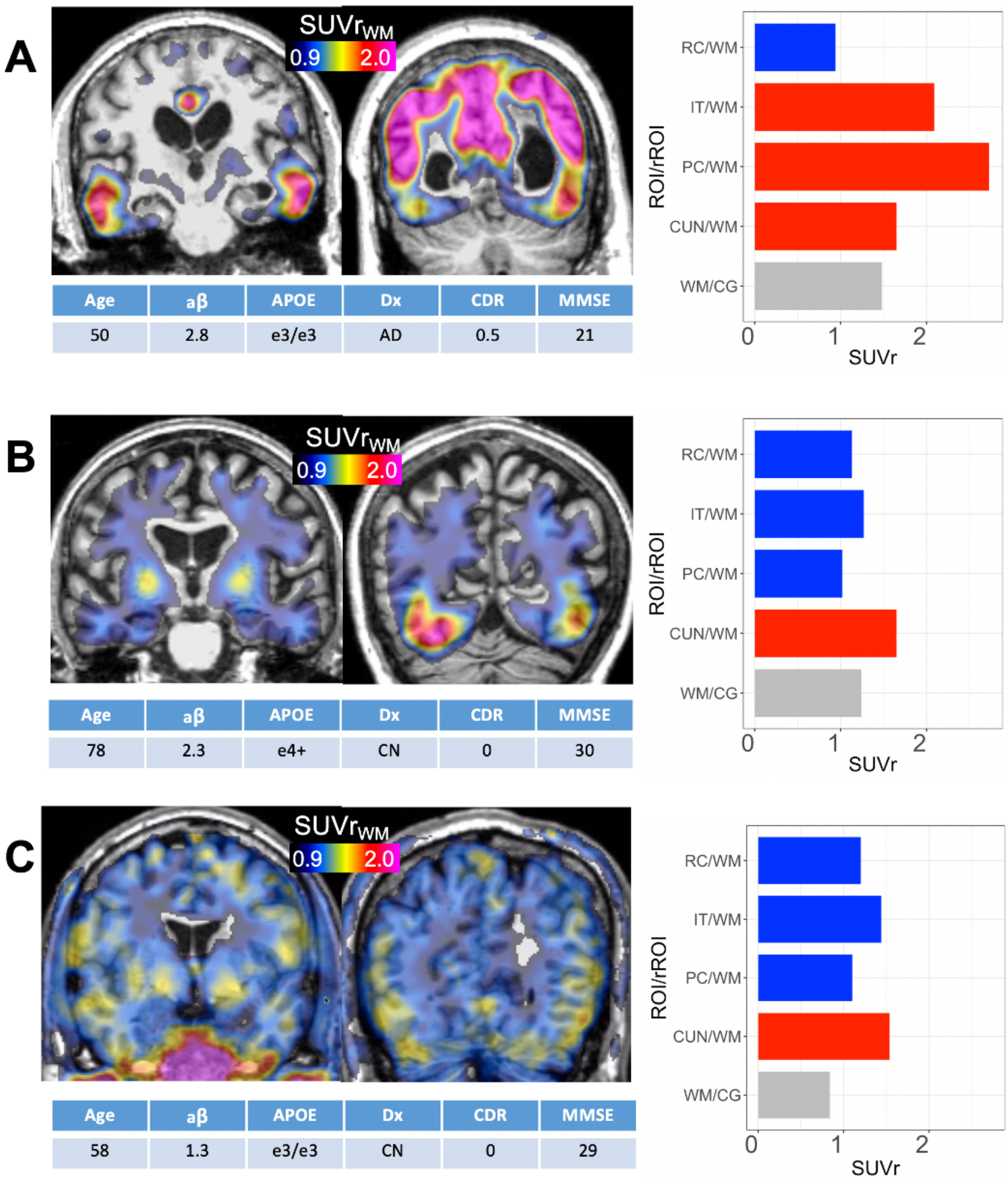


Fig. S5. Atypical TAU PET cases. For each case A-D, coronal slice images of 18F-Flortaucipir (FTP) PET standard uptake value ratios (SUVr) normalized to cerebral white matter

(WM) overlaid on T1-weighted MP-RAGE image; demographic information in table below images: Aβ=global PiB DVR (normalized to cerebellar grey matter, partial volume corrected (PVC)), Dx=diagnosis, CDR=clinical dementia rating, MMSE=mini mental state exam; bar plot at right of PVC mean FTP standard uptake value ratios (SUVr) for regions of interest (ROI) normalized to a reference ROI (rROI). RC=rhinal cortex, IT=inferior temporal cortex, PC=precuneus, CUN=cuneus, WM=cerebral white matter, CG=cerebellar grey matter. Red bars indicate SUVr values above ROI SUVr/WM threshold derived from full sample GMM (RC: 1.21, IT: 1.56; PC: 1.42; CUN: 1.44), blue indicates SUVr values below threshold; all WM/CG SUVrs shown in grey.

(A) Participant with clinical diagnosis of Alzheimer's dementia (AD), high FTP uptake in most of cortex with lower SUVr in medial temporal lobes (MTL). Participant was classified as low-RC, high-IT, high-PC. May represent a case of hippocampal-sparing AD, or atrophy in medial temporal lobes may be contributing to low SUVr values, despite all SUVrs being PVCd.

(B) Clinically normal participant with elevated Aβ and low TAU in RC, IT, and PC, but elevated FTP signal confined to occipital cortices, exemplified by CUN (SUVr=1.65). This was the only case we observed with elevated Aβ, low RC TAU, and elevated TAU in another region; may represent onset of atypical Alzheimer's, although available clinical and neuropsychological evaluations did not allow us to confirm this.

(C) Clinically normal participant with low Aβ and low TAU in RC, IT, and PC, but elevated FTP in parahippocampal, fusiform, middle and superior temporal, cuneus, and inferior parietal cortices (Fig. 3A). May represent the onset of atypical Alzheimer's, although the case showed substantial off-target binding in extra-cerebral regions, which may be elevating cortical signal. This case was also notable for having low WM uptake compared to cerebellum cortex (WM/CG SUVr=0.84, low-Aβ CN mean±SD = 1.15 ±0.12), possibly due to FTP signal spill-in to cerebellum from extra-cerebral sources.

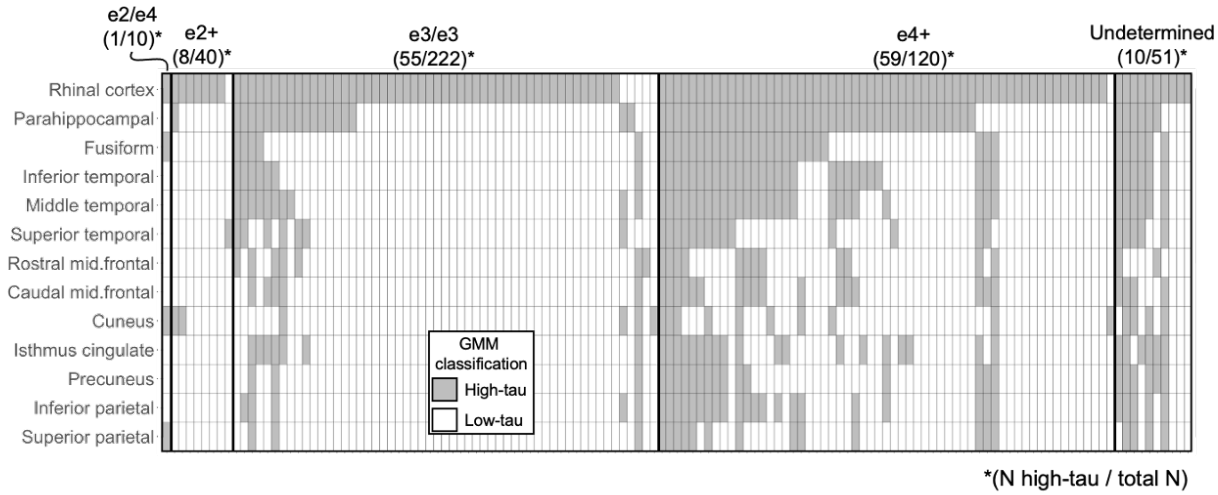


Fig. S6. Tau PET classification by *APOE* genotype. Cross-sectional patterns of elevated TAU in participants who had elevated TAU in at least one region of interest (ROI) at baseline. Each column represents an individual participant, and filled cells indicate in which ROIs (rows) TAU was elevated in each participant; columns are ordered by *APOE* genotype for visualization. We observed an effect of *APOE* genotype on the anatomical distribution of TAU PET: e2 carriers generally showed TAU limited to medial temporal regions; TAU in temporal neocortex was more common among e3 homozygotes, and widespread TAU including parietal regions was observed in e4 carriers.

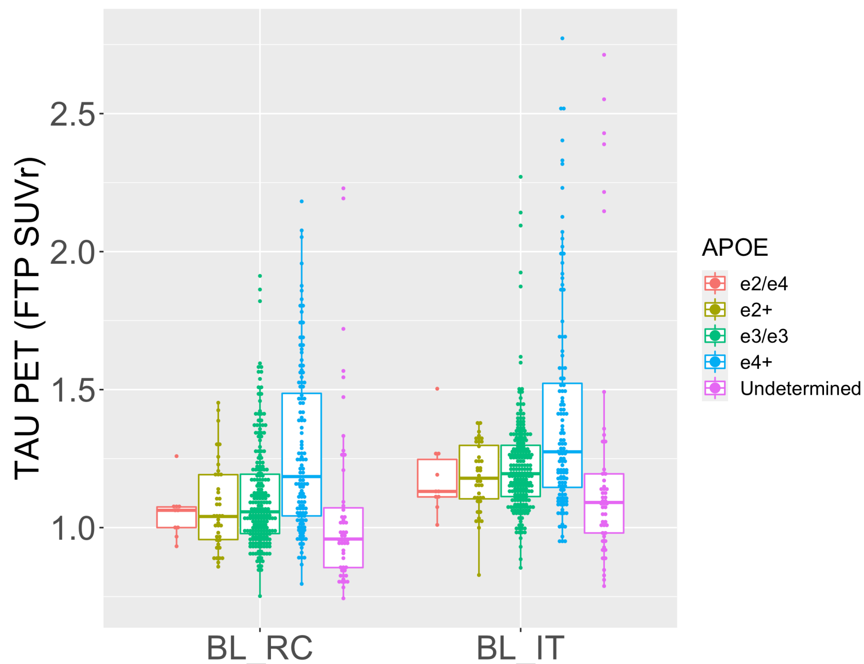


Fig. S7. TAU PET SUVr by *APOE* genotype. For *APOE*, e2+ includes e2/e3, e2/e2; e4+ includes e4/e3, e4/e4. BL=baseline, RC=rhinal cortex, IT=inferior temporal cortex, FTP=Flortaucipir, SUVr=standardized uptake value ratio. 55 subjects did not have *APOE* genotype information available (purple).

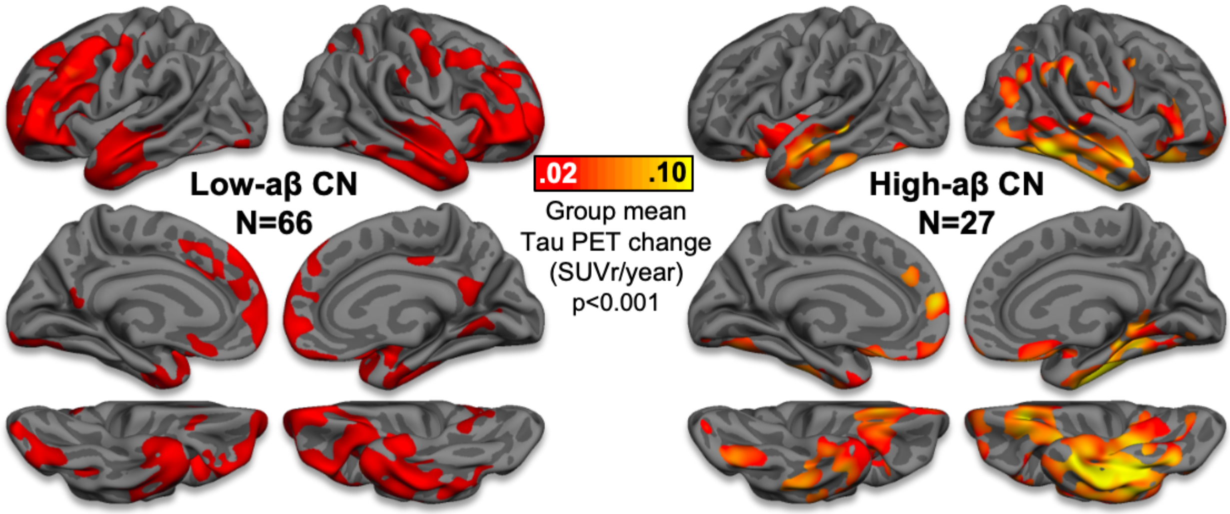
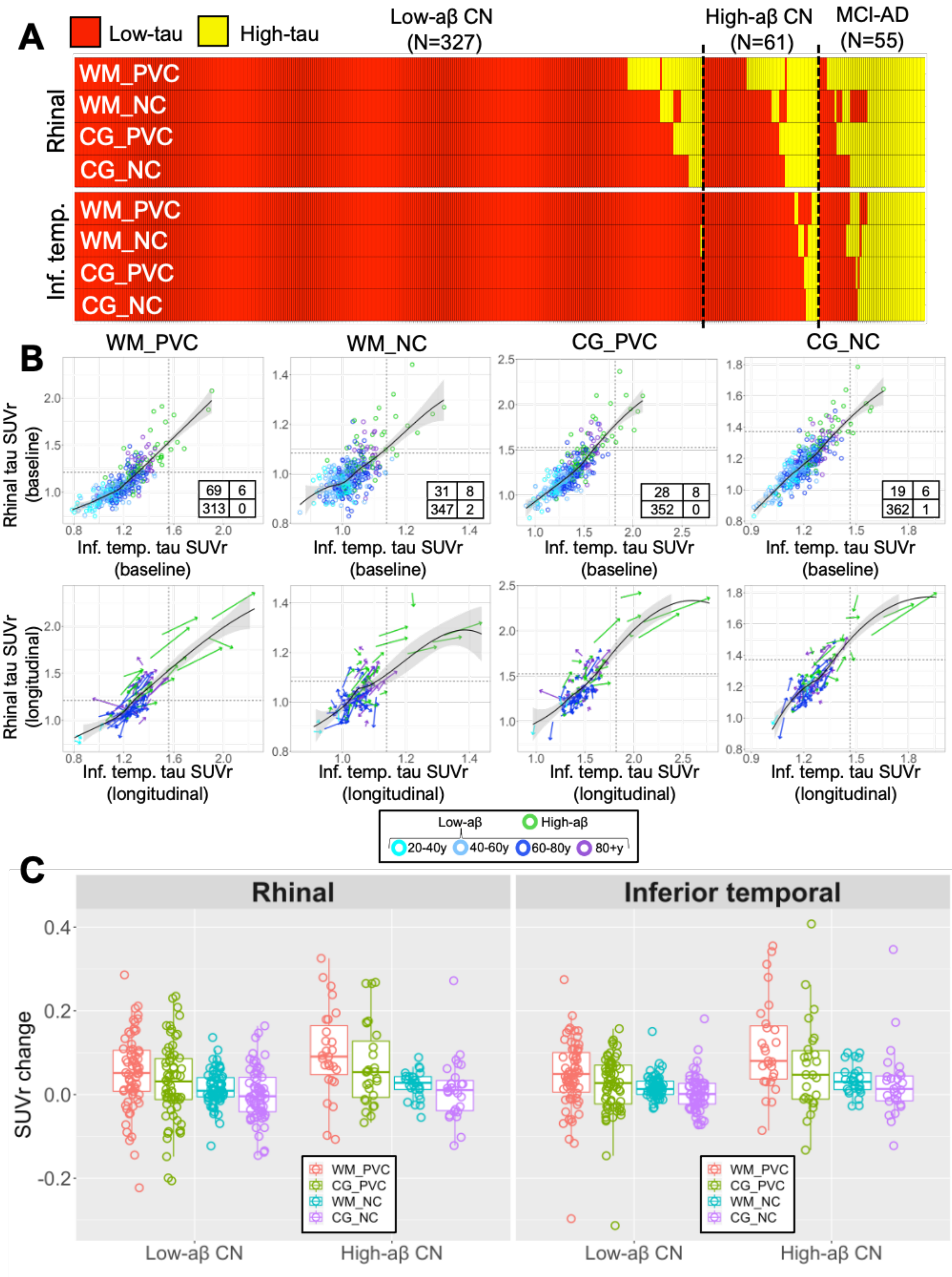


Fig. S8. Adjusted surface maps of mean TAU PET change by Aβ subgroup.
Surface maps show group mean annualized TAU PET change rates across the cortical surface in the low-Aβ (*left*) and high-Aβ (*right*) subgroups. Mean rates at each vertex were tested using one-sample t-tests, and a threshold of $p<0.001$ after cluster-wise multiple comparisons correction (minimum cluster extent=100mm^2) was applied to the resulting maps. Vertex-wise rates of change in MCI-AD were not assessed in this way due to small sample size.



A
Low-tau
High-tau
Low-aβ CN (N=327)
High-aβ CN (N=61)
MCI-AD (N=55)
Rhinal
Inf. temp.
WM_PVC
WM_NC
CG_PVC
CG_NC
WM_PVC
WM_NC
CG_PVC
CG_NC
B
WM_PVC
WM_NC
CG_PVC
CG_NC
Rhinal tau SUVr (baseline)
Inf. temp. tau SUVr (baseline)
69 6
313 0
31 8
347 2
28 8
352 0
19 6
362 1
Rhinal tau SUVr (longitudinal)
Inf. temp. tau SUVr (longitudinal)
Low-aβ
High-aβ
20-40y
40-60y
60-80y
80+y
C
Rhinal
Inferior temporal
SUVr change
WM_PVC
CG_PVC
WM_NC
CG_NC
Low-aβ CN
High-aβ CN

Fig. S9. Effect of reference region, partial volume correction on TAU PET results.

(A) Bar plot showing participants classified as high- and low-TAU for rhinal (top) and inferior temporal (bottom) cortices based on thresholds derived from two-component Gaussian mixture models (GMM) in the full sample. Each bar is a participant; yellow indicates high-TAU and red indicates low-TAU. Results are shown for two reference regions (rROI): cerebral white matter (WM) and cerebellar gray matter (CG), and for partial volume-corrected (PVC) and uncorrected (NC) SUVrs, for a total of four processing streams (rROI-PVC combinations), indicated at left. Participants are arranged by subgroup (low-Aβ clinically normal (CN), high-Aβ CN, mild cognitive impairment to Alzheimer's dementia (MCI-AD)) as indicated by dashed line. Regardless of processing stream used, more participants were classified as high-TAU in rhinal cortex than in inferior temporal, particularly in the low-Aβ CN subgroup.

(B) Plots showing rhinal vs inferior temporal TAU for the baseline sample (top) and the longitudinal sample (bottom), with follow-up time point indicated by arrowhead. Participants color-encoded by subgroup as defined in the legend below. Plots shown for each combination of rROI and PVC/NC, as indicated at top; dashed lines indicate SUVr thresholds, specific to each region and processing stream, derived from GMM in the full sample. Inset tables in the bottom-right corners of baseline plots give the number of participants in each quadrant. For each processing stream we found that elevated RC TAU in the absence of elevated IT TAU occurred more frequently than the converse, suggesting that this finding was not dependent on choice of rROI or PVC method.

(C) Box plot showing individual SUVr changes over 2-year follow-up in rhinal (left panel) and inferior temporal (right panel) for each processing stream, in CN participants separated by Aβ status. In general, WM rROI yielded higher mean and lower standard deviation (SD) compared with CG rROI, and PVC increased both the mean and the SD of the distributions.

	Lo-Aβ Lo-RC	Lo-Aβ Hi-RC	P value
N	296	31	
Age	58.8 ± 13.6 (21-93)	79.8 ± 7.8 (62-90)	<0.0001
Females, N (%)	152 (51.4)	18 (58.1)	0.003
MMSE	29.4 ± 0.9 (25-30)	29.1 ± 1.1 (26-30)	0.601
Aβ burden (PiB DVR)	1.14 ± 0.07 (0.9-1.35)	1.17 ± 0.05 (1.08-1.35)	0.157
Education (Y)	15.2 ± 3.2 (2-20)	15.8 ± 3.3 (8-20)	0.329
APOEe2+ N (%)	33 (12.8)	2 (6.5)	0.461
APOEe4+ N (%)	48 (18.7)	3 (9.7)	0.322

Table S1. Demographics of low- versus high-RC TAU within low-Aβ CN. Presented as mean +/- SD (range) for continuous variables; groups were compared with t-test for continuous variables and chi-squared for dichotomous. 39 (13%) of low-Aβ low-RC group did not have *APOE* genotype information available.

Model/predictor	Estimate (SE)	p value
I. RCbin ~ Age + PiB.DVR + Edu		
Age	0.179 (0.029)	<0.001***
PiB.DVR	-0.773 (3.111)	0.804
Edu	0.082 (0.075)	0.271
II. RCbin ~ Age + Edu		
Age	0.178 (0.029)	<0.001***
Edu	0.081 (0.075)	0.277
III. RCbin ~ PiB.DVR + Edu		
PiB.DVR	6.105 (2.603)	0.019*
Edu	0.049 (0.065)	0.447

Table S2. Logistic regressions predicting binary RC TAU (RCbin) in low-Aβ CN (N=327). Model I: For every year of Age (mean+/-SD [range] = 61+/-15 [21-93]), log odds of being high RC TAU (determined by GMM) increase by 0.179. PiB DVR does not significantly affect odds of being high-RC TAU with age in the model. Model III: Without age in the model, higher PiB DVR increases odds of being high-RC TAU. $^{\dagger}p<0.1$; $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

	Low-Aβ CN (N=327)	High-Aβ CN (N=61)	MCI-AD (N=55)	All (N=443)
Rhinal Cortex				
SUVr mean ± SD [range]	1.05 ± 0.14 [0.74-1.59]	1.30 ± 0.25 [0.94-2.08]	1.55 ± 0.27 [0.94-2.23]	1.14 ± 0.25 [0.74-2.23]
GMM fit / threshold N high / N low	2(E) / 1.24 31 / 296	2(E) / 1.60 7 / 54	1(X) / -- --	2(V) / 1.21 126 / 317
LRT / p	43.7 / 0.001	17.0 / 0.001	10.4 / 0.049	183.7 / 0.001
Entorhinal				
SUVr mean ± SD [range]	1.03 ± 0.14 [0.69-1.58]	1.29 ± 0.26 [0.95-2.05]	1.56 ± 0.26 [0.87-2.21]	1.13 ± 0.26 [0.69-2.21]
GMM fit / threshold N high / N low	2(E) / 1.25 24 / 303	2(E) / 1.53 11 / 50	1(X) / -- --	2(V) / 1.22 118 / 325
LRT / p	40.7 / 0.001	18.2 / 0.001	8.4 / 0.096	187.5 / 0.001
Medial Entorhinal				
SUVr mean ± SD [range]	1.02 ± 0.14 [0.58-1.47]	1.25 ± 0.23 [0.95-1.86]	1.51 ± 0.26 [0.83-2.13]	1.11 ± 0.24 [0.58-2.13]
GMM fit / threshold N high / N low	2(E) / 1.26 18 / 309	2(E) / 1.43 13 / 48	1(X) / -- --	2(V) / 1.21 100 / 343
LRT / p	14.2 / 0.001	20.0 / 0.001	0.0 / 0.841	151.6 / 0.001
Parahippocampal				
SUVr mean ± SD [range]	1.00 ± 0.11 [0.68-1.35]	1.19 ± 0.17 [0.84-1.75]	1.39 ± 0.24 [1.00-2.18]	1.08 ± 0.20 [0.68-2.18]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.48 4 / 57	1(X) / -- --	2(V) / 1.24 66 / 377
LRT / p	9.9 / 0.045	8.7 / 0.009	7.6 / 0.024	131.8 / 0.001
Fusiform				
SUVr mean ± SD [range]	1.07 ± 0.11 [0.76-1.33]	1.22 ± 0.16 [0.98-1.74]	1.55 ± 0.35 [1.06-2.62]	1.15 ± 0.23 [0.76-2.62]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.49 3 / 58	2(V) / 1.49 26 / 29	2(V) / 1.40 37 / 406
LRT / p	2.1 / 0.286	11.5 / 0.003	12.3 / 0.021	275.4 / 0.001
Inferiortemporal				
SUVr mean ± SD [range]	1.16 ± 0.13 [0.79-1.45]	1.35 ± 0.18 [1.05-1.92]	1.83 ± 0.44 [1.08-2.77]	1.27 ± 0.30 [0.79-2.77]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.78 2 / 59	2(E) / 1.87 26 / 29	2(V) / 1.56 41 / 402
LRT / p	0.0 / 0.710	8.5 / 0.009	8.7 / 0.019	333.4 / 0.001
Middletemporal				
SUVr mean ± SD [range]	1.10 ± 0.13 [0.73-1.49]	1.27 ± 0.16 [0.99-1.76]	1.72 ± 0.42 [0.98-2.64]	1.20 ± 0.28 [0.73-2.64]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(E) / 1.73 26 / 29	2(V) / 1.48 42 / 401
LRT / p	0.0 / 0.709	6.5 / 0.038	9.9 / 0.009	306.2 / 0.001
Superiortemporal				
SUVr mean ± SD [range]	1.07 ± 0.13 [0.76-1.57]	1.17 ± 0.14 [0.80-1.57]	1.34 ± 0.28 [0.75-2.23]	1.12 ± 0.18 [0.75-2.23]

GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	1(X) / -- --	2(V) / 1.40 27 / 416
LRT / p	-0.1 / 1.000	4.0 / 0.084	4.6 / 0.069	92.6 / 0.001
Cuneus				
SUVr mean ± SD [range]	1.00 ± 0.15 [0.60-1.63]	1.11 ± 0.18 [0.79-1.65]	1.35 ± 0.52 [0.77-3.28]	1.06 ± 0.26 [0.60-3.28]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.37 5 / 56	2(V) / 1.56 12 / 43	2(V) / 1.44 21 / 422
LRT / p	9.5 / 0.005	8.3 / 0.010	37.3 / 0.001	288.6 / 0.001
Precuneus				
SUVr mean ± SD [range]	0.99 ± 0.12 [0.54-1.34]	1.12 ± 0.14 [0.85-1.43]	1.52 ± 0.48 [0.99-2.73]	1.08 ± 0.27 [0.54-2.73]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(V) / 1.55 18 / 37	2(V) / 1.42 24 / 419
LRT / p	-0.2 / 0.998	3.4 / 0.141	35.5 / 0.001	358.9 / 0.001
Inferiorparietal				
SUVr mean ± SD [range]	1.03 ± 0.13 [0.69-1.53]	1.17 ± 0.15 [0.72-1.48]	1.88 ± 0.80 [0.90-4.13]	1.16 ± 0.41 [0.69-4.13]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(V) / 1.65 25 / 30	2(V) / 1.51 31 / 412
LRT / p	6.5 / 0.054	0.0 / 0.799	30.0 / 0.001	605.9 / 0.001
Superiorparietal				
SUVr mean ± SD [range]	0.98 ± 0.14 [0.58-1.39]	1.09 ± 0.17 [0.57-1.41]	1.62 ± 0.84 [0.79-4.22]	1.07 ± 0.38 [0.57-4.22]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(V) / 1.57 19 / 36	2(V) / 1.45 21 / 422
LRT / p	-0.1 / 0.943	2.4 / 0.128	45.0 / 0.001	575.7 / 0.001
Isthmuscingulate				
SUVr mean ± SD [range]	0.88 ± 0.10 [0.48-1.15]	0.96 ± 0.12 [0.70-1.24]	1.27 ± 0.38 [0.71-2.23]	0.94 ± 0.21 [0.48-2.23]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(V) / 1.15 26 / 29	2(V) / 1.16 32 / 411
LRT / p	-0.4 / 1.000	5.0 / 0.059	24.6 / 0.001	362.3 / 0.001
Posteriorcingulate				
SUVr mean ± SD [range]	0.86 ± 0.10 [0.43-1.14]	0.95 ± 0.15 [0.66-1.41]	1.15 ± 0.26 [0.73-1.85]	0.91 ± 0.17 [0.43-1.85]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	2(E) / 1.36 13 / 42	2(V) / 1.13 30 / 413
LRT / p	-0.1 / 0.996	5.0 / 0.049	15.5 / 0.002	178.9 / 0.001
Caudalanteriorcingulate				
SUVr mean ± SD [range]	1.14 ± 0.19 [-0.22-1.62]	1.20 ± 0.22 [0.72-2.02]	1.13 ± 0.23 [0.57-1.73]	1.14 ± 0.20 [-0.22-2.02]
GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	1(X) / -- --	2(V) / 1.36 47 / 396
LRT / p	0.0 / 0.999	7.6 / 0.015	1.1 / 0.300	57.7 / 0.001
Rostralanteriorcingulate				
SUVr mean ± SD [range]	1.10 ± 0.16 [0.49-1.61]	1.19 ± 0.15 [0.92-1.57]	1.15 ± 0.30 [0.48-1.91]	1.11 ± 0.18 [0.48-1.91]

GMM fit / threshold N high / N low	1(X) / -- --	1(X) / -- --	1(X) / -- --	2(V) / 1.35 35 / 408
LRT / p	7.8 / 0.012	0.7 / 0.671	6.0 / 0.225	29.1 / 0.002
Caudalmiddlefrontal				
SUVr mean ± SD [range]	1.03 ± 0.13 [0.57-1.44]	1.14 ± 0.17 [0.85-1.79]	1.66 ± 0.69 [0.76-4.03]	1.12 ± 0.34 [0.57-4.03]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.46 3 / 58	2(V) / 1.63 18 / 37	2(V) / 1.47 26 / 417
LRT / p	-0.2 / 0.998	8.7 / 0.010	41.5 / 0.001	506.2 / 0.001
Rostralmiddlefrontal				
SUVr mean ± SD [range]	1.06 ± 0.14 [0.61-1.72]	1.17 ± 0.18 [0.79-1.87]	1.40 ± 0.48 [0.72-3.02]	1.12 ± 0.24 [0.61-3.02]
GMM fit / threshold N high / N low	1(X) / -- --	2(E) / 1.51 3 / 58	2(E) / 2.27 4 / 51	2(V) / 1.49 21 / 422
LRT / p	11.3 / 0.002	8.7 / 0.008	35.5 / 0.001	259.6 / 0.001

Table S3. Descriptive and Gaussian mixture model (GMM) statistics for TAU PET by region, subgroup.

Tau PET in cortical regions of interest was quantified as standard uptake value ratio (SUVr) normalized to cerebral white matter, partial volume-corrected using Muller-Gartner. SD=standard deviation.

“GMM fit” indicates the number of mixture components (1 or 2) and covariance parametrization (“E” for equal variance or “V” for varying/unequal variance; X=unimodal) for the best-fit model based on Bayesian information criterion (BIC).

N high / N low indicates for bimodal distributions the number of participants in each mode; threshold is the SUVr cut-point between components for bimodal distributions (-- for unimodal). Thresholds were defined as the midpoint between the highest SUVr in the lower component and lowest SUVr in the upper component.

LRT is the value of the likelihood ratio test for bimodality (comparing fit likelihood for 2- versus 1-component GMM), with high LRT values indicating bimodality, and p values obtained by bootstrapping (1000 resamples).

Medial entorhinal = portion of FreeSurfer-defined entorhinal cortex that did not overlap with rhinal cortex (RC). See Fig. S2.

Baseline SUVr	N	SUVr Mean ± SD (range)	Age β (SE)	Age p	PiB β (SE)	PiB p
Rhinal cortex						
Lo-aβ CN	327	1.046 ± 0.14 (0.744-1.585)	0.006 (0.000)	<0.001***	0.023 (0.095)	0.804
Hi-aβ CN	61	1.302 ± 0.252 (0.935-2.077)	0.016 (0.004)	<0.001***	0.121 (0.072)	0.098†
MCI-AD	55	1.555 ± 0.268 (0.939-2.229)	0.005 (0.004)	0.223	0.131 (0.067)	0.057†
All CN	388	1.087 ± 0.188 (0.744-2.077)	0.006 (0.001)	<0.001***	0.203 (0.023)	<0.001***
All	443	1.145 ± 0.252 (0.744-2.229)	0.006 (0.001)	<0.001***	0.276 (0.017)	<0.001***
Inferior temporal						
Lo-aβ CN	327	1.159 ± 0.127 (0.788-1.451)	0.006 (0.000)	<0.001***	0.039 (0.079)	0.626
Hi-aβ CN	61	1.346 ± 0.177 (1.054-1.92)	0.009 (0.003)	0.003**	0.077 (0.056)	0.178
MCI-AD	55	1.828 ± 0.442 (1.078-2.773)	-0.005 (0.006)	0.374	0.418 (0.091)	<0.001***
All CN	388	1.188 ± 0.152 (0.788-1.92)	0.006 (0.000)	<0.001***	0.126 (0.018)	<0.001***
All	443	1.268 ± 0.298 (0.788-2.773)	0.004 (0.001)	<0.001***	0.418 (0.020)	<0.001***

SUVr / year	N	SUVr / year Mean ± SD (range)	Mean p value	CoV	Age β (SE)	Age p	PiB β (SE)	PiB p
Rhinal cortex								
Lo-aβ CN	66	0.022 ± 0.043 (-0.097-0.163)	<0.001***	1.940	0.001 (0.000)	0.062†	-0.054 (0.075)	0.477
Hi-aβ CN	27	0.053 ± 0.055 (-0.084-0.155)	<0.001***	1.052	0.000 (0.002)	0.864	0.048 (0.029)	0.116
MCI-AD	11	0.016 ± 0.057 (-0.122-0.081)	0.374	3.568	-0.001 (0.003)	0.702	-0.060 (0.090)	0.526
All CN	93	0.031 ± 0.049 (-0.097-0.163)	<0.001***	1.568	0.001 (0.000)	0.174	0.033 (0.010)	0.002**
All	104	0.03 ± 0.05 (-0.122-0.163)	<0.001***	1.682	0.001 (0.000)	0.068†	0.018 (0.009)	0.046*
Inferior temporal								
Lo-aβ CN	66	0.022 ± 0.039 (-0.114-0.136)	<0.001***	1.806	0.000 (0.000)	0.360	-0.158 (0.068)	0.024*
Hi-aβ CN	27	0.06 ± 0.058 (-0.074-0.171)	<0.001***	0.978	0.000 (0.002)	0.983	0.047 (0.031)	0.139
MCI-AD	11	0.104 ± 0.068 (0.002-0.21)	<0.001***	0.652	-0.005 (0.002)	0.069†	-0.037 (0.084)	0.674
All CN	93	0.033 ± 0.049 (-0.114-0.171)	<0.001***	1.480	0.000 (0.000)	0.681	0.039 (0.010)	<0.001***
All	104	0.04 ± 0.055 (-0.114-0.21)	<0.001***	1.365	0.000 (0.000)	0.372	0.050 (0.009)	<0.001***

Table S4. Effects of age, Aβ on ROI TAU in each subgroup. *Top,* baseline TAU SUVr; *Bottom*, longitudinal (annualized) rates of TAU SUVr change. For TAU change measures (bottom), "Mean p value" gives the significance estimate of a one-sample t-test; β=model slope estimate, SE=standard error, CoV=Coefficient of variation, defined as SD/mean. Full model: ROI mean TAU SUVr ~ Age + PiB DVR + Sex + Education. $^{\dagger}p<0.1$; $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

	N	SUVr Mean±SD (range)	Age β (SE)	Age p	PiB β (SE)	PiB p	APOE4 β (SE)	APOE4 p
Rhinal Cortex								
Lo-aβ CN	288	1.046 ± 0.14 (0.744-1.585)	0.006 (0.001)	<0.001***	0.027 (0.101)	0.792	0.005 (0.018)	0.759
Hi-aβ CN	59	1.302 ± 0.252 (0.935-2.077)	0.017 (0.004)	<0.001***	0.105 (0.075)	0.166	0.044 (0.060)	0.466
MCI-AD	45	1.555 ± 0.268 (0.939-2.229)	0.003 (0.004)	0.522	-0.032 (0.073)	0.663	0.161 (0.093)	0.092†
All CN	347	1.087 ± 0.188 (0.744-2.077)	0.007 (0.001)	<0.001***	0.184 (0.027)	<0.001***	0.026 (0.019)	0.173
All	392	1.145 ± 0.252 (0.744-2.229)	0.007 (0.001)	<0.001***	0.244 (0.021)	<0.001***	0.049 (0.021)	0.020*
Entorhinal								
Lo-aβ CN	288	1.034 ± 0.143 (0.692-1.576)	0.006 (0.001)	<0.001***	0.017 (0.109)	0.878	0.007 (0.019)	0.703
Hi-aβ CN	59	1.291 ± 0.256 (0.949-2.054)	0.015 (0.004)	<0.001***	0.101 (0.080)	0.210	0.074 (0.064)	0.253
MCI-AD	45	1.56 ± 0.26 (0.866-2.207)	0.002 (0.004)	0.676	-0.079 (0.074)	0.295	0.211 (0.094)	0.031*
All CN	347	1.074 ± 0.191 (0.692-2.054)	0.006 (0.001)	<0.001***	0.191 (0.028)	<0.001***	0.035 (0.020)	0.079†
All	392	1.134 ± 0.256 (0.692-2.207)	0.006 (0.001)	<0.001***	0.249 (0.022)	<0.001***	0.065 (0.022)	0.004**
Medial Entorhinal								
Lo-aβ CN	288	1.016 ± 0.141 (0.576-1.472)	0.004 (0.001)	<0.001***	0.009 (0.111)	0.937	-0.001 (0.020)	0.948
Hi-aβ CN	59	1.249 ± 0.233 (0.947-1.857)	0.010 (0.004)	0.013*	0.105 (0.076)	0.174	0.090 (0.061)	0.144
MCI-AD	45	1.508 ± 0.258 (0.833-2.134)	0.001 (0.004)	0.804	-0.081 (0.077)	0.300	0.205 (0.098)	0.043*
All CN	347	1.053 ± 0.18 (0.576-1.857)	0.004 (0.001)	<0.001***	0.191 (0.028)	<0.001***	0.033 (0.020)	0.098†
All	392	1.109 ± 0.243 (0.576-2.134)	0.004 (0.001)	<0.001***	0.239 (0.022)	<0.001***	0.064 (0.022)	0.005**
Parahippocampal								
Lo-aβ CN	288	1.002 ± 0.112 (0.681-1.348)	0.004 (0.000)	<0.001***	0.170 (0.077)	0.028*	-0.015 (0.014)	0.264
Hi-aβ CN	59	1.188 ± 0.169 (0.842-1.75)	0.010 (0.003)	<0.001***	0.061 (0.052)	0.248	0.013 (0.042)	0.759
MCI-AD	45	1.392 ± 0.237 (0.997-2.179)	-0.002 (0.004)	0.631	-0.025 (0.066)	0.707	0.102 (0.084)	0.232
All CN	347	1.031 ± 0.14 (0.681-1.75)	0.005 (0.000)	<0.001***	0.143 (0.020)	<0.001***	0.001 (0.014)	0.968
All	392	1.076 ± 0.195 (0.681-2.179)	0.004 (0.001)	<0.001***	0.203 (0.017)	<0.001***	0.019 (0.017)	0.254
Fusiform								
Lo-aβ CN	288	1.065 ± 0.107 (0.763-1.331)	0.005 (0.000)	<0.001***	0.030 (0.074)	0.692	-0.004 (0.013)	0.752

Hi-aβ CN	59	1.223 ± 0.156 (0.978-1.745)	0.011 (0.002)	<0.001***	0.046 (0.046)	0.322	0.022 (0.037)	0.551
MCI-AD	45	1.551 ± 0.353 (1.065-2.621)	-0.009 (0.005)	0.084†	0.136 (0.090)	0.137	0.008 (0.114)	0.943
All CN	347	1.09 ± 0.129 (0.763-1.745)	0.005 (0.000)	<0.001***	0.099 (0.018)	<0.001***	0.011 (0.013)	0.400
All	392	1.147 ± 0.23 (0.763-2.621)	0.003 (0.001)	<0.001***	0.259 (0.019)	<0.001***	0.013 (0.019)	0.505
Inferiortemporal								
Lo-aβ CN	288	1.159 ± 0.127 (0.788-1.451)	0.006 (0.000)	<0.001***	0.076 (0.082)	0.355	-0.012 (0.014)	0.406
Hi-aβ CN	59	1.346 ± 0.177 (1.054-1.92)	0.010 (0.003)	0.001**	0.059 (0.058)	0.312	0.042 (0.046)	0.371
MCI-AD	45	1.828 ± 0.442 (1.078-2.773)	-0.010 (0.006)	0.123	0.304 (0.114)	0.011*	-0.052 (0.145)	0.719
All CN	347	1.188 ± 0.152 (0.788-1.92)	0.006 (0.000)	<0.001***	0.119 (0.021)	<0.001***	0.010 (0.015)	0.497
All	392	1.268 ± 0.298 (0.788-2.773)	0.004 (0.001)	<0.001***	0.372 (0.024)	<0.001***	0.004 (0.024)	0.858
Middletemporal								
Lo-aβ CN	288	1.102 ± 0.129 (0.731-1.494)	0.006 (0.000)	<0.001***	0.138 (0.087)	0.113	0.000 (0.015)	0.996
Hi-aβ CN	59	1.269 ± 0.157 (0.99-1.762)	0.008 (0.003)	0.005**	0.043 (0.051)	0.410	0.016 (0.041)	0.707
MCI-AD	45	1.715 ± 0.422 (0.985-2.644)	-0.014 (0.006)	0.019*	0.297 (0.105)	0.008**	-0.105 (0.134)	0.438
All CN	347	1.128 ± 0.147 (0.731-1.762)	0.006 (0.000)	<0.001***	0.095 (0.021)	<0.001***	0.012 (0.014)	0.423
All	392	1.201 ± 0.279 (0.731-2.644)	0.003 (0.001)	<0.001***	0.358 (0.023)	<0.001***	-0.002 (0.023)	0.933
Superiortemporal								
Lo-aβ CN	288	1.069 ± 0.133 (0.758-1.566)	0.004 (0.001)	<0.001***	0.113 (0.103)	0.274	-0.009 (0.018)	0.619
Hi-aβ CN	59	1.172 ± 0.141 (0.804-1.568)	0.007 (0.002)	0.002**	0.010 (0.042)	0.811	-0.051 (0.034)	0.139
MCI-AD	45	1.338 ± 0.277 (0.749-2.235)	-0.004 (0.005)	0.398	-0.023 (0.092)	0.805	0.073 (0.117)	0.535
All CN	347	1.086 ± 0.139 (0.758-1.568)	0.005 (0.001)	<0.001***	0.053 (0.022)	0.017*	-0.012 (0.016)	0.461
All	392	1.117 ± 0.183 (0.749-2.235)	0.004 (0.001)	<0.001***	0.133 (0.019)	<0.001***	0.000 (0.019)	0.991
Cuneus								
Lo-aβ CN	288	1.003 ± 0.151 (0.598-1.631)	0.005 (0.001)	<0.001***	0.096 (0.124)	0.438	-0.015 (0.022)	0.505
Hi-aβ CN	59	1.109 ± 0.177 (0.786-1.647)	0.010 (0.003)	0.002**	0.009 (0.057)	0.875	0.013 (0.046)	0.780
MCI-AD	45	1.353 ± 0.523 (0.774-3.281)	-0.003 (0.009)	0.765	0.128 (0.153)	0.407	-0.146 (0.194)	0.458
All CN	347	1.02 ± 0.16 (0.598-1.647)	0.005 (0.001)	<0.001***	0.038 (0.027)	0.161	-0.002 (0.019)	0.918

All	392	1.061 ± 0.261 (0.598-3.281)	0.004 (0.001)	<0.001***	0.166 (0.026)	<0.001***	-0.018 (0.026)	0.491
Precuneus								
Lo-aβ CN	288	0.992 ± 0.125 (0.538-1.335)	0.006 (0.000)	<0.001***	0.134 (0.088)	0.127	0.004 (0.015)	0.786
Hi-aβ CN	59	1.122 ± 0.135 (0.854-1.427)	0.006 (0.002)	0.005**	0.003 (0.044)	0.949	-0.029 (0.035)	0.408
MCI-AD	45	1.521 ± 0.484 (0.992-2.732)	-0.033 (0.005)	<0.001***	0.206 (0.090)	0.028*	-0.399 (0.114)	0.001**
All CN	347	1.013 ± 0.135 (0.538-1.427)	0.006 (0.000)	<0.001***	0.048 (0.020)	0.016*	0.002 (0.014)	0.874
All	392	1.076 ± 0.27 (0.538-2.732)	0.002 (0.001)	0.026*	0.327 (0.025)	<0.001***	-0.042 (0.025)	0.103
Inferiorparietal								
Lo-aβ CN	288	1.034 ± 0.131 (0.694-1.532)	0.004 (0.001)	<0.001***	0.300 (0.099)	0.003**	0.001 (0.017)	0.934
Hi-aβ CN	59	1.17 ± 0.151 (0.724-1.478)	0.005 (0.002)	0.021*	0.048 (0.044)	0.281	0.000 (0.036)	0.998
MCI-AD	45	1.876 ± 0.795 (0.903-4.134)	-0.053 (0.008)	<0.001***	0.511 (0.140)	<0.001***	-0.523 (0.178)	0.006**
All CN	347	1.055 ± 0.143 (0.694-1.532)	0.005 (0.001)	<0.001***	0.088 (0.022)	<0.001***	0.007 (0.015)	0.643
All	392	1.157 ± 0.41 (0.694-4.134)	-0.002 (0.001)	0.118	0.578 (0.037)	<0.001***	-0.057 (0.037)	0.124
Superiorparietal								
Lo-aβ CN	288	0.98 ± 0.141 (0.576-1.39)	0.003 (0.001)	<0.001***	0.230 (0.120)	0.057†	-0.018 (0.021)	0.385
Hi-aβ CN	59	1.088 ± 0.168 (0.573-1.409)	0.006 (0.002)	0.024*	0.022 (0.049)	0.651	-0.015 (0.039)	0.703
MCI-AD	45	1.62 ± 0.836 (0.793-4.218)	-0.043 (0.012)	<0.001***	0.398 (0.212)	0.069†	-0.394 (0.270)	0.153
All CN	347	0.997 ± 0.151 (0.573-1.409)	0.003 (0.001)	<0.001***	0.079 (0.026)	0.003**	-0.012 (0.018)	0.508
All	392	1.074 ± 0.384 (0.573-4.218)	-0.002 (0.001)	0.153	0.438 (0.038)	<0.001***	-0.053 (0.038)	0.170
Isthmuscingulate								
Lo-aβ CN	288	0.878 ± 0.096 (0.48-1.153)	0.003 (0.000)	<0.001***	0.073 (0.077)	0.345	0.006 (0.014)	0.662
Hi-aβ CN	59	0.964 ± 0.119 (0.702-1.244)	0.005 (0.002)	0.014*	-0.027 (0.039)	0.489	-0.031 (0.031)	0.323
MCI-AD	45	1.268 ± 0.377 (0.714-2.232)	-0.028 (0.005)	<0.001***	0.096 (0.090)	0.292	-0.201 (0.114)	0.087†
All CN	347	0.891 ± 0.105 (0.48-1.244)	0.003 (0.000)	<0.001***	0.036 (0.018)	0.039*	0.006 (0.012)	0.644
All	392	0.938 ± 0.206 (0.48-2.232)	0.000 (0.001)	0.815	0.248 (0.022)	<0.001***	-0.014 (0.022)	0.528
Posteriorcingulate								
Lo-aβ CN	288	0.861 ± 0.101 (0.431-1.14)	0.003 (0.000)	<0.001***	0.110 (0.083)	0.189	0.007 (0.015)	0.612
Hi-aβ CN	59	0.955 ± 0.147 (0.66-1.409)	0.005 (0.002)	0.035*	-0.061 (0.049)	0.216	-0.032 (0.039)	0.418

MCI-AD	45	1.153 ± 0.264 (0.727-1.851)	-0.018 (0.003)	<0.001***	0.055 (0.061)	0.374	-0.139 (0.078)	0.081†
All CN	347	0.876 ± 0.114 (0.431-1.409)	0.003 (0.000)	<0.001***	0.025 (0.020)	0.203	0.005 (0.014)	0.726
All	392	0.91 ± 0.168 (0.431-1.851)	0.001 (0.001)	0.035*	0.168 (0.018)	<0.001***	-0.009 (0.018)	0.621
Caudalanteriorcingulate								
Lo-aβ CN	288	1.135 ± 0.185 (-0.218-1.623)	0.002 (0.001)	0.017*	0.366 (0.160)	0.023*	-0.012 (0.028)	0.661
Hi-aβ CN	59	1.2 ± 0.224 (0.717-2.019)	0.005 (0.004)	0.182	-0.118 (0.071)	0.101	-0.052 (0.057)	0.364
MCI-AD	45	1.132 ± 0.233 (0.573-1.733)	0.003 (0.004)	0.464	-0.198 (0.065)	0.004**	0.022 (0.083)	0.790
All CN	347	1.145 ± 0.193 (-0.218-2.019)	0.003 (0.001)	<0.001***	-0.008 (0.035)	0.817	-0.015 (0.025)	0.554
All	392	1.144 ± 0.198 (-0.218-2.019)	0.004 (0.001)	<0.001***	-0.060 (0.023)	0.011*	-0.004 (0.023)	0.857
Rostralanteriorcingulate								
Lo-aβ CN	288	1.096 ± 0.159 (0.49-1.61)	0.005 (0.001)	<0.001***	0.224 (0.120)	0.063†	0.001 (0.021)	0.973
Hi-aβ CN	59	1.191 ± 0.15 (0.92-1.573)	0.006 (0.003)	0.016*	-0.061 (0.052)	0.242	-0.012 (0.041)	0.774
MCI-AD	45	1.146 ± 0.302 (0.482-1.909)	0.017 (0.005)	0.001**	-0.055 (0.087)	0.526	0.090 (0.110)	0.421
All CN	347	1.11 ± 0.162 (0.49-1.61)	0.006 (0.001)	<0.001***	0.001 (0.026)	0.975	0.000 (0.018)	0.988
All	392	1.115 ± 0.185 (0.482-1.909)	0.007 (0.001)	<0.001***	-0.019 (0.020)	0.339	0.009 (0.020)	0.638
Caudalmiddlefrontal								
Lo-aβ CN	288	1.027 ± 0.134 (0.57-1.436)	0.004 (0.001)	<0.001***	0.119 (0.105)	0.258	0.010 (0.018)	0.605
Hi-aβ CN	59	1.142 ± 0.168 (0.849-1.791)	0.006 (0.003)	0.074†	0.034 (0.060)	0.571	-0.039 (0.048)	0.421
MCI-AD	45	1.658 ± 0.691 (0.762-4.026)	-0.034 (0.010)	0.002**	0.589 (0.187)	0.003**	-0.584 (0.237)	0.019*
All CN	347	1.045 ± 0.146 (0.57-1.791)	0.005 (0.001)	<0.001***	0.052 (0.024)	0.031*	-0.002 (0.017)	0.900
All	392	1.121 ± 0.343 (0.57-4.026)	0.000 (0.001)	0.715	0.470 (0.036)	<0.001***	-0.074 (0.036)	0.040*
Rostralmiddlefrontal								
Lo-aβ CN	288	1.061 ± 0.144 (0.613-1.719)	0.004 (0.001)	<0.001***	0.196 (0.118)	0.098†	0.006 (0.021)	0.765
Hi-aβ CN	59	1.172 ± 0.18 (0.788-1.866)	0.003 (0.003)	0.217	-0.016 (0.055)	0.779	-0.078 (0.044)	0.080†
MCI-AD	45	1.395 ± 0.478 (0.719-3.02)	-0.024 (0.009)	0.010**	0.190 (0.154)	0.225	-0.295 (0.196)	0.141
All CN	347	1.079 ± 0.155 (0.613-1.866)	0.004 (0.001)	<0.001***	0.045 (0.026)	0.087†	-0.007 (0.018)	0.683
All	392	1.118 ± 0.245 (0.613-3.02)	0.001 (0.001)	0.237	0.239 (0.028)	<0.001***	-0.036 (0.028)	0.201

Table S5. Effects of Age, Aβ, *APOE*e4 on ROI TAU in each subgroup. β=model slope estimate, SE=standard error. Full model: ROI mean TAU SUVr ~ Age + PiB + *APOE*e4 + Sex + Education. †p<0.1; *p<0.05; **p<0.01; ***p<0.001. Medial entorhinal = portion of FreeSurfer-defined entorhinal cortex that did not overlap with rhinal cortex (RC). See Fig. S2.

Model / Predictor	Estimate (SE)	p
I. BL_RC ~ Age (r.sq=0.293, p<0.0001)		
Age	0.009 (0.001)	<0.0001***
II. BL_RC ~ BL_PiB (r.sq=0.450, p<0.0001)		
BL_PiB	0.341 (0.018)	<0.0001***
III. BL_RC ~ APOEe4 (r.sq=0.111, p<0.0001)		
APOEe4e4+	0.173 (0.025)	<0.0001***
IV. BL_RC ~ APOEe2 (r.sq=0.015, p=0.018)		
APOEe2e2+	-0.096 (0.040)	0.018*
V. BL_RC ~ Age + BL_PiB (r.sq=0.567, p<0.0001)		
Age	0.006 (0.001)	<0.0001***
BL_PiB	0.282 (0.017)	<0.0001***
VI. BL_RC ~ Age + APOEe4 (r.sq=0.356, p<0.0001)		
Age	0.009 (0.001)	<0.0001***
APOEe4e4+	0.171 (0.021)	<0.0001***
VII. BL_RC ~ Age + APOEe2 (r.sq=0.255, p<0.0001)		
Age	0.009 (0.001)	<0.0001***
APOEe2e2+	-0.063 (0.035)	0.072†
VIII. BL_RC ~ BL_PiB + APOEe4 (r.sq=0.427, p<0.0001)		
BL_PiB	0.318 (0.022)	<0.0001***
APOEe4e4+	0.014 (0.023)	0.533
IX. BL_RC ~ BL_PiB + APOEe2 (r.sq=0.427, p<0.0001)		
BL_PiB	0.323 (0.020)	<0.0001***
APOEe2e2+	-0.022 (0.031)	0.481
X. BL_RC ~ Age + BL_PiB + APOEe4 (r.sq=0.538, p<0.0001)		
Age	0.007 (0.001)	<0.0001***
BL_PiB	0.255 (0.021)	<0.0001***
APOEe4e4+	0.044 (0.021)	0.035*
XI. BL_RC ~ Age + BL_PiB + APOEe2 (r.sq=0.533, p<0.0001)		
Age	0.006 (0.001)	<0.0001***
BL_PiB	0.276 (0.018)	<0.0001***
APOEe2e2+	-0.010 (0.028)	0.712

Table S6. Hierarchical models predicting RC TAU. For models I-XI, the R^2 (“r.sq”) and p value for the full model are given in parentheses; Estimate, standard error (SE), and p value for each variable shown in columns 2 and 3. BL=Baseline, RC=rhinal cortex TAU (SUVr), PiB=PiB

DVR (PVC, cerebellar cortex ref). *APOE*e2+ included e2/e2 and e2/e3; *APOE*e4+ included e4/e4 and e3/e4. Full sample, N=443.

Model / predictor	Estimate (SE)	p
I. BL_IT ~ Age (r.sq=0.167, p<0.0001)		
Age	0.008 (0.001)	<0.0001***
II. BL_IT ~ BL_PiB (r.sq=0.558, p<0.0001)		
BL_PiB	0.450 (0.019)	<0.0001***
III. BL_IT ~ APOEe4 (r.sq=0.100, p<0.0001)		
APOEe4e4+	0.185 (0.028)	<0.0001***
IV. BL_IT ~ APOEe2 (r.sq=0.014, p=0.020)		
APOEe2e2+	-0.106 (0.045)	0.020*
V. BL_IT ~ Age + BL_PiB (r.sq=0.589, p<0.0001)		
Age	0.004 (0.001)	<0.0001***
BL_PiB	0.413 (0.019)	<0.0001***
VI. BL_IT ~ Age + APOEe4 (r.sq=0.223, p<0.0001)		
Age	0.007 (0.001)	<0.0001***
APOEe4e4+	0.183 (0.026)	<0.0001***
VII. BL_IT ~ Age + APOEe2 (r.sq=0.133, p<0.0001)		
Age	0.007 (0.001)	<0.0001***
APOEe2e2+	-0.080 (0.043)	0.061†
VIII. BL_IT ~ BL_PiB + APOEe4 (r.sq=0.504, p<0.0001)		
BL_PiB	0.403 (0.023)	<0.0001***
APOEe4e4+	-0.016 (0.024)	0.500
IX. BL_IT ~ BL_PiB + APOEe2 (r.sq=0.504, p<0.0001)		
BL_PiB	0.394 (0.020)	<0.0001***
APOEe2e2+	-0.015 (0.032)	0.636
X. BL_IT ~ Age + BL_PiB + APOEe4 (r.sq=0.528, p<0.0001)		
Age	0.004 (0.001)	<0.0001***
BL_PiB	0.370 (0.024)	<0.0001***
APOEe4e4+	-0.001 (0.024)	0.982
XI. BL_IT ~ Age + BL_PiB + APOEe2 (r.sq=0.528, p<0.0001)		
Age	0.003 (0.001)	<0.0001***
BL_PiB	0.369 (0.021)	<0.0001***
APOEe2e2+	-0.009 (0.032)	0.774

Table S7. Hierarchical models predicting IT TAU. For models I-XI, the R^2 ("r.sq") and p value for the full model are given in parentheses; Estimate, standard error (SE), and p value for each variable shown in columns 2 and 3. BL=Baseline, IT=inferior temporal cortex TAU

(SUVr), PiB=PiB DVR (PVC, cerebellar cortex ref). *APOE*e2+ included e2/e2 and e2/e3; *APOE*e4+ included e4/e4 and e3/e4. Full sample, N=443.

	N	SUVr/year Mean±SD (range)	Mean p value	CoV	Age β (SE)	Age p	PiB β (SE)	PiB p	APOE4 β (SE)	APOE4 p
Rhinal Cortex										
Lo-aβ CN	63	0.022 ± 0.043 (-0.097-0.163)	<0.001***	1.940	0.001 (0.001)	0.230	-0.052 (0.078)	0.507	-0.002 (0.015)	0.873
Hi-aβ CN	27	0.053 ± 0.055 (-0.084-0.155)	<0.001***	1.052	0.001 (0.002)	0.639	0.047 (0.029)	0.121	0.023 (0.025)	0.375
MCI-AD	10	0.016 ± 0.057 (-0.122-0.081)	0.374	3.568	-0.002 (0.003)	0.615	-0.005 (0.137)	0.974	-0.047 (0.060)	0.476
All CN	90	0.031 ± 0.049 (-0.097-0.163)	<0.001***	1.568	0.001 (0.001)	0.352	0.031 (0.012)	0.010*	0.004 (0.012)	0.725
All	100	0.03 ± 0.05 (-0.122-0.163)	<0.001***	1.682	0.001 (0.001)	0.097†	0.017 (0.010)	0.103	0.003 (0.012)	0.789
Entorhinal										
Lo-aβ CN	63	0.025 ± 0.042 (-0.11-0.158)	<0.001***	1.733	0.001 (0.001)	0.086†	0.021 (0.077)	0.784	-0.001 (0.015)	0.940
Hi-aβ CN	27	0.05 ± 0.037 (-0.06-0.106)	<0.001***	0.731	0.002 (0.001)	0.167	0.023 (0.018)	0.226	0.026 (0.015)	0.107
MCI-AD	10	0.006 ± 0.069 (-0.115-0.126)	0.768	10.930	-0.003 (0.003)	0.375	0.074 (0.150)	0.649	-0.024 (0.066)	0.734
All CN	90	0.032 ± 0.042 (-0.11-0.158)	<0.001***	1.324	0.001 (0.001)	0.048*	0.021 (0.010)	0.045*	0.008 (0.011)	0.481
All	100	0.029 ± 0.046 (-0.115-0.158)	<0.001***	1.577	0.001 (0.001)	0.069†	0.009 (0.010)	0.343	0.006 (0.011)	0.573
Medial Entorhinal										
Lo-aβ CN	63	0.022 ± 0.043 (-0.105-0.128)	<0.001***	1.982	0.002 (0.001)	0.041*	0.078 (0.076)	0.309	0.007 (0.015)	0.618
Hi-aβ CN	27	0.044 ± 0.029 (-0.028-0.087)	<0.001***	0.671	0.002 (0.001)	0.063†	-0.002 (0.015)	0.902	0.009 (0.012)	0.477
MCI-AD	10	-0.006 ± 0.104 (-0.226-0.195)	0.850	-17.044	-0.006 (0.004)	0.192	0.234 (0.165)	0.230	-0.061 (0.072)	0.448
All CN	90	0.028 ± 0.04 (-0.105-0.128)	<0.001***	1.444	0.002 (0.001)	0.007**	0.013 (0.010)	0.196	0.007 (0.010)	0.520
All	100	0.024 ± 0.051 (-0.226-0.195)	<0.001***	2.099	0.001 (0.001)	0.163	0.005 (0.011)	0.679	0.002 (0.013)	0.892
Parahippocampal										
Lo-aβ CN	63	0.004 ± 0.04 (-0.11-0.117)	0.434	10.326	0.002 (0.001)	0.021*	-0.075 (0.070)	0.284	0.015 (0.014)	0.274
Hi-aβ CN	27	0.037 ± 0.046 (-0.039-0.144)	<0.001***	1.259	0.001 (0.002)	0.818	0.022 (0.026)	0.410	-0.001 (0.022)	0.952
MCI-AD	10	0.004 ± 0.044 (-0.078-0.063)	0.775	11.316	0.001 (0.001)	0.412	-0.013 (0.062)	0.846	0.034 (0.027)	0.284
All CN	90	0.013 ± 0.044 (-0.11-0.144)	0.004**	3.297	0.002 (0.001)	0.029*	0.025 (0.011)	0.019*	0.009 (0.011)	0.390
All	100	0.012 ± 0.044 (-0.11-0.144)	0.005**	3.553	0.002 (0.001)	<0.001***	0.015 (0.009)	0.076†	0.015 (0.010)	0.136
Fusiform										
Lo-aβ CN	63	0.014 ± 0.036 (-0.079-0.171)	0.002**	2.492	0.001 (0.001)	0.152	-0.062 (0.064)	0.338	0.009 (0.013)	0.488
Hi-aβ CN	27	0.052 ± 0.048 (-0.06-0.156)	<0.001***	0.907	0.001 (0.002)	0.705	0.042 (0.024)	0.101	0.021 (0.021)	0.314

MCI-AD	10	0.061 ± 0.041 (0.022-0.143)	<0.001***	0.671	-0.004 (0.001)	0.055†	-0.039 (0.065)	0.580	-0.013 (0.028)	0.668
All CN	90	0.025 ± 0.043 (-0.079-0.171)	<0.001***	1.690	0.001 (0.001)	0.207	0.035 (0.010)	<0.001***	0.013 (0.010)	0.211
All	100	0.029 ± 0.044 (-0.079-0.171)	<0.001***	1.507	0.000 (0.001)	0.608	0.035 (0.008)	<0.001***	0.011 (0.010)	0.238
Inferiortemporal										
Lo-aβ CN	63	0.022 ± 0.039 (-0.114-0.136)	<0.001***	1.806	0.000 (0.001)	0.527	-0.162 (0.070)	0.024*	0.015 (0.014)	0.265
Hi-aβ CN	27	0.06 ± 0.058 (-0.074-0.171)	<0.001***	0.978	0.001 (0.003)	0.702	0.046 (0.030)	0.142	0.027 (0.026)	0.303
MCI-AD	10	0.104 ± 0.068 (0.002-0.21)	<0.001***	0.652	-0.005 (0.003)	0.165	-0.066 (0.139)	0.657	0.017 (0.061)	0.794
All CN	90	0.033 ± 0.049 (-0.114-0.171)	<0.001***	1.480	0.000 (0.001)	0.578	0.031 (0.011)	0.009**	0.020 (0.012)	0.101
All	100	0.04 ± 0.055 (-0.114-0.21)	<0.001***	1.365	-0.001 (0.001)	0.171	0.041 (0.010)	<0.001***	0.017 (0.012)	0.146
Middletemporal										
Lo-aβ CN	63	0.022 ± 0.05 (-0.063-0.301)	<0.001***	2.211	0.000 (0.001)	0.752	-0.251 (0.088)	0.006**	0.008 (0.017)	0.651
Hi-aβ CN	27	0.052 ± 0.053 (-0.063-0.157)	<0.001***	1.017	0.001 (0.002)	0.829	0.032 (0.028)	0.264	0.031 (0.024)	0.211
MCI-AD	10	0.099 ± 0.074 (0.009-0.224)	0.001**	0.748	-0.006 (0.003)	0.121	-0.159 (0.135)	0.303	0.012 (0.059)	0.849
All CN	90	0.031 ± 0.052 (-0.063-0.301)	<0.001***	1.678	0.000 (0.001)	0.778	0.020 (0.013)	0.138	0.019 (0.014)	0.163
All	100	0.038 ± 0.058 (-0.063-0.301)	<0.001***	1.524	-0.001 (0.001)	0.144	0.030 (0.012)	0.011*	0.017 (0.013)	0.215
Superiortemporal										
Lo-aβ CN	63	0.024 ± 0.039 (-0.046-0.168)	<0.001***	1.596	0.001 (0.001)	0.063†	-0.105 (0.067)	0.124	0.027 (0.013)	0.044*
Hi-aβ CN	27	0.046 ± 0.047 (-0.046-0.147)	<0.001***	1.040	0.000 (0.002)	0.916	0.020 (0.026)	0.447	0.014 (0.022)	0.541
MCI-AD	10	0.06 ± 0.107 (-0.111-0.224)	0.095†	1.798	-0.003 (0.005)	0.625	-0.249 (0.258)	0.389	0.028 (0.113)	0.814
All CN	90	0.03 ± 0.042 (-0.046-0.168)	<0.001***	1.389	0.001 (0.001)	0.111	0.011 (0.010)	0.303	0.023 (0.011)	0.034*
All	100	0.034 ± 0.053 (-0.111-0.224)	<0.001***	1.578	0.001 (0.001)	0.458	0.012 (0.011)	0.275	0.024 (0.013)	0.065†
Cuneus										
Lo-aβ CN	63	0.007 ± 0.054 (-0.131-0.182)	0.327	8.231	0.000 (0.001)	0.846	-0.182 (0.097)	0.067†	0.013 (0.019)	0.511
Hi-aβ CN	27	0.042 ± 0.069 (-0.052-0.202)	0.004**	1.651	-0.001 (0.003)	0.710	0.032 (0.036)	0.393	0.003 (0.031)	0.922
MCI-AD	10	0.032 ± 0.078 (-0.058-0.171)	0.197	2.398	-0.004 (0.003)	0.268	-0.060 (0.142)	0.694	-0.104 (0.062)	0.170
All CN	90	0.017 ± 0.06 (-0.131-0.202)	0.009**	3.594	0.000 (0.001)	0.747	0.032 (0.015)	0.036*	0.010 (0.016)	0.512
All	100	0.018 ± 0.062 (-0.131-0.202)	0.003**	3.370	0.000 (0.001)	0.868	0.023 (0.013)	0.077†	0.004 (0.015)	0.811
Precuneus										

Lo-aβ CN	63	0.011 ± 0.042 (-0.144-0.14)	0.042*	3.923	0.001 (0.001)	0.326	-0.144 (0.076)	0.065†	0.001 (0.015)	0.936
Hi-aβ CN	27	0.033 ± 0.058 (-0.06-0.196)	0.007**	1.764	-0.001 (0.002)	0.806	0.046 (0.030)	0.146	0.008 (0.026)	0.747
MCI-AD	10	0.079 ± 0.074 (-0.047-0.216)	0.005**	0.937	-0.007 (0.001)	0.006**	-0.148 (0.056)	0.058†	0.060 (0.025)	0.071†
All CN	90	0.017 ± 0.048 (-0.144-0.196)	<0.001***	2.796	0.000 (0.001)	0.619	0.025 (0.012)	0.041*	0.006 (0.012)	0.652
All	100	0.024 ± 0.054 (-0.144-0.216)	<0.001***	2.293	-0.001 (0.001)	0.151	0.032 (0.011)	0.004**	0.010 (0.012)	0.410
Inferiorparietal										
Lo-aβ CN	63	0.01 ± 0.052 (-0.08-0.276)	0.135	5.365	0.000 (0.001)	0.726	-0.171 (0.096)	0.080†	0.009 (0.019)	0.652
Hi-aβ CN	27	0.04 ± 0.052 (-0.036-0.159)	<0.001***	1.285	-0.002 (0.002)	0.475	0.002 (0.029)	0.949	-0.002 (0.025)	0.942
MCI-AD	10	0.027 ± 0.156 (-0.27-0.247)	0.582	5.829	0.002 (0.007)	0.786	-0.470 (0.313)	0.208	0.125 (0.137)	0.415
All CN	90	0.019 ± 0.054 (-0.08-0.276)	0.001**	2.885	0.000 (0.001)	0.702	0.021 (0.014)	0.125	0.011 (0.014)	0.432
All	100	0.019 ± 0.07 (-0.27-0.276)	0.006**	3.611	0.001 (0.001)	0.440	0.004 (0.015)	0.767	0.028 (0.017)	0.115
Superiorparietal										
Lo-aβ CN	63	0.005 ± 0.059 (-0.13-0.192)	0.485	11.568	0.001 (0.001)	0.515	-0.149 (0.107)	0.170	0.015 (0.021)	0.480
Hi-aβ CN	27	0.035 ± 0.075 (-0.14-0.195)	0.024*	2.163	-0.004 (0.003)	0.255	0.008 (0.040)	0.853	0.016 (0.034)	0.650
MCI-AD	10	0.006 ± 0.12 (-0.202-0.174)	0.866	19.143	-0.004 (0.005)	0.448	0.042 (0.243)	0.870	0.058 (0.106)	0.615
All CN	90	0.014 ± 0.065 (-0.14-0.195)	0.045*	4.749	0.000 (0.001)	0.972	0.019 (0.016)	0.238	0.022 (0.017)	0.190
All	100	0.013 ± 0.072 (-0.202-0.195)	0.071†	5.586	0.000 (0.001)	0.806	0.011 (0.015)	0.468	0.025 (0.017)	0.162
Isthmuscingulate										
Lo-aβ CN	63	0.004 ± 0.04 (-0.089-0.125)	0.478	11.381	0.002 (0.001)	0.047*	-0.152 (0.069)	0.031*	0.026 (0.013)	0.057†
Hi-aβ CN	27	0.022 ± 0.042 (-0.091-0.099)	0.013*	1.945	-0.002 (0.002)	0.320	0.028 (0.023)	0.225	-0.013 (0.019)	0.495
MCI-AD	10	0.058 ± 0.087 (-0.068-0.255)	0.053†	1.510	-0.004 (0.003)	0.298	-0.120 (0.158)	0.491	-0.131 (0.069)	0.131
All CN	90	0.009 ± 0.041 (-0.091-0.125)	0.043*	4.699	0.001 (0.001)	0.230	0.014 (0.010)	0.169	0.013 (0.011)	0.242
All	100	0.014 ± 0.05 (-0.091-0.255)	0.005**	3.573	0.000 (0.001)	0.607	0.028 (0.010)	0.007**	-0.003 (0.012)	0.771
Posteriorcingulate										
Lo-aβ CN	63	-0.003 ± 0.042 (-0.105-0.127)	0.548	-13.443	0.000 (0.001)	0.606	0.039 (0.079)	0.630	0.007 (0.016)	0.678
Hi-aβ CN	27	0.003 ± 0.078 (-0.196-0.228)	0.868	30.909	-0.001 (0.004)	0.861	0.017 (0.042)	0.694	0.019 (0.036)	0.613
MCI-AD	10	0.049 ± 0.106 (-0.083-0.287)	0.157	2.166	-0.010 (0.002)	0.006**	0.035 (0.090)	0.717	-0.086 (0.039)	0.095†
All CN	90	-0.001 ± 0.055 (-0.196-0.228)	0.791	-36.355	0.000 (0.001)	0.898	0.007 (0.014)	0.628	0.011 (0.015)	0.466

All	100	0.004 ± 0.063 (-0.196-0.287)	0.538	16.510	-0.002 (0.001)	0.038*	0.020 (0.013)	0.122	-0.003 (0.015)	0.833
Caudalanteriorcingulate										
Lo-aβ CN	63	0.003 ± 0.064 (-0.168-0.171)	0.694	20.591	0.002 (0.001)	0.134	-0.040 (0.109)	0.715	0.029 (0.021)	0.178
Hi-aβ CN	27	0.03 ± 0.082 (-0.206-0.148)	0.071†	2.757	0.003 (0.003)	0.403	0.092 (0.041)	0.036*	0.014 (0.035)	0.682
MCI-AD	10	0.007 ± 0.141 (-0.305-0.276)	0.873	20.152	-0.006 (0.007)	0.458	0.055 (0.332)	0.877	-0.122 (0.145)	0.449
All CN	90	0.011 ± 0.07 (-0.206-0.171)	0.140	6.484	0.002 (0.001)	0.193	0.034 (0.017)	0.053†	0.016 (0.018)	0.366
All	100	0.01 ± 0.08 (-0.305-0.276)	0.184	7.632	0.001 (0.001)	0.441	0.034 (0.017)	0.044*	-0.001 (0.019)	0.958
Rostralanteriorcingulate										
Lo-aβ CN	63	0.008 ± 0.061 (-0.158-0.183)	0.290	7.615	0.001 (0.001)	0.361	-0.240 (0.104)	0.025*	0.014 (0.020)	0.505
Hi-aβ CN	27	0.019 ± 0.064 (-0.169-0.128)	0.126	3.287	-0.002 (0.003)	0.593	0.045 (0.034)	0.203	-0.006 (0.029)	0.849
MCI-AD	10	0.041 ± 0.076 (-0.158-0.141)	0.100†	1.828	-0.002 (0.003)	0.647	0.009 (0.162)	0.960	-0.118 (0.071)	0.173
All CN	90	0.011 ± 0.062 (-0.169-0.183)	0.080†	5.455	0.000 (0.001)	0.785	0.015 (0.016)	0.344	0.006 (0.016)	0.730
All	100	0.015 ± 0.064 (-0.169-0.183)	0.022*	4.391	0.000 (0.001)	0.959	0.022 (0.014)	0.107	-0.003 (0.016)	0.830
Caudalmiddlefrontal										
Lo-aβ CN	63	0.022 ± 0.054 (-0.124-0.178)	0.002**	2.464	0.001 (0.001)	0.506	-0.163 (0.096)	0.095†	0.025 (0.019)	0.194
Hi-aβ CN	27	0.04 ± 0.063 (-0.053-0.227)	0.003**	1.574	-0.002 (0.003)	0.378	0.034 (0.032)	0.293	0.018 (0.027)	0.504
MCI-AD	10	0.1 ± 0.111 (-0.067-0.291)	0.014*	1.112	-0.002 (0.005)	0.736	-0.053 (0.217)	0.820	0.110 (0.095)	0.311
All CN	90	0.027 ± 0.057 (-0.124-0.227)	<0.001***	2.098	0.000 (0.001)	0.990	0.013 (0.014)	0.349	0.025 (0.015)	0.090†
All	100	0.035 ± 0.068 (-0.124-0.291)	<0.001***	1.948	0.000 (0.001)	0.634	0.021 (0.013)	0.116	0.037 (0.016)	0.019*
Rostralmiddlefrontal										
Lo-aβ CN	63	0.028 ± 0.056 (-0.075-0.196)	<0.001***	2.023	0.001 (0.001)	0.578	-0.204 (0.100)	0.047*	0.017 (0.020)	0.379
Hi-aβ CN	27	0.031 ± 0.052 (-0.06-0.194)	0.005**	1.697	-0.002 (0.002)	0.320	0.025 (0.027)	0.355	0.020 (0.023)	0.386
MCI-AD	10	0.131 ± 0.092 (-0.003-0.308)	<0.001***	0.705	-0.009 (0.002)	0.005**	0.136 (0.071)	0.126	-0.149 (0.031)	0.009**
All CN	90	0.029 ± 0.055 (-0.075-0.196)	<0.001***	1.914	0.000 (0.001)	0.855	-0.001 (0.014)	0.943	0.020 (0.014)	0.178
All	100	0.039 ± 0.067 (-0.075-0.308)	<0.001***	1.701	-0.002 (0.001)	0.005**	0.031 (0.013)	0.022*	0.003 (0.015)	0.867

Table S8. Effects of Age, Aβ, *APOE*e4 on ROI TAU change rate in each subgroup. "Mean p value" (column 4) gives the significance estimate of a one-sample t-test, indicating whether mean change was significantly different from zero. CoV=Coefficient of variation, defined as SD/mean. Full model: ROI TAU change ~ Age + PiB + *APOE*e4 + Sex + Education. $^{\dagger}p<0.1$; $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

Model / predictor	All CN (N=93)	
	Estimate (SE)	p
I. dRC ~ Age (r.sq=0.032, p=0.085)		
Age	0.001 (0.001)	0.085†
II. dRC ~ BL_PiB (r.sq=0.103, p=0.002)		
BL_PiB	0.033 (0.010)	0.002**
III. dRC ~ APOEe4 (r.sq=0.024, p=0.147)		
APOEe4e4+	0.017 (0.011)	0.147
IV. dRC ~ APOEe2 (r.sq=0.027, p=0.126)		
APOEe2e2+	-0.030 (0.019)	0.126
V. dRC ~ Age + BL_PiB (r.sq=0.119, p=0.003)		
Age	0.001 (0.000)	0.197
BL_PiB	0.031 (0.010)	0.004**
VI. dRC ~ Age + APOEe4 (r.sq=0.046, p=0.134)		
Age	0.001 (0.001)	0.166
APOEe4e4+	0.017 (0.011)	0.127
VII. dRC ~ Age + APOEe2 (r.sq=0.052, p=0.101)		
Age	0.001 (0.001)	0.133
APOEe2e2+	-0.033 (0.019)	0.089†
VIII. dRC ~ BL_PiB + APOEe4 (r.sq=0.096, p=0.013)		
BL_PiB	0.031 (0.012)	0.010*
APOEe4e4+	0.002 (0.012)	0.88
IX. dRC ~ BL_PiB + APOEe2 (r.sq=0.117, p=0.005)		
BL_PiB	0.031 (0.010)	0.004**
APOEe2e2+	-0.026 (0.019)	0.157
X. dRC ~ Age + BL_PiB + APOEe4 (r.sq=0.109, p=0.020)		
Age	0.001 (0.001)	0.284
BL_PiB	0.029 (0.012)	0.016*
APOEe4e4+	0.003 (0.012)	0.789
XI. dRC ~ Age + BL_PiB + APOEe2 (r.sq=0.133, p=0.007)		
Age	0.001 (0.001)	0.213
BL_PiB	0.029 (0.010)	0.006**
APOEe2e2+	-0.029 (0.019)	0.119

Table S9. Hierarchical models predicting RC TAU change rate. For models I-XI, the R^2 ("r.sq") and p value for the full model are given in parentheses; Estimate, standard error (SE), and p value for each variable shown in columns 2 and 3. dRC=RC TAU change rate

(SUVr/year), BL=Baseline, PiB=PiB DVR (PVC, cerebellar cortex ref). *APOE*e2+ included e2/e2 and e2/e3; *APOE*e4+ included e4/e4 and e3/e4.

	All CN (N=93)	
Model / predictor	**Estimate (SE)**	**p**
I. dIT ~ Age (r.sq=0.011, p=0.319)		
Age	0.001 (0.001)	0.319
II. dIT ~ BL_PiB (r.sq=0.157, p=8.42e-05)		
BL_PiB	0.041 (0.010)	8.42e-05***
III. dIT ~ APOEe4 (r.sq=0.092, p=0.004)		
APOEe4e4+	0.032 (0.011)	0.004**
IV. dIT ~ APOEe2 (r.sq=0.002, p=0.691)		
APOEe2e2+	-0.008 (0.019)	0.691
V. dIT ~ Age + BL_PiB (r.sq=0.159, p=4.21e-04)		
Age	0.000 (0.000)	0.682
BL_PiB	0.040 (0.010)	1.42e-04***
VI. dIT ~ Age + APOEe4 (r.sq=0.098, p=0.012)		
Age	0.001 (0.001)	0.43
APOEe4e4+	0.033 (0.011)	0.004**
VII. dIT ~ Age + APOEe2 (r.sq=0.007, p=0.743)		
Age	0.001 (0.001)	0.51
APOEe2e2+	-0.009 (0.020)	0.639
VIII. dIT ~ BL_PiB + APOEe4 (r.sq=0.172, p=3.04e-04)		
BL_PiB	0.032 (0.011)	0.005**
APOEe4e4+	0.017 (0.012)	0.154
IX. dIT ~ BL_PiB + APOEe2 (r.sq=0.152, p=8.29e-04)		
BL_PiB	0.040 (0.010)	1.87e-04***
APOEe2e2+	-0.003 (0.018)	0.849
X. dIT ~ Age + BL_PiB + APOEe4 (r.sq=0.173, p=9.92e-04)		
Age	0.000 (0.001)	0.673
BL_PiB	0.032 (0.011)	0.007**
APOEe4e4+	0.017 (0.012)	0.146
XI. dIT ~ Age + BL_PiB + APOEe2 (r.sq=0.153, p=0.003)		
Age	0.000 (0.001)	0.775
BL_PiB	0.039 (0.010)	2.46e-04***
APOEe2e2+	-0.004 (0.018)	0.824

Table S10. Hierarchical models predicting IT TAU change rate. For models I-XI, the R^2 ("r.sq") and p value for the full model are given in parentheses; Estimate, standard error (SE), and p value for each variable shown in columns 2 and 3. dIT=IT TAU change rate (SUVr/year), BL=Baseline, PiB=PiB DVR (PVC, cerebellar cortex ref). *APOE*e2+ included e2/e2 and e2/e3; *APOE*e4+ included e4/e4 and e3/e4.

Race	*Ethnicity* Hispanic	Non-Hispanic	Unknown	**Total**
Asian	0	5	0	5
Black	2	28	0	30
White	27	371	2	400
Multiracial*	0	4	1	5
Unknown	0	0	3	3
Total	29	408	6	443

Table S11. Self-identified race and ethnicity of participants. Number of participants self-identifying as a particular race (rows) and ethnicity (columns) are given in each cell of table. Options for racial self-report were modeled after the United Sates' Federal Office of Management and Budget guidelines. *Multiracial participants: 1 Black/Native American, 1 Black/White, 2 Native American/White, 1 Undisclosed.