

# **Initial levels of $\beta$ -amyloid and tau deposition have distinct effects on longitudinal tau accumulation in Alzheimer's disease**

## ***Supplementary material***

### **Supplemental Methods**

MRI imaging processing

### **Supplemental Figures and Tables**

Figures S1-16, Tables S1-15

### **Supplemental References**

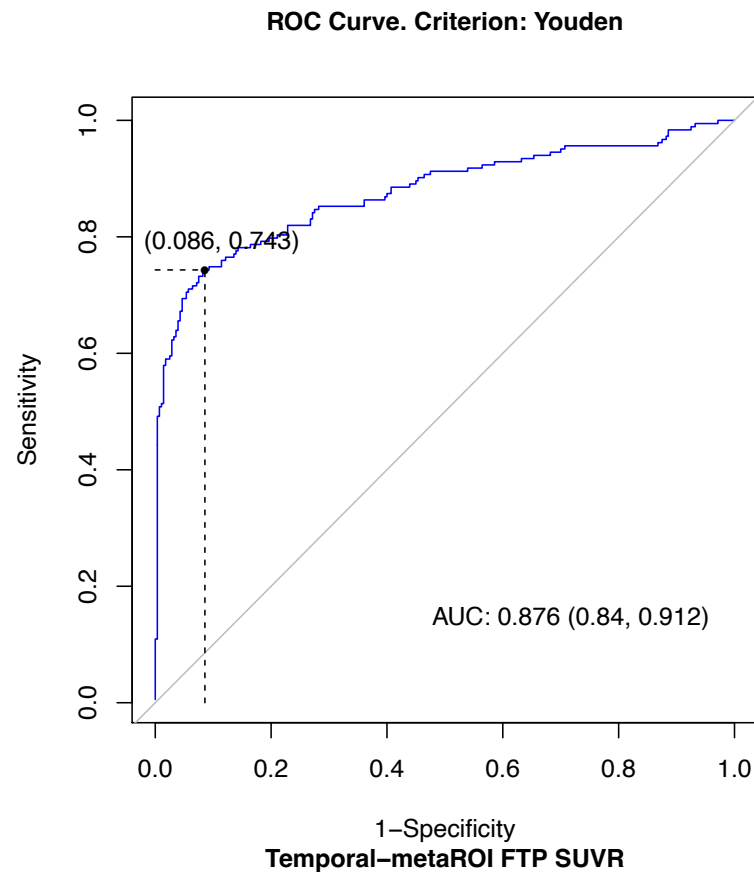
## Supplemental Methods

### MRI imaging processing

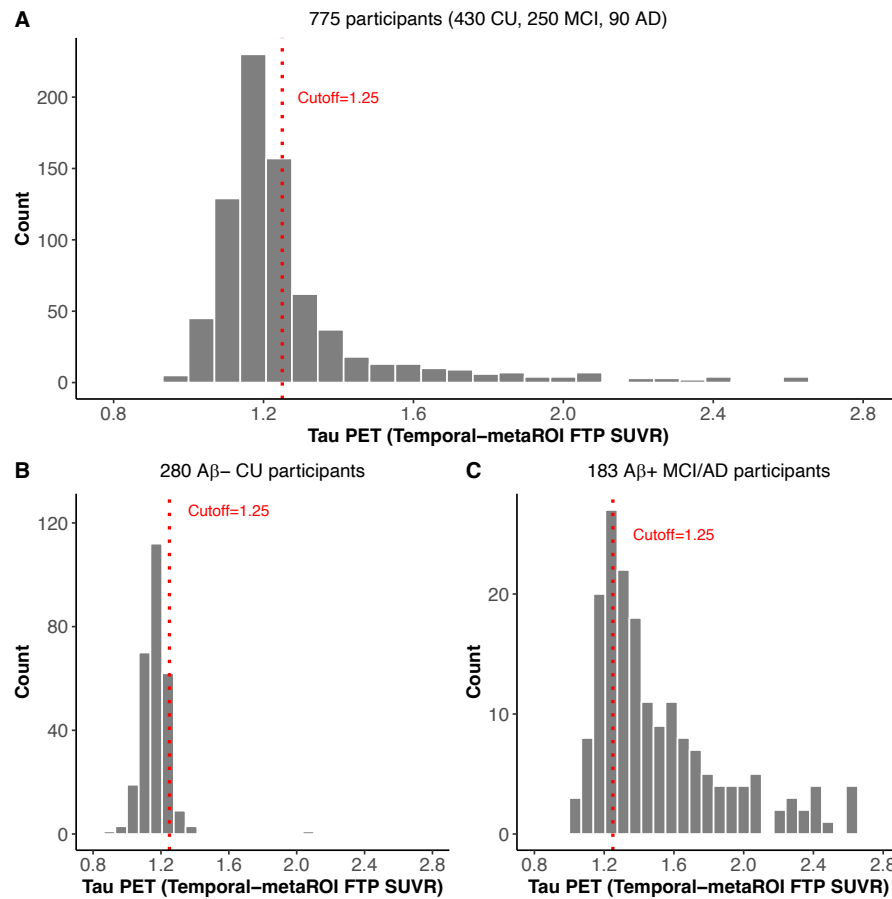
T1-weighted anatomical MRI images were acquired on Siemens, GE or Philips MRI scanners according to a standard protocol (8), and more details can be found elsewhere (<http://adni-info.org>). The most fully pre-processed format anatomical MRI images were downloaded from the LONI website ([ida.loni.usc.edu](http://ida.loni.usc.edu)). Hippocampal volume (HCV) ( $\text{cm}^3$ ) was calculated across hemispheres from the anatomical MRI scan that was closest to baseline FTP PET scan using FreeSurfer and adjusted by the estimated total intracranial volume (ICV) using the approach reported by the Mayo group (9). The residual HCV (rHCV) was calculated as the difference between the raw HCV and the expected HCV as we described previously (10). Cortical thickness in 68 ROIs were also calculated using FreeSurfer, and the mean Temporal-metaROI cortical thickness was calculated as a surface-area weighted average of the mean cortical thickness in individual ROI of the Temporal-metaROI region. The thresholds of residual hippocampal volume (rHCV) and Temporal-metaROI cortical thickness were set as  $\leq -0.67 \text{ cm}^3$  and  $\leq 2.60 \text{ mm}$  respectively according to receiver operating characteristic curve (ROC) analysis using the Youden index classifying 435 A- ADNI CU participants, 579 A+ ADNI MCI and AD patients as the endpoint as described in the Supplement (Figure S3-S6).

## Supplemental Figures and Tables

### Cutoff of Temporal-metaROI FTP SUVR

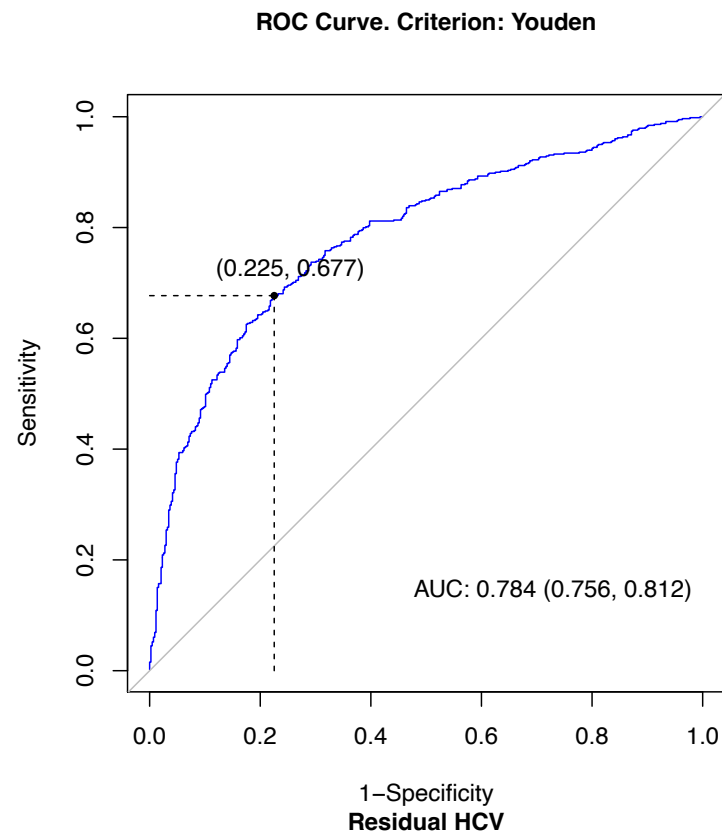


**Figure S1. The ROC (receiver operating characteristic curve) analysis using cutoff  $\geq 1.25$  for Temporal-metaROI FTP SUVR.** The analysis using the Youden index classifying 280  $A\beta^-$  ADNI cognitively unimpaired (CU) participants and 183  $A\beta^+$  ADNI MCI (mild cognitive impairment) and Alzheimer's disease (AD) patients as the endpoint to define the cutoff  $\geq 1.25$  for Temporal-metaROI FTP SUVR. AUC (area under the curve): 0.876 [95% ci, 0.84 ~ 0.912].



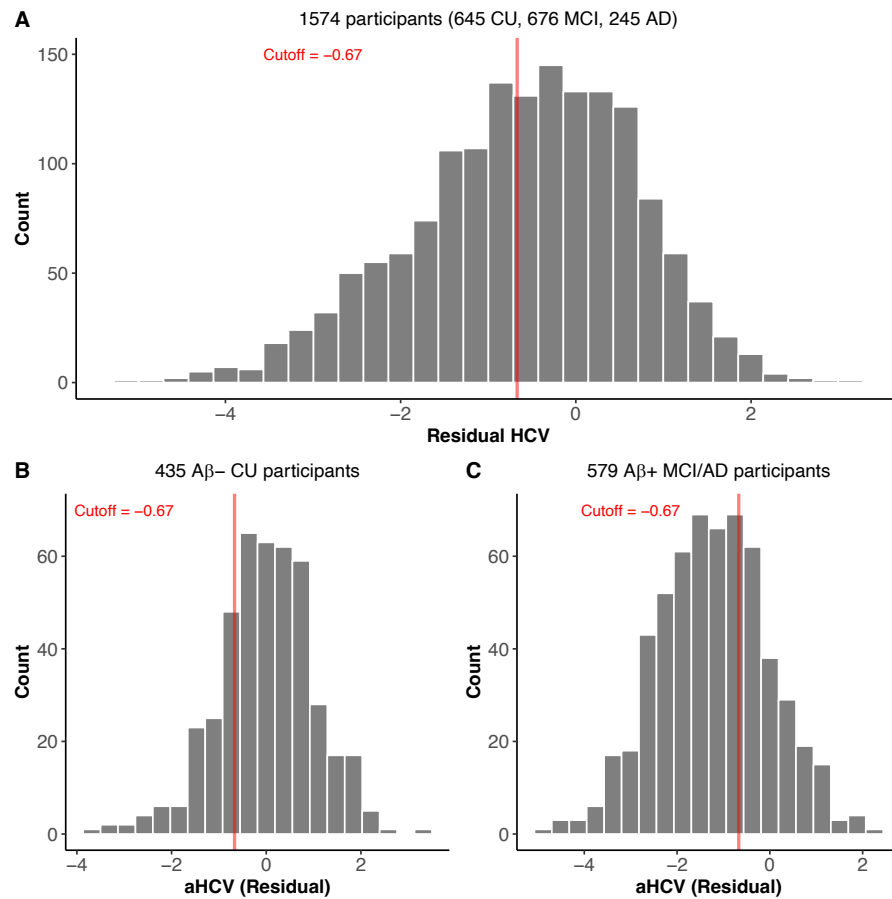
**Figure S2. Histograms of Temporal-metaROI FTP SUVRs within different groups. (A)** All 775 ADNI participants, **(B)** 280 A $\beta$ - ADNI CU participants and **(C)** 183 A $\beta$ + ADNI MCI and AD patients with tau PET scan. Red dotted line is the cutoff of Temporal-metaROI FTP SUVR (1.25).

### Cutoff of residual hippocampal volume (rHCV)

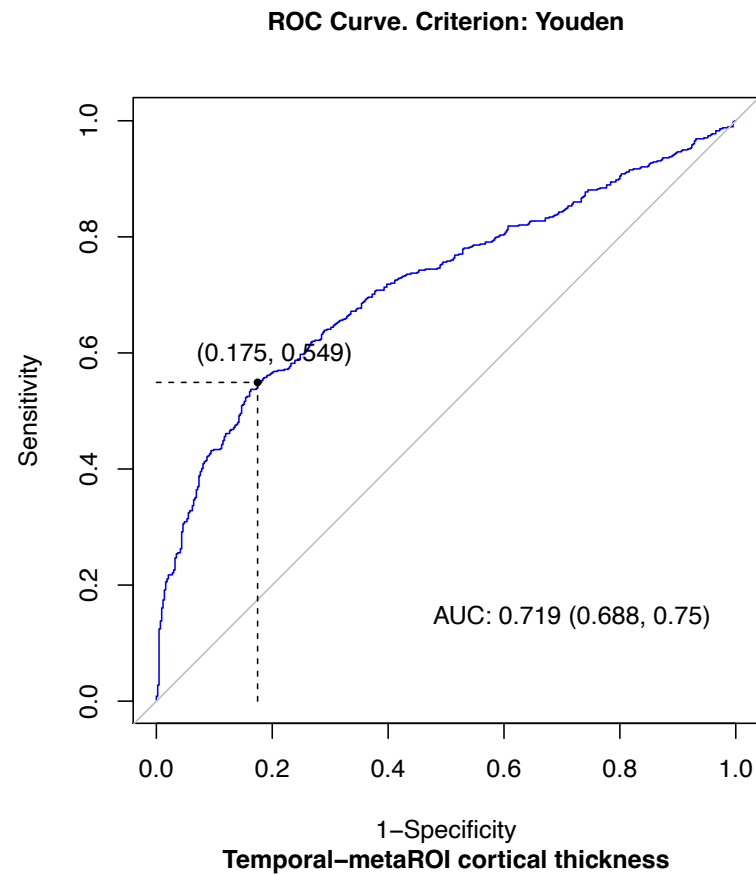


**Figure S3. The ROC analysis using cutoff  $\leq -0.67 \text{ cm}^3$  for rHCV.**

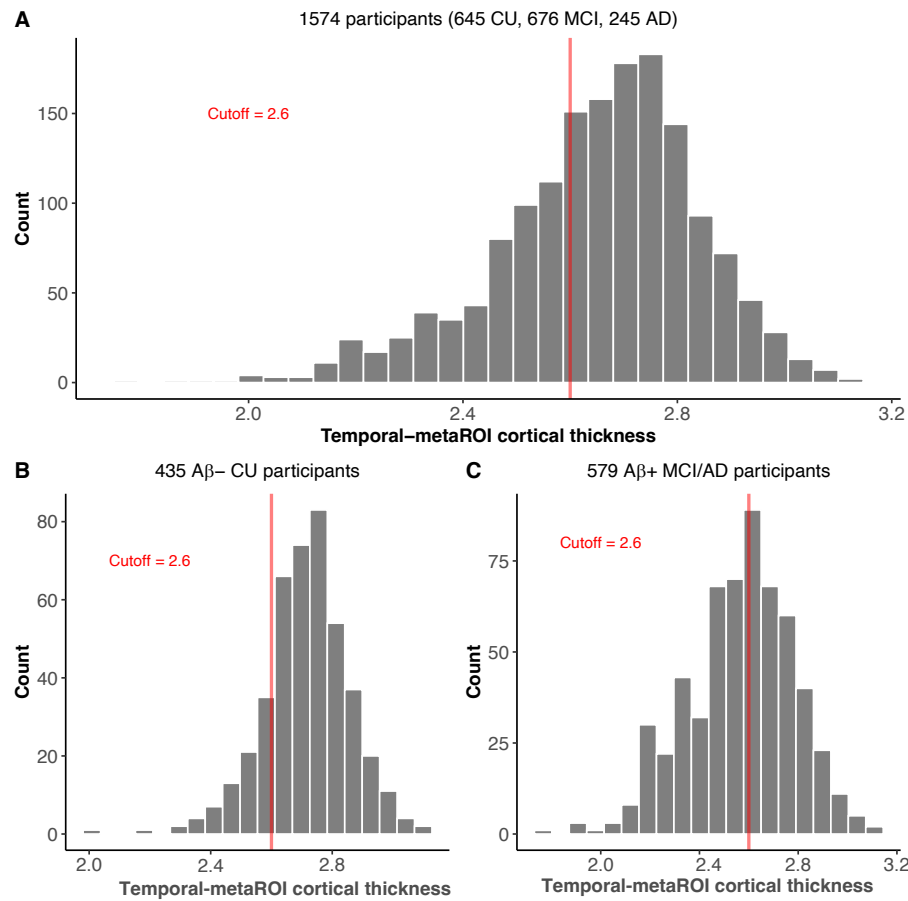
The analysis using the Youden index classifying ADNI 435  $A\beta^-$  CU participants and 579  $A\beta^+$  MCI and AD patients as the endpoint to define the cutoff  $\leq -0.67 \text{ cm}^3$  for rHCV. AUC: 0.78 [95% ci, -0.756 ~ 0.812].



**Figure S4. Histograms of rHCVs within different groups.** (A) All 1574 ADNI participants, (B) 435 A $\beta$ - ADNI CU participants and (C) 579 A $\beta$ + ADNI MCI and Alzheimer's disease patients with rHCV data. Red dotted line is the cutoff of rHCV -0.67.

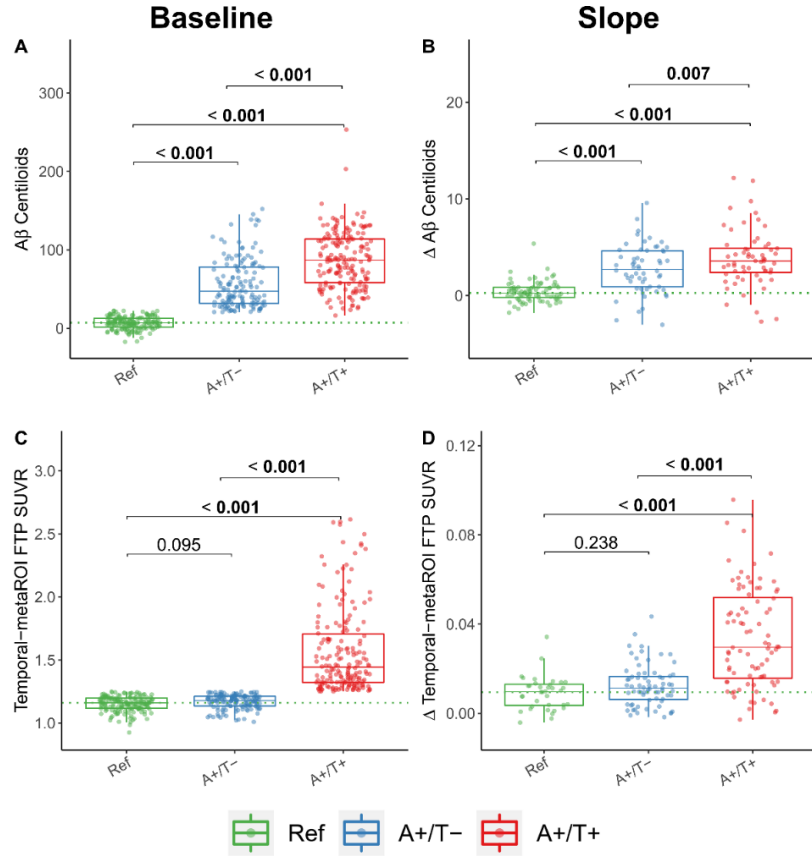


**Figure S5. The ROC analysis using cutoff  $\geq 2.60$  for Temporal-metaROI cortical thickness.** The analysis using Youden index classifying 435  $A\beta^-$  ADNI CU participants and 579  $A\beta^+$  ADNI MCI and AD patients as the endpoint to define the cutoff  $\geq 2.60$  for Temporal-metaROI cortical thickness. AUC: 0.72 [95% ci, 0.688 ~ 0.75].



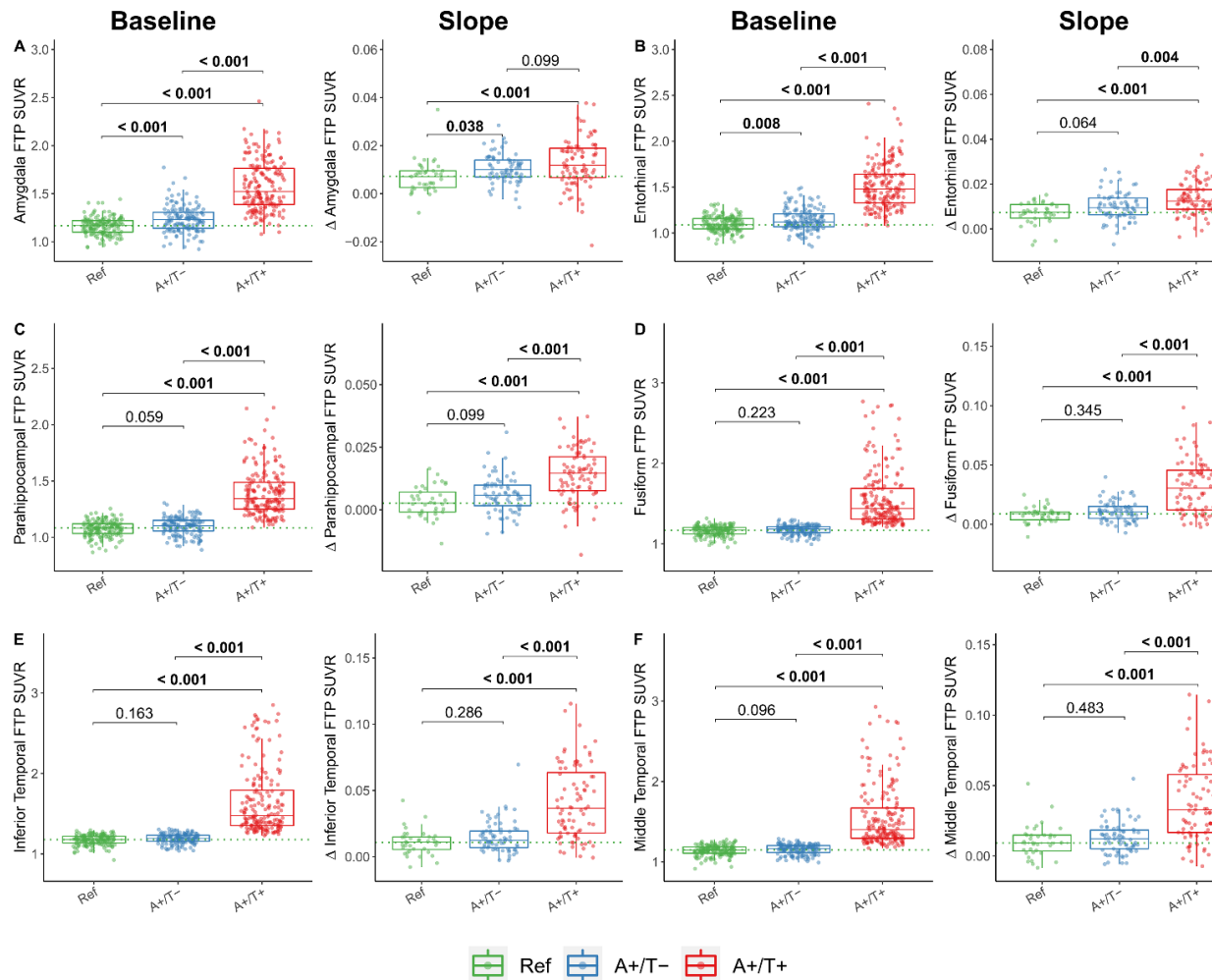
**Figure S6. Histograms of Temporal-metaROI cortical thickness within different groups.** (A) All 1574 ADNI participants, (B) 435 A $\beta$ - ADNI CU participants and (C) 579 A $\beta$ + ADNI MCI and AD patients with MRI data. Red dotted line is the cutoff of Temporal-metaROI cortical thickness (2.60).

### Comparisons of baseline and slope of A $\beta$ Centiloids and tau PET in Temporal-metaROI



**Figure S7. Comparisons of baseline and slope of tau PET in Temporal-metaROI region among Ref, A+/T- and A+/T+ groups.** Comparisons of baseline and slopes of (A-B) A $\beta$  PET Centiloids, (C-D) tau PET of Temporal-metaROI region. The boxplot whiskers extended to the lowest and highest data points within 1.5 times the interquartile range from the lower to the upper quartiles. Ref, A+/T- and A+/T+ individuals were colored in green, blue and red respectively. Green dashed lines represented the median value of the Ref group.  $P < 0.05$  were marked in bold.

As we defined, while both A+/T- and A+/T+ groups had higher A $\beta$  Centiloids (standardized  $\beta$  ( $\beta_{std}$ ) = 1.087, [95% confidence interval (ci), 0.936 ~ 1.237],  $p < 0.001$ ;  $\beta_{std}$  = 1.781, [95% ci, 1.639 ~ 1.923],  $p < 0.001$ ) and faster rates of A $\beta$  Centiloids ( $\beta_{std}$  = 0.875, [95% ci, 0.593 ~ 1.157],  $p < 0.001$ ;  $\beta_{std}$  = 1.291, [95% ci, 1.013 ~ 1.568],  $p < 0.001$ ) than the Ref group, A+/T+ but not A+/T- individuals had higher Temporal-metaROI FTP SUVR ( $\beta_{std}$  = 1.534, [95% ci, 1.374 ~ 1.693],  $p < 0.001$ ) and faster rates of Temporal-metaROI FTP SUVR ( $\beta_{std}$  = 1.285, [95% ci, 0.968 ~ 1.602],  $p < 0.001$ ) compared to Ref group (Table S1 and Figure S7). Besides, A+/T+ individuals also had higher baseline ( $\beta_{std}$  = 0.694, [95% ci, 0.554 ~ 0.834],  $p < 0.001$ ) and slope of A $\beta$  Centiloids ( $\beta_{std}$  = 0.416, [95% ci, 0.116 ~ 0.715],  $p = 0.007$ ), and higher baseline ( $\beta_{std}$  = 1.389, [95% ci, 1.231 ~ 1.547],  $p < 0.001$ ) and slope of Temporal-metaROI FTP SUVR ( $\beta_{std}$  = 1.089, [95% ci 0.830 ~ 1.348],  $p < 0.001$ ) than A+/T- individuals (Table S1 and Figure S7).



**Figure S8. Comparisons of baseline and slopes of tau PET of individual ROIs within Temporal-metaROI among Ref, A+/T- and A+/T+ groups.** Comparisons of baseline and slopes of tau PET in (A) amygdala, (B) entorhinal, (C) parahippocampal, (D) fusiform, (E) inferior temporal and (F) middle temporal regions. The boxplot whiskers extended to the lowest and highest data points within 1.5 times the interquartile range from the lower to the upper quartiles. Ref, A+/T- and A+/T+ individuals were colored in green, blue and red respectively. Green dashed lines represented the median value of the Ref group.  $P < 0.05$  were marked in bold.

**Table S1. Comparisons of baseline and slopes of A $\beta$ , regional tau PET of Temporal-metaROI.**

|                               |               | Ref vs. A+/T-     | Ref vs. A+/T+     | A+/T- vs. A+/T+   |                        |               | Ref vs. A+/T- | Ref vs. A+/T+     | A+/T- vs. A+/T+   |
|-------------------------------|---------------|-------------------|-------------------|-------------------|------------------------|---------------|---------------|-------------------|-------------------|
| A $\beta$                     | $\beta_{std}$ | 1.087             | 1.781             | 0.694             | Parahip. tau           | $\beta_{std}$ | 0.153         | 1.625             | 1.472             |
|                               | 95% ci        | 0.936~1.237       | 1.639~1.923       | 0.554~0.834       |                        | 95% ci        | -0.006~0.311  | 1.475~1.774       | 1.324~1.620       |
|                               | <i>p</i>      | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |                        | <i>p</i>      | 0.059         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| $\Delta$ A $\beta$            | $\beta_{std}$ | 0.875             | 1.291             | 0.416             | $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.296         | 1.142             | 0.847             |
|                               | 95% ci        | 0.593~1.157       | 1.013~1.568       | 0.116~0.715       |                        | 95% ci        | -0.054~0.646  | 0.802~1.483       | 0.569~1.125       |
|                               | <i>p</i>      | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> | <b>0.007</b>      |                        | <i>p</i>      | 0.099         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| Temporal-metaROI tau          | $\beta_{std}$ | 0.144             | 1.534             | 1.389             | Fusi. tau              | $\beta_{std}$ | 0.110         | 1.438             | 1.327             |
|                               | 95% ci        | -0.025~0.314      | 1.374~1.693       | 1.231~1.547       |                        | 95% ci        | -0.067~0.288  | 1.270~1.605       | 1.162~1.493       |
|                               | <i>p</i>      | 0.095             | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |                        | <i>p</i>      | 0.223         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| $\Delta$ Temporal-metaROI tau | $\beta_{std}$ | 0.197             | 1.285             | 1.089             | $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.160         | 1.220             | 1.059             |
|                               | 95% ci        | -0.129~0.522      | 0.968~1.602       | 0.830~1.348       |                        | 95% ci        | -0.171~0.492  | 0.897~1.543       | 0.796~1.323       |
|                               | <i>p</i>      | 0.238             | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |                        | <i>p</i>      | 0.345         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| Amygd. tau                    | $\beta_{std}$ | 0.276             | 1.617             | 1.341             | Inf-temp. tau          | $\beta_{std}$ | 0.124         | 1.477             | 1.352             |
|                               | 95% ci        | 0.113~0.439       | 1.463~1.770       | 0.312~0.392       |                        | 95% ci        | -0.050~0.299  | 1.312~1.641       | 1.190~1.515       |
|                               | <i>p</i>      | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |                        | <i>p</i>      | 0.163         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| $\Delta$ Amygd. tau           | $\beta_{std}$ | 0.414             | 0.674             | 0.260             | $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.179         | 1.264             | 1.085             |
|                               | 95% ci        | 0.027~0.801       | 0.297~1.050       | -0.048~0.568      |                        | 95% ci        | -0.149~0.506  | 0.945~1.582       | 0.825~1.345       |
|                               | <i>p</i>      | <b>0.038</b>      | <b>&lt; 0.001</b> | 0.099             |                        | <i>p</i>      | 0.286         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| Entorh. tau                   | $\beta_{std}$ | 0.212             | 1.662             | 1.450             | Mid-temp. tau          | $\beta_{std}$ | 0.152         | 1.448             | 1.296             |
|                               | 95% ci        | 0.056~0.367       | 1.515~1.809       | 1.305~1.595       |                        | 95% ci        | -0.027~0.330  | 1.279~1.616       | 1.130~1.463       |
|                               | <i>p</i>      | <b>0.008</b>      | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |                        | <i>p</i>      | 0.096         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |
| $\Delta$ Entorh. tau          | $\beta_{std}$ | 0.361             | 0.810             | 0.449             | $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.121         | 1.156             | 1.035             |
|                               | 95% ci        | -0.018~0.741      | 0.441~1.179       | 0.147~0.750       |                        | 95% ci        | -0.216~0.458  | 0.828~1.484       | 0.768~1.303       |
|                               | <i>p</i>      | 0.064             | <b>&lt; 0.001</b> | <b>0.004</b>      |                        | <i>p</i>      | 0.483         | <b>&lt; 0.001</b> | <b>&lt; 0.001</b> |

A $\beta$ : amyloid- $\beta$ ;  $\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.*P* < 0.05 was indicated in bold.

**Table S2. Interregional partial correlations of baseline FTP SUVRs in 6 ROIs within Temporal-metaROI region.**

|               |            | Entorh. tau    | Amygd. tau     | Parahip. tau   | Fusi. tau      | Inf-temp. tau  | Mid-temp. tau  |
|---------------|------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Entorh. tau   | <i>Rho</i> | 1.000          | 0.546          | 0.452          | -0.158         | 0.240          | -0.188         |
|               | <i>p</i>   | 1.000          | < <b>0.001</b> | < <b>0.001</b> | 0.222          | <b>0.001</b>   | <b>0.039</b>   |
| Amygd. tau    | <i>Rho</i> | 0.546          | 1.000          | 0.269          | -0.119         | -0.166         | 0.170          |
|               | <i>p</i>   | < <b>0.001</b> | 1.000          | < <b>0.001</b> | 1.000          | 0.142          | 0.112          |
| Parahip. tau  | <i>Rho</i> | 0.452          | 0.269          | 1.000          | 0.461          | 0.047          | -0.003         |
|               | <i>p</i>   | < <b>0.001</b> | < <b>0.001</b> | 1.000          | < <b>0.001</b> | 1.000          | 1.000          |
| Fusi. tau     | <i>Rho</i> | -0.158         | -0.119         | 0.461          | 1.000          | 0.562          | -0.203         |
|               | <i>p</i>   | 0.222          | 1.000          | < <b>0.001</b> | 1.000          | < <b>0.001</b> | <b>0.015</b>   |
| Inf-temp. tau | <i>Rho</i> | 0.240          | -0.166         | 0.047          | 0.562          | 1.000          | 0.823          |
|               | <i>p</i>   | <b>0.001</b>   | 0.142          | 1.000          | < <b>0.001</b> | 1.000          | < <b>0.001</b> |
| Mid-temp. tau | <i>Rho</i> | -0.188         | 0.170          | -0.003         | -0.203         | 0.823          | 1.000          |
|               | <i>p</i>   | <b>0.039</b>   | 0.112          | 1.000          | <b>0.015</b>   | < <b>0.001</b> | 1.000          |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

Bonferroni-corrected for multiple comparisons at  $p < 0.05$ , and  $p < 0.05$  was indicated in bold.

*Rho*: correlation coefficients.

**Table S3. Interregional partial correlations of longitudinal FTP SUVR changes in 6 ROIs within Temporal-metaROI region.**

|                        |            | $\Delta$ Entorh. tau | $\Delta$ Amygd. tau | $\Delta$ Parahip. tau | $\Delta$ Fusi. tau | $\Delta$ Inf-temp. tau | $\Delta$ Mid-temp. tau |
|------------------------|------------|----------------------|---------------------|-----------------------|--------------------|------------------------|------------------------|
| $\Delta$ Entorh. tau   | <i>Rho</i> | 1.000                | 0.091               | 0.547                 | -0.170             | 0.097                  | -0.062                 |
|                        | <i>p</i>   | 1.000                | 1.000               | <b>&lt; 0.001</b>     | 0.109              | 1.000                  | 1.000                  |
| $\Delta$ Amygd. tau    | <i>Rho</i> | 0.091                | 1.000               | 0.380                 | 0.114              | -0.154                 | -0.020                 |
|                        | <i>p</i>   | 1.000                | 1.000               | <b>&lt; 0.001</b>     | 1.000              | 0.270                  | 1.000                  |
| $\Delta$ Parahip. tau  | <i>Rho</i> | 0.547                | 0.380               | 1.000                 | 0.240              | 0.081                  | 0.065                  |
|                        | <i>p</i>   | <b>&lt; 0.001</b>    | <b>&lt; 0.001</b>   | 1.000                 | <b>0.001</b>       | 1.000                  | 1.000                  |
| $\Delta$ Fusi. tau     | <i>Rho</i> | -0.170               | 0.114               | 0.240                 | 1.000              | 0.544                  | -0.064                 |
|                        | <i>p</i>   | 0.109                | 1.000               | <b>0.001</b>          | 1.000              | <b>&lt; 0.001</b>      | 1.000                  |
| $\Delta$ Inf-temp. tau | <i>Rho</i> | 0.097                | -0.154              | 0.081                 | 0.544              | 1.000                  | 0.791                  |
|                        | <i>p</i>   | 1.000                | 0.270               | 1.000                 | <b>&lt; 0.001</b>  | 1.000                  | <b>&lt; 0.001</b>      |
| $\Delta$ Mid-temp. tau | <i>Rho</i> | -0.062               | -0.020              | 0.065                 | -0.064             | 0.791                  | 1.000                  |
|                        | <i>p</i>   | 1.000                | 1.000               | 1.000                 | 1.000              | <b>&lt; 0.001</b>      | 1.000                  |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

Bonferroni-corrected for multiple comparisons at  $p < 0.05$ , and  $p < 0.05$  was indicated in bold.

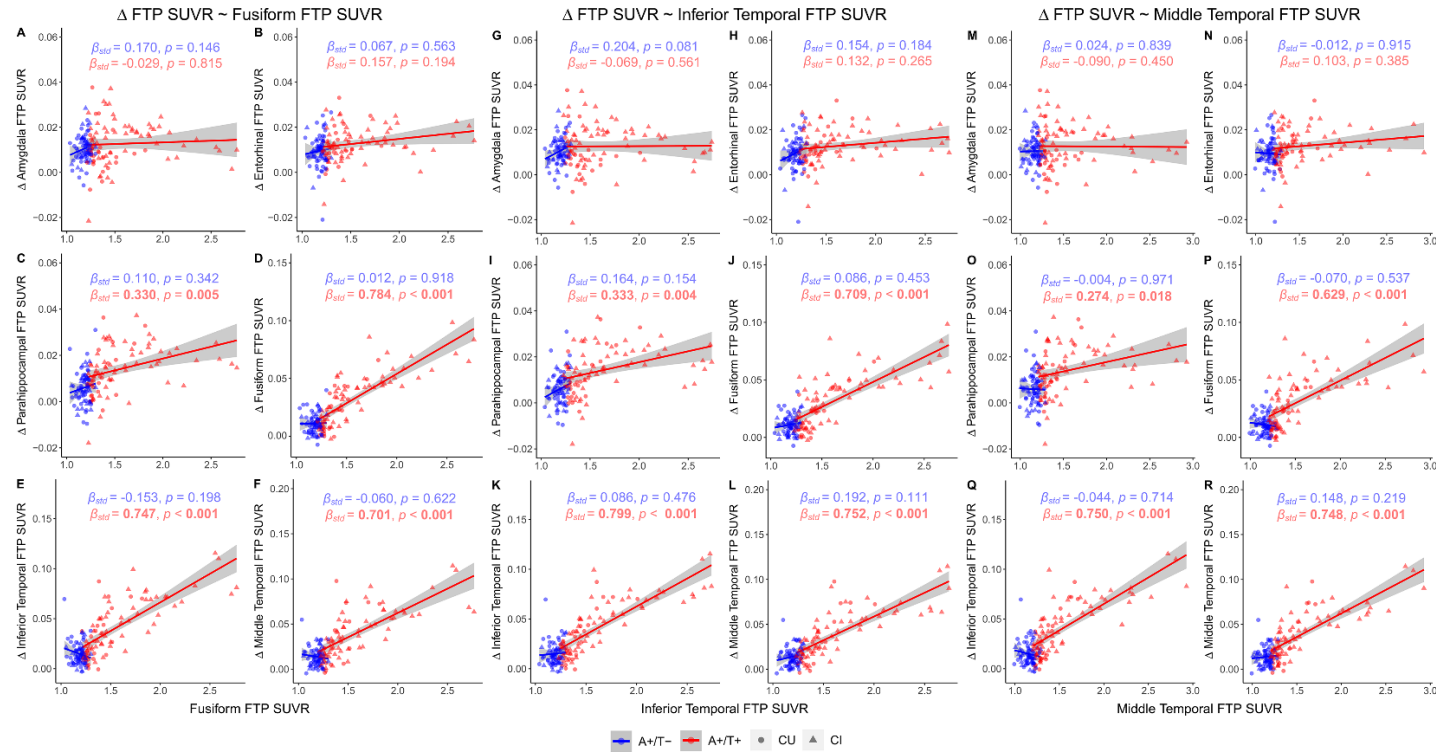
*Rho*: correlation coefficients.

**Table S4. Longitudinal tau accumulation prediction by baseline amygdala tau or entorhinal tau adjusted for baseline A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Amygd. tau |                   |              |                   | A $\beta$ + Entorh. tau |                   |              |                   |
|------------------------|---------------|------------------------|-------------------|--------------|-------------------|-------------------------|-------------------|--------------|-------------------|
|                        |               | A+/T-                  |                   | A+/T+        |                   | A+/T-                   |                   | A+/T+        |                   |
|                        |               | A $\beta$              | Amygd. tau        | A $\beta$    | Amygd. tau        | A $\beta$               | Entorh. tau       | A $\beta$    | Entorh. tau       |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.241                  | 0.509             | 0.051        | 0.485             | 0.192                   | 0.577             | 0.044        | 0.452             |
|                        | 95% ci        | 0.045~0.437            | 0.313~0.704       | -0.144~0.245 | 0.290~0.680       | 0.391~0.763             | 0.006~0.378       | 0.251~0.652  | -0.157~0.245      |
|                        | <i>p</i>      | <b>0.019</b>           | <b>&lt; 0.001</b> | 0.612        | <b>&lt; 0.001</b> | <b>0.047</b>            | <b>&lt; 0.001</b> | 0.671        | <b>&lt; 0.001</b> |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.294                  | 0.080             | 0.184        | 0.092             | 0.272                   | 0.233             | 0.128        | 0.279             |
|                        | 95% ci        | 0.068~0.520            | -0.146~0.306      | -0.035~0.403 | -0.127~0.311      | 0.012~0.455             | 0.050~0.493       | 0.065~0.493  | -0.086~0.341      |
|                        | <i>p</i>      | <b>0.013</b>           | 0.491             | 0.104        | 0.414             | <b>0.019</b>            | <b>0.043</b>      | 0.245        | <b>0.012</b>      |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.314                  | 0.088             | 0.156        | 0.306             | 0.284                   | 0.309             | 0.100        | 0.471             |
|                        | 95% ci        | 0.089~0.538            | -0.136~0.313      | -0.052~0.365 | 0.098~0.515       | 0.094~0.523             | 0.070~0.499       | 0.275~0.666  | -0.096~0.295      |
|                        | <i>p</i>      | <b>0.008</b>           | 0.444             | 0.145        | <b>0.005</b>      | <b>0.012</b>            | <b>0.006</b>      | 0.322        | <b>&lt; 0.001</b> |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.353                  | -0.045            | 0.337        | 0.259             | 0.337                   | 0.142             | 0.240        | 0.569             |
|                        | 95% ci        | 0.130~0.575            | -0.267~0.178      | 0.138~0.535  | 0.060~0.457       | -0.079~0.363            | 0.116~0.558       | 0.402~0.736  | 0.073~0.407       |
|                        | <i>p</i>      | <b>0.003</b>           | 0.696             | <b>0.002</b> | <b>0.012</b>      | <b>0.004</b>            | 0.211             | <b>0.006</b> | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.179                  | -0.113            | 0.284        | 0.261             | 0.173                   | 0.041             | 0.180        | 0.597             |
|                        | 95% ci        | -0.053~0.412           | -0.345~0.119      | 0.081~0.487  | 0.058~0.464       | -0.194~0.276            | -0.062~0.408      | 0.428~0.765  | 0.011~0.348       |
|                        | <i>p</i>      | 0.135                  | 0.344             | <b>0.008</b> | <b>0.014</b>      | 0.153                   | 0.733             | <b>0.040</b> | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.095                  | -0.060            | 0.282        | 0.282             | 0.082                   | 0.112             | 0.186        | 0.585             |
|                        | 95% ci        | -0.142~0.331           | -0.297~0.176      | 0.080~0.483  | 0.080~0.483       | -0.125~0.348            | -0.154~0.319      | 0.415~0.755  | 0.016~0.356       |
|                        | <i>p</i>      | 0.436                  | 0.618             | <b>0.008</b> | <b>0.008</b>      | 0.497                   | 0.358             | <b>0.035</b> | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

*P* < 0.05 was indicated in bold.



**Figure S9. Prediction of longitudinal tau accumulation by baseline tau in fusiform, inferior temporal or middle temporal regions.** Models have been accounted for age, sex and baseline A $\beta$  Centiloids. Prediction of longitudinal FTP SUVR increases in (A) amygdala, (B) entorhinal, (C) parahippocampal, (D) fusiform, (E) inferior temporal and (F) middle temporal regions by baseline fusiform FTP SUVR. Prediction of longitudinal FTP SUVR increases in (G) amygdala, (H) entorhinal, (I) parahippocampal, (J) fusiform, (K) inferior temporal and (L) middle temporal regions by baseline inferior temporal FTP SUVR. Prediction of longitudinal FTP SUVR increases in (M) amygdala, (N) entorhinal, (O) parahippocampal, (P) fusiform, (Q) inferior temporal and (R) middle temporal regions by baseline middle temporal FTP SUVR. Linear regression lines, each individual point,  $\beta_{std}$  and  $p$  values of A+/T- and A+/T+ groups were colored in blue and red, and CU and CI individuals were represented by circle and triangle respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.

**Table S5. Longitudinal tau accumulation prediction by baseline parahippocampal tau or fusiform tau adjusted for A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Parahip. tau |              |              |                   | A $\beta$ + Fusi. tau |              |              |                   |
|------------------------|---------------|--------------------------|--------------|--------------|-------------------|-----------------------|--------------|--------------|-------------------|
|                        |               | A+/T-                    |              | A+/T+        |                   | A+/T-                 |              | A+/T+        |                   |
|                        |               | A $\beta$                | Parahip. tau | A $\beta$    | Parahip. tau      | A $\beta$             | Fusi. tau    | A $\beta$    | Fusi. tau         |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.258                    | 0.294        | 0.118        | 0.148             | 0.247                 | 0.170        | 0.184        | -0.029            |
|                        | 95% ci        | 0.075~0.513              | 0.039~0.478  | -0.080~0.376 | -0.110~0.346      | -0.056~0.397          | 0.020~0.473  | -0.267~0.210 | -0.055~0.423      |
|                        | <i>p</i>      | <b>0.024</b>             | <b>0.011</b> | 0.315        | 0.206             | <b>0.036</b>          | 0.146        | 0.135        | 0.815             |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.299                    | 0.119        | 0.116        | 0.250             | 0.294                 | 0.067        | 0.138        | 0.157             |
|                        | 95% ci        | -0.106~0.345             | 0.073~0.524  | 0.028~0.472  | -0.106~0.338      | -0.159~0.294          | 0.067~0.521  | -0.078~0.392 | -0.097~0.372      |
|                        | <i>p</i>      | <b>0.012</b>             | 0.303        | 0.309        | <b>0.030</b>      | <b>0.013</b>          | 0.563        | 0.254        | 0.194             |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.321                    | 0.200        | 0.045        | 0.519             | 0.313                 | 0.110        | 0.087        | 0.330             |
|                        | 95% ci        | -0.020~0.421             | 0.100~0.541  | 0.322~0.716  | -0.153~0.242      | -0.115~0.334          | 0.089~0.537  | 0.106~0.555  | -0.137~0.312      |
|                        | <i>p</i>      | <b>0.006</b>             | 0.080        | 0.660        | <b>&lt; 0.001</b> | <b>0.008</b>          | 0.342        | 0.448        | <b>0.005</b>      |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.352                    | 0.003        | 0.138        | 0.724             | 0.352                 | 0.012        | 0.056        | 0.784             |
|                        | 95% ci        | -0.219~0.226             | 0.129~0.574  | 0.580~0.869  | -0.007~0.283      | -0.211~0.234          | 0.129~0.574  | 0.642~0.926  | -0.086~0.198      |
|                        | <i>p</i>      | <b>0.003</b>             | 0.976        | 0.065        | <b>&lt; 0.001</b> | <b>0.003</b>          | 0.918        | 0.441        | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.172                    | -0.188       | 0.074        | 0.758             | 0.180                 | -0.153       | 0.020        | 0.747             |
|                        | 95% ci        | -0.418~0.042             | -0.058~0.402 | 0.614~0.902  | -0.070~0.218      | -0.384~0.078          | -0.051~0.411 | 0.588~0.906  | -0.139~0.179      |
|                        | <i>p</i>      | 0.147                    | 0.113        | 0.319        | <b>&lt; 0.001</b> | 0.131                 | 0.198        | 0.806        | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.091                    | -0.091       | 0.082        | 0.745             | 0.095                 | -0.060       | 0.044        | 0.701             |
|                        | 95% ci        | -0.327~0.145             | -0.145~0.327 | 0.598~0.892  | -0.065~0.228      | -0.296~0.177          | -0.142~0.331 | 0.533~0.869  | -0.125~0.212      |
|                        | <i>p</i>      | 0.452                    | 0.452        | 0.280        | <b>&lt; 0.001</b> | 0.435                 | 0.622        | 0.613        | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

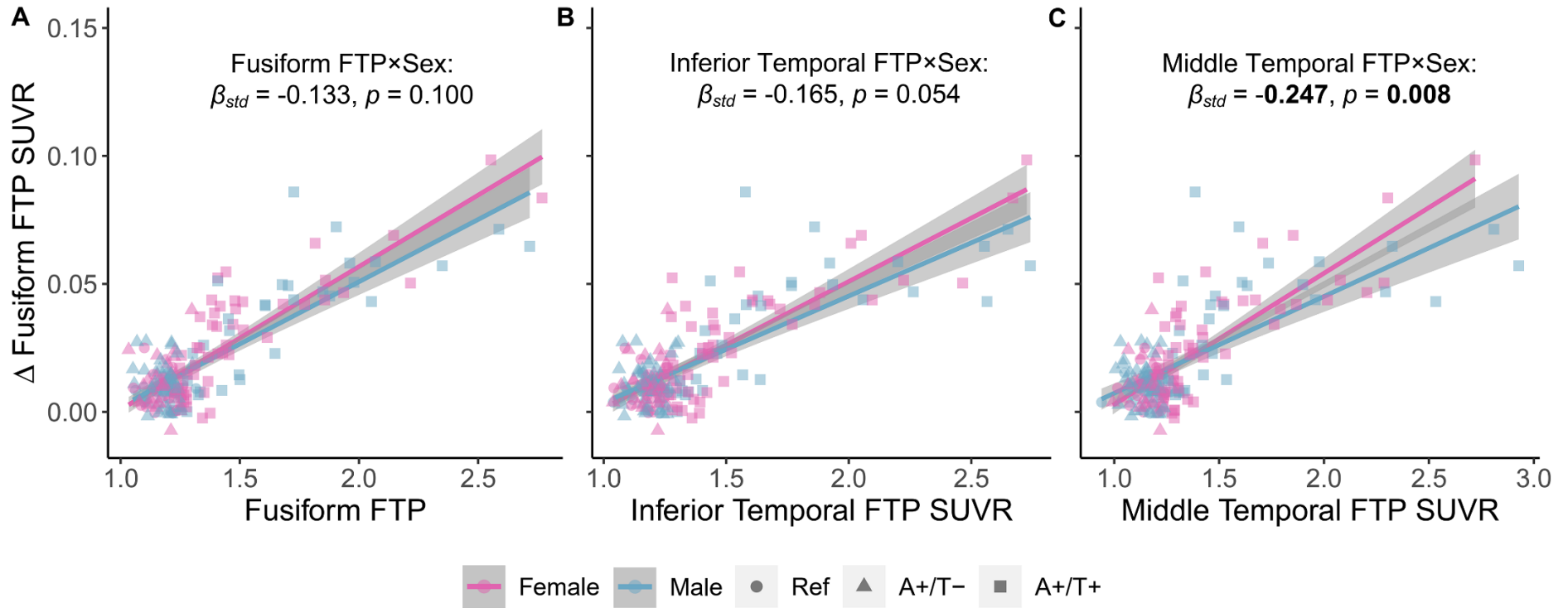
*P* < 0.05 was indicated in bold.

**Table S6. Longitudinal tau accumulation prediction by baseline inferior temporal tau or middle temporal tau adjusted for A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Inf-temp. tau |               |              |                   | A $\beta$ + Mid-temp. tau |               |              |                   |
|------------------------|---------------|---------------------------|---------------|--------------|-------------------|---------------------------|---------------|--------------|-------------------|
|                        |               | A+/-                      |               | A+/-         |                   | A+/-                      |               | A+/-         |                   |
|                        |               | A $\beta$                 | Inf-temp. tau | A $\beta$    | Inf-temp. tau     | A $\beta$                 | Mid-temp. tau | A $\beta$    | Mid-temp. tau     |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.230                     | 0.204         | 0.198        | -0.069            | 0.251                     | 0.024         | 0.206        | -0.090            |
|                        | 95% ci        | -0.022~0.431              | 0.004~0.456   | -0.302~0.163 | -0.034~0.431      | -0.206~0.254              | 0.021~0.482   | -0.322~0.142 | -0.026~0.438      |
|                        | <i>p</i>      | <b>0.050</b>              | 0.081         | 0.098        | 0.561             | <b>0.036</b>              | 0.839         | 0.085        | 0.450             |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.280                     | 0.154         | 0.155        | 0.132             | 0.295                     | -0.012        | 0.167        | 0.103             |
|                        | 95% ci        | -0.071~0.379              | 0.055~0.505   | -0.098~0.361 | -0.074~0.385      | -0.240~0.215              | 0.067~0.522   | -0.128~0.333 | -0.063~0.397      |
|                        | <i>p</i>      | <b>0.017</b>              | 0.184         | 0.188        | 0.265             | <b>0.013</b>              | 0.915         | 0.160        | 0.385             |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.299                     | 0.164         | 0.103        | 0.333             | 0.315                     | -0.004        | 0.126        | 0.274             |
|                        | 95% ci        | -0.059~0.388              | 0.076~0.522   | 0.115~0.551  | -0.115~0.321      | -0.230~0.222              | 0.089~0.541   | 0.052~0.496  | -0.096~0.348      |
|                        | <i>p</i>      | <b>0.011</b>              | 0.154         | 0.357        | <b>0.004</b>      | <b>0.008</b>              | 0.971         | 0.269        | <b>0.018</b>      |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.343                     | 0.086         | 0.125        | 0.709             | 0.348                     | -0.070        | 0.157        | 0.629             |
|                        | 95% ci        | -0.137~0.308              | 0.121~0.566   | 0.557~0.861  | -0.027~0.277      | -0.292~0.152              | 0.126~0.571   | 0.461~0.797  | -0.011~0.324      |
|                        | <i>p</i>      | <b>0.004</b>              | 0.453         | 0.110        | <b>&lt; 0.001</b> | <b>0.003</b>              | 0.537         | 0.071        | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.169                     | 0.086         | 0.038        | 0.799             | 0.175                     | -0.044        | 0.057        | 0.750             |
|                        | 95% ci        | -0.149~0.320              | -0.065~0.403  | 0.662~0.936  | -0.099~0.175      | -0.278~0.190              | -0.059~0.409  | 0.601~0.900  | -0.092~0.207      |
|                        | <i>p</i>      | 0.162                     | 0.476         | 0.591        | <b>&lt; 0.001</b> | 0.147                     | 0.714         | 0.455        | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.075                     | 0.192         | 0.059        | 0.752             | 0.101                     | 0.148         | 0.061        | 0.748             |
|                        | 95% ci        | -0.041~0.426              | -0.159~0.308  | 0.604~0.901  | -0.090~0.208      | -0.086~0.383              | -0.134~0.335  | 0.598~0.897  | -0.088~0.211      |
|                        | <i>p</i>      | 0.533                     | 0.111         | 0.438        | <b>&lt; 0.001</b> | 0.403                     | 0.219         | 0.424        | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

*P* < 0.05 was indicated in bold.



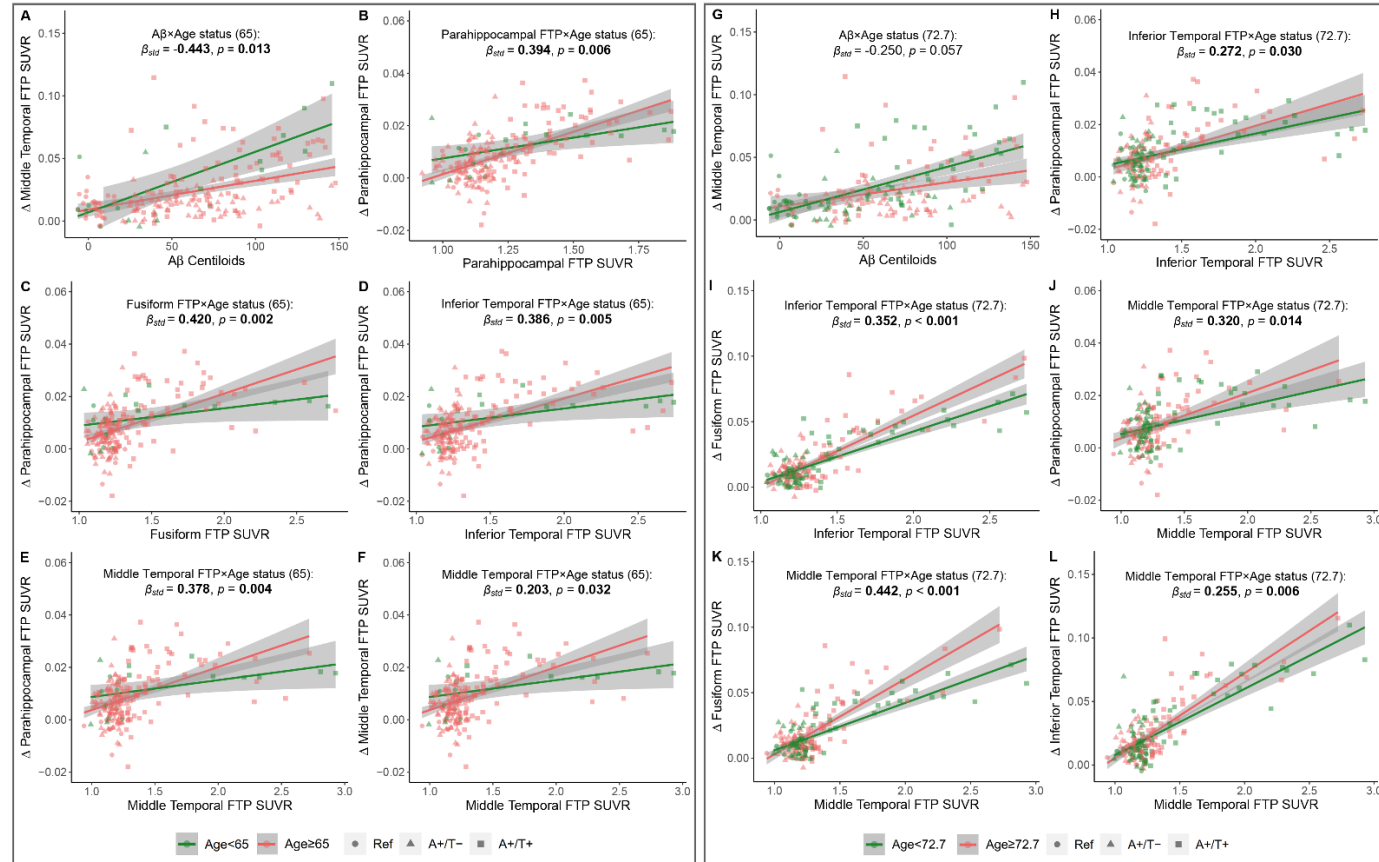
**Figure S10. A $\beta$  and tau related longitudinal tau accumulation in female and male adults.** Positive interactions of (A) female  $\times$  fusiform FTP SUVR, (B) female  $\times$  inferior temporal FTP SUVR, and (C) female  $\times$  middle temporal FTP SUVR on longitudinal tau accumulations in fusiform. Linear regression lines and each individual point of females and males were colored in violet and pacific blue, and Ref, A+/T- and A+/T+ groups were represented by circle, triangle and square respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.

**Table S7. Prediction of longitudinal tau accumulation by interactions of sex and baseline A $\beta$ /tau level.**

|                              |                                                                  | Statistics    | $\Delta$ Amygd. tau | $\Delta$ Entorh. tau | $\Delta$ Parahip. tau | $\Delta$ Fusi. tau | $\Delta$ Inf-temp. tau | $\Delta$ Mid-temp. tau |
|------------------------------|------------------------------------------------------------------|---------------|---------------------|----------------------|-----------------------|--------------------|------------------------|------------------------|
| Sex<br>(female as reference) | <i>A<math>\beta</math> <math>\times</math> Sex</i>               | $\beta_{std}$ | 0.158               | -0.031               | 0.054                 | 0.168              | 0.198                  | 0.212                  |
|                              |                                                                  | 95% ci        | -0.115~0.431        | -0.298~0.237         | -0.203~0.310          | -0.076~0.412       | -0.051~0.448           | -0.043~0.466           |
|                              |                                                                  | <i>p</i>      | 0.259               | 0.822                | 0.683                 | 0.178              | 0.121                  | 0.105                  |
|                              | <i>A<math>\beta</math>+Amygd. tau <math>\times</math> Sex</i>    | $\beta_{std}$ | 0.076               | 0.034                | 0.007                 | 0.048              | 0.046                  | 0.050                  |
|                              |                                                                  | 95% ci        | -0.177~0.328        | -0.233~0.302         | -0.237~0.250          | -0.182~0.278       | -0.189~0.282           | -0.189~0.289           |
|                              |                                                                  | <i>p</i>      | 0.557               | 0.802                | 0.958                 | 0.682              | 0.699                  | 0.681                  |
|                              | <i>A<math>\beta</math>+Entorh. tau <math>\times</math> Sex</i>   | $\beta_{std}$ | 0.087               | 0.022                | -0.010                | 0.052              | 0.087                  | 0.092                  |
|                              |                                                                  | 95% ci        | -0.170~0.344        | -0.240~0.284         | -0.238~0.217          | -0.147~0.251       | -0.116~0.291           | -0.116~0.301           |
|                              |                                                                  | <i>p</i>      | 0.509               | 0.870                | 0.929                 | 0.609              | 0.401                  | 0.387                  |
|                              | <i>A<math>\beta</math>+Parahip. tau <math>\times</math> Sex</i>  | $\beta_{std}$ | 0.110               | 0.090                | -0.009                | -0.038             | 0.017                  | 0.024                  |
|                              |                                                                  | 95% ci        | -0.161~0.381        | -0.172~0.351         | -0.235~0.217          | -0.212~0.136       | -0.164~0.198           | -0.162~0.210           |
|                              |                                                                  | <i>p</i>      | 0.426               | 0.501                | 0.936                 | 0.665              | 0.858                  | 0.802                  |
|                              | <i>A<math>\beta</math>+Fusi. tau <math>\times</math> Sex</i>     | $\beta_{std}$ | 0.057               | 0.123                | -0.067                | -0.133             | -0.007                 | 0.007                  |
|                              |                                                                  | 95% ci        | -0.218~0.332        | -0.143~0.388         | -0.309~0.175          | -0.290~0.025       | -0.185~0.171           | -0.181~0.195           |
|                              |                                                                  | <i>p</i>      | 0.684               | 0.365                | 0.589                 | 0.100              | 0.938                  | 0.944                  |
|                              | <i>A<math>\beta</math>+Inf-temp. tau <math>\times</math> Sex</i> | $\beta_{std}$ | 0.036               | 0.062                | -0.127                | -0.165             | -0.058                 | -0.055                 |
|                              |                                                                  | 95% ci        | -0.239~0.311        | -0.204~0.329         | -0.367~0.113          | -0.331~0.002       | -0.220~0.104           | -0.228~0.119           |
|                              |                                                                  | <i>p</i>      | 0.798               | 0.648                | 0.301                 | 0.054              | 0.484                  | 0.536                  |
|                              | <i>A<math>\beta</math>+Mid-temp. tau <math>\times</math> Sex</i> | $\beta_{std}$ | 0.009               | 0.026                | -0.188                | -0.247             | -0.133                 | -0.144                 |
|                              |                                                                  | 95% ci        | -0.268~0.287        | -0.244~0.296         | -0.434~0.058          | -0.428~-0.065      | -0.306~0.041           | -0.319~0.030           |
|                              |                                                                  | <i>p</i>      | 0.947               | 0.849                | 0.135                 | <b>0.008</b>       | 0.137                  | 0.107                  |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

Interaction term was marked in italic, and  $p < 0.05$  was indicated in bold.



**Figure S11. A $\beta$  and tau related longitudinal tau accumulation in early-life and late-life elderly adults.** Results based on cut age of 65 year and median age (72.7 year) were depicted respectively in left (A-F) and right (G-L) panels. Linear regression lines and each individual point of early-life elderly adults (age < 65 and age < 72.7 years) and late-life elderly adults (age  $\geq$  65 and age  $\geq$  72.7 years) were colored in salmon and green, and Ref, A+/T- and A+/T+ groups were represented by circle, triangle and square respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.

**Table S8. Prediction of longitudinal tau accumulation by interactions of age status (cut age of 65 year) and baseline A $\beta$ /tau level.**

|                                          |                                                                         | Statistics    | $\Delta$ Amygd. tau | $\Delta$ Entorh. tau | $\Delta$ Parahip. tau | $\Delta$ Fusi. tau | $\Delta$ Inf-temp. tau | $\Delta$ Mid-temp. tau |
|------------------------------------------|-------------------------------------------------------------------------|---------------|---------------------|----------------------|-----------------------|--------------------|------------------------|------------------------|
| Age status (65)<br>(age<65 as reference) | <i>A<math>\beta</math> <math>\times</math> Age status</i>               | $\beta_{std}$ | 0.145               | -0.001               | 0.124                 | -0.329             | -0.374                 | -0.443                 |
|                                          |                                                                         | 95% ci        | -0.237~0.526        | -0.374~0.372         | -0.232~0.481          | -0.662~0.005       | -0.714~-0.034          | -0.790~-0.096          |
|                                          |                                                                         | <i>p</i>      | 0.458               | 0.995                | 0.495                 | 0.055              | <b>0.032</b>           | <b>0.013</b>           |
|                                          | <i>A<math>\beta</math>+Amygd. Tau <math>\times</math> Age status</i>    | $\beta_{std}$ | 0.251               | 0.063                | 0.212                 | 0.010              | -0.019                 | -0.179                 |
|                                          |                                                                         | 95% ci        | -0.065~0.566        | -0.273~0.399         | -0.091~0.516          | -0.275~0.295       | -0.310~0.273           | -0.475~0.117           |
|                                          |                                                                         | <i>p</i>      | 0.121               | 0.713                | 0.172                 | 0.946              | 0.899                  | 0.238                  |
|                                          | <i>A<math>\beta</math>+Entorh. Tau <math>\times</math> Age status</i>   | $\beta_{std}$ | 0.192               | 0.097                | 0.263                 | 0.002              | -0.036                 | -0.169                 |
|                                          |                                                                         | 95% ci        | -0.158~0.543        | -0.261~0.454         | -0.044~0.570          | -0.267~0.271       | -0.310~0.239           | -0.452~0.114           |
|                                          |                                                                         | <i>p</i>      | 0.283               | 0.597                | 0.095                 | 0.989              | 0.798                  | 0.243                  |
|                                          | <i>A<math>\beta</math>+Parahip. Tau <math>\times</math> Age status</i>  | $\beta_{std}$ | 0.267               | 0.117                | 0.394                 | 0.158              | 0.097                  | -0.063                 |
|                                          |                                                                         | 95% ci        | -0.071~0.604        | -0.211~0.445         | 0.117~0.671           | -0.057~0.374       | -0.127~0.321           | -0.295~0.169           |
|                                          |                                                                         | <i>p</i>      | 0.124               | 0.484                | <b>0.006</b>          | 0.152              | 0.398                  | 0.596                  |
|                                          | <i>A<math>\beta</math>+Fusi. Tau <math>\times</math> Age status</i>     | $\beta_{std}$ | 0.316               | 0.086                | 0.420                 | 0.338              | 0.257                  | 0.140                  |
|                                          |                                                                         | 95% ci        | 0.015~0.618         | -0.209~0.382         | 0.157~0.682           | 0.168~0.507        | 0.063~0.451            | -0.068~0.348           |
|                                          |                                                                         | <i>p</i>      | <b>0.041</b>        | 0.567                | <b>0.002</b>          | <b>&lt; 0.001</b>  | <b>0.010</b>           | 0.189                  |
|                                          | <i>A<math>\beta</math>+Inf-temp. tau <math>\times</math> Age status</i> | $\beta_{std}$ | 0.232               | 0.084                | 0.386                 | 0.292              | 0.233                  | 0.110                  |
|                                          |                                                                         | 95% ci        | -0.076~0.541        | -0.216~0.385         | 0.120~0.652           | 0.107~0.477        | 0.054~0.413            | -0.086~0.305           |
|                                          |                                                                         | <i>p</i>      | 0.141               | 0.583                | <b>0.005</b>          | <b>0.002</b>       | <b>0.012</b>           | 0.273                  |
|                                          | <i>A<math>\beta</math>+Mid-temp. tau <math>\times</math> Age status</i> | $\beta_{std}$ | 0.178               | 0.084                | 0.378                 | 0.350              | 0.322                  | 0.203                  |
|                                          |                                                                         | 95% ci        | -0.114~0.469        | -0.201~0.369         | 0.121~0.634           | 0.160~0.540        | 0.143~0.502            | 0.018~0.388            |
|                                          |                                                                         | <i>p</i>      | 0.234               | 0.565                | <b>0.004</b>          | <b>&lt; 0.001</b>  | <b>0.001</b>           | <b>0.032</b>           |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

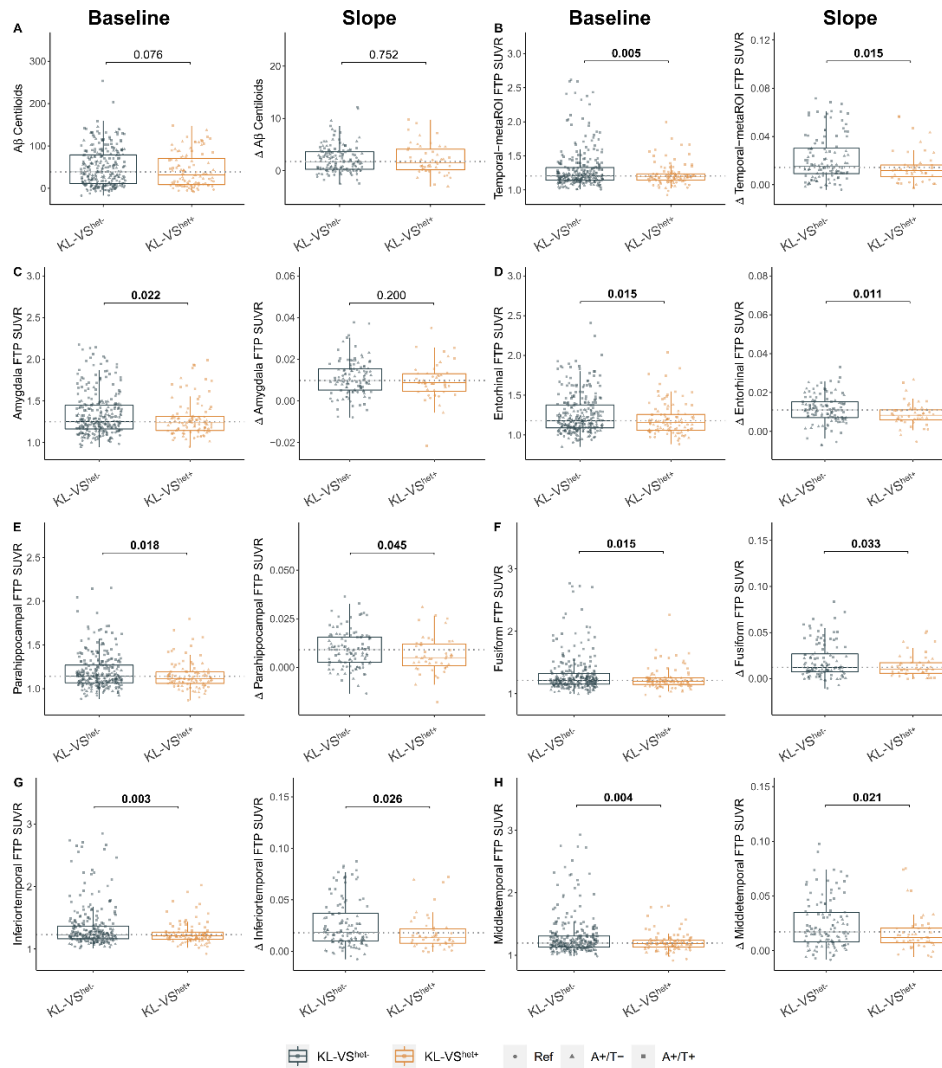
Interaction term was marked in italic, and  $p < 0.05$  was indicated in bold.

**Table S9. Prediction of longitudinal tau accumulation by interactions of age status (cut age of 72.7 year) and baseline A $\beta$ /tau level.**

|                                              |                                                     | Statistics    | $\Delta$ Amygd. Tau | $\Delta$ Entorh. Tau | $\Delta$ Parahip. Tau | $\Delta$ Fusi. Tau | $\Delta$ Inf-temp. tau | $\Delta$ Mid-temp. tau |
|----------------------------------------------|-----------------------------------------------------|---------------|---------------------|----------------------|-----------------------|--------------------|------------------------|------------------------|
| Age status (72.7)<br>(age<72.7 as reference) | <i>A<math>\beta</math>×Age status</i>               | $\beta_{std}$ | 0.161               | 0.162                | 0.144                 | -0.086             | -0.233                 | -0.250                 |
|                                              |                                                     | 95% ci        | -0.114~0.436        | -0.108~0.432         | -0.116~0.403          | -0.334~0.162       | -0.484~0.019           | -0.507~0.006           |
|                                              |                                                     | <i>p</i>      | 0.252               | 0.241                | 0.279                 | 0.499              | 0.071                  | 0.057                  |
|                                              | <i>A<math>\beta</math>+Amygd. Tau×Age status</i>    | $\beta_{std}$ | 0.089               | 0.042                | 0.118                 | 0.158              | 0.030                  | -0.033                 |
|                                              |                                                     | 95% ci        | -0.164~0.343        | -0.228~0.311         | -0.127~0.363          | -0.073~0.389       | -0.206~0.267           | -0.274~0.208           |
|                                              |                                                     | <i>p</i>      | 0.492               | 0.761                | 0.347                 | 0.182              | 0.802                  | 0.790                  |
|                                              | <i>A<math>\beta</math>+Entorh. Tau×Age status</i>   | $\beta_{std}$ | 0.067               | 0.153                | 0.228                 | 0.264              | 0.107                  | 0.065                  |
|                                              |                                                     | 95% ci        | -0.192~0.326        | -0.111~0.417         | 0.001~0.456           | 0.066~0.462        | -0.098~0.312           | -0.146~0.277           |
|                                              |                                                     | <i>p</i>      | 0.614               | 0.258                | 0.050                 | <b>0.010</b>       | 0.310                  | 0.547                  |
|                                              | <i>A<math>\beta</math>+Parahip. Tau×Age status</i>  | $\beta_{std}$ | 0.179               | 0.035                | 0.158                 | 0.167              | -0.004                 | -0.079                 |
|                                              |                                                     | 95% ci        | -0.097~0.456        | -0.235~0.304         | -0.073~0.39           | -0.011~0.345       | -0.190~0.181           | -0.270~0.112           |
|                                              |                                                     | <i>p</i>      | 0.205               | 0.801                | 0.181                 | 0.067              | 0.963                  | 0.416                  |
|                                              | <i>A<math>\beta</math>+Fusi. Tau×Age status</i>     | $\beta_{std}$ | 0.247               | 0.076                | 0.256                 | 0.267              | 0.069                  | -0.012                 |
|                                              |                                                     | 95% ci        | -0.029~0.522        | -0.195~0.346         | 0.013~0.5             | 0.110~0.425        | -0.112~0.25            | -0.204~0.179           |
|                                              |                                                     | <i>p</i>      | 0.081               | 0.584                | <b>0.041</b>          | <b>0.001</b>       | 0.457                  | 0.901                  |
|                                              | <i>A<math>\beta</math>+Inf-temp. tau×Age status</i> | $\beta_{std}$ | 0.207               | 0.079                | 0.272                 | 0.352              | 0.135                  | 0.058                  |
|                                              |                                                     | 95% ci        | -0.071~0.484        | -0.193~0.350         | 0.029~0.515           | 0.187~0.516        | -0.030~0.300           | -0.120~0.236           |
|                                              |                                                     | <i>p</i>      | 0.146               | 0.571                | <b>0.030</b>          | <b>&lt; 0.001</b>  | 0.110                  | 0.523                  |
|                                              | <i>A<math>\beta</math>+Mid-temp. tau×Age status</i> | $\beta_{std}$ | 0.166               | 0.087                | 0.320                 | 0.442              | 0.255                  | 0.170                  |
|                                              |                                                     | 95% ci        | -0.120~0.451        | -0.193~0.367         | 0.066~0.574           | 0.260~0.624        | 0.076~0.434            | -0.011~0.352           |
|                                              |                                                     | <i>p</i>      | 0.257               | 0.545                | <b>0.014</b>          | <b>&lt; 0.001</b>  | <b>0.006</b>           | 0.068                  |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

Interaction term was marked in italic, and  $p < 0.05$  was indicated in bold.



**Table S10. Comparisons of baseline and slopes of A $\beta$  Centiloids, regional tau PET in Temporal-metaROI between KL-VS<sup>het-</sup> and KL-VS<sup>het+</sup>.**

| Statistics                    |               |               | Statistics             |               |               |
|-------------------------------|---------------|---------------|------------------------|---------------|---------------|
| A $\beta$                     | $\beta_{std}$ | -0.182        | Parahip. tau           | $\beta_{std}$ | -0.263        |
|                               | 95% ci        | -0.382~-0.018 |                        | 95% ci        | -0.481~-0.046 |
|                               | <i>p</i>      | 0.076         |                        | <i>p</i>      | <b>0.018</b>  |
| $\Delta$ A $\beta$            | $\beta_{std}$ | -0.052        | $\Delta$ Parahip. tau  | $\beta_{std}$ | -0.340        |
|                               | 95% ci        | -0.372~-0.269 |                        | 95% ci        | -0.669~-0.011 |
|                               | <i>p</i>      | 0.752         |                        | <i>p</i>      | <b>0.045</b>  |
| Temporal-metaROI tau          | $\beta_{std}$ | -0.317        | Fusi. tau              | $\beta_{std}$ | -0.276        |
|                               | 95% ci        | -0.536~-0.098 |                        | 95% ci        | -0.497~-0.055 |
|                               | <i>p</i>      | <b>0.005</b>  |                        | <i>p</i>      | <b>0.015</b>  |
| $\Delta$ Temporal-metaROI tau | $\beta_{std}$ | -0.413        | $\Delta$ Fusi. tau     | $\beta_{std}$ | -0.362        |
|                               | 95% ci        | -0.742~-0.083 |                        | 95% ci        | -0.692~-0.031 |
|                               | <i>p</i>      | <b>0.015</b>  |                        | <i>p</i>      | <b>0.033</b>  |
| Amygd. tau                    | $\beta_{std}$ | -0.241        | Inf-temp. tau          | $\beta_{std}$ | -0.330        |
|                               | 95% ci        | -0.448~-0.035 |                        | 95% ci        | -0.550~-0.110 |
|                               | <i>p</i>      | <b>0.022</b>  |                        | <i>p</i>      | <b>0.003</b>  |
| $\Delta$ Amygd. tau           | $\beta_{std}$ | -0.216        | $\Delta$ Inf-temp. tau | $\beta_{std}$ | -0.379        |
|                               | 95% ci        | -0.546~-0.113 |                        | 95% ci        | -0.710~-0.047 |
|                               | <i>p</i>      | 0.200         |                        | <i>p</i>      | <b>0.026</b>  |
| Entorh. tau                   | $\beta_{std}$ | -0.263        | Mid-temp. tau          | $\beta_{std}$ | -0.328        |
|                               | 95% ci        | -0.474~-0.052 |                        | 95% ci        | -0.548~-0.107 |
|                               | <i>p</i>      | <b>0.015</b>  |                        | <i>p</i>      | <b>0.004</b>  |
| $\Delta$ Entorh. tau          | $\beta_{std}$ | -0.430        | $\Delta$ Mid-temp. tau | $\beta_{std}$ | -0.396        |
|                               | 95% ci        | -0.756~-0.104 |                        | 95% ci        | -0.730~-0.062 |
|                               | <i>p</i>      | <b>0.011</b>  |                        | <i>p</i>      | <b>0.021</b>  |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

*P* < 0.05 was indicated in bold.

**Table S11. Prediction of longitudinal tau increase by interactions of KL-VS<sup>het</sup> genotype and baseline A $\beta$ /tau level.**

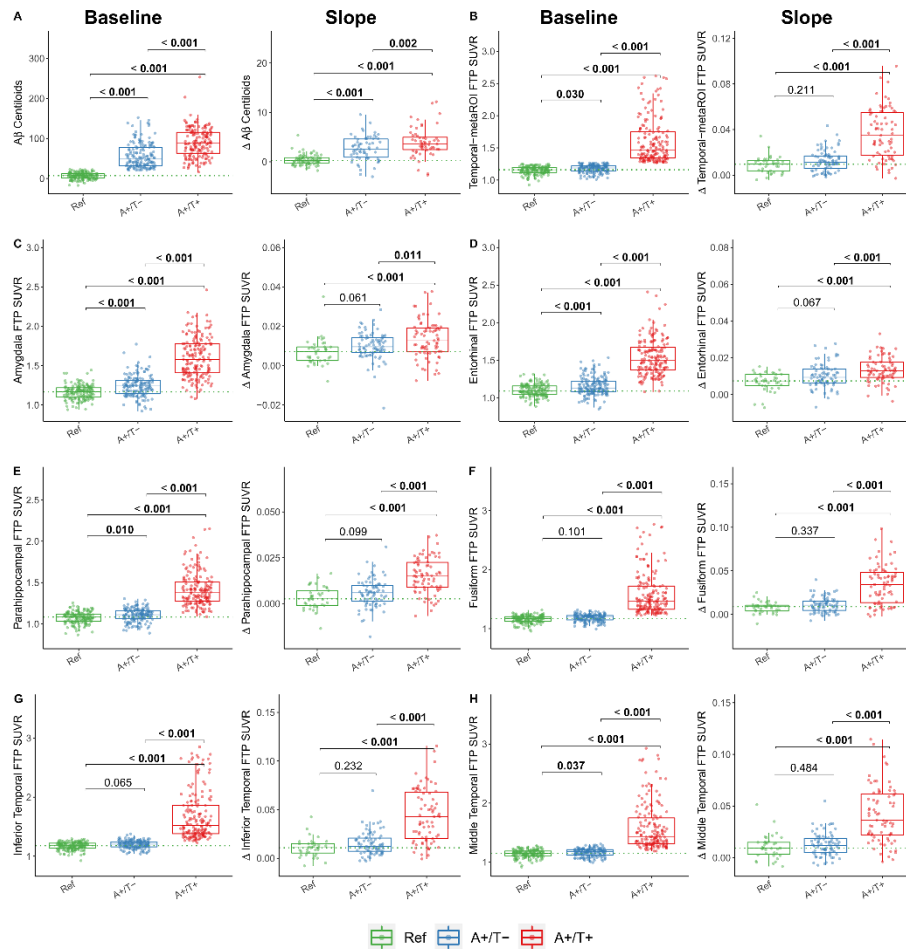
|                                                             |                                                                | Statistics    | $\Delta$ Amygd. Tau | $\Delta$ Entorh. Tau | $\Delta$ Parahip. Tau | $\Delta$ Fusi. Tau | $\Delta$ Inf-temp. tau | $\Delta$ Mid-temp. tau |
|-------------------------------------------------------------|----------------------------------------------------------------|---------------|---------------------|----------------------|-----------------------|--------------------|------------------------|------------------------|
| KL-VS <sup>het</sup><br>(Reference: KL-VS <sup>het-</sup> ) | <i>A<math>\beta</math> × KL-VS<sup>het</sup></i>               | $\beta_{std}$ | -0.193              | -0.184               | -0.359                | -0.374             | -0.405                 | -0.366                 |
|                                                             |                                                                | 95% ci        | -0.516~-0.129       | -0.501~-0.133        | -0.647~-0.071         | -0.622~-0.127      | -0.662~-0.148          | -0.629~-0.103          |
|                                                             |                                                                | <i>p</i>      | 0.242               | 0.257                | <b>0.016</b>          | <b>0.003</b>       | <b>0.002</b>           | <b>0.007</b>           |
|                                                             | <i>A<math>\beta</math>+Amygd. tau × KL-VS<sup>het</sup></i>    | $\beta_{std}$ | 0.050               | -0.087               | -0.108                | -0.185             | -0.220                 | -0.175                 |
|                                                             |                                                                | 95% ci        | -0.299~0.400        | -0.450~0.276         | -0.431~0.215          | -0.450~0.080       | -0.500~0.060           | -0.459~0.108           |
|                                                             |                                                                | <i>p</i>      | 0.778               | 0.639                | 0.512                 | 0.174              | 0.125                  | 0.227                  |
|                                                             | <i>A<math>\beta</math>+Entorh. tau × KL-VS<sup>het</sup></i>   | $\beta_{std}$ | 0.106               | -0.028               | -0.080                | -0.286             | -0.289                 | -0.196                 |
|                                                             |                                                                | 95% ci        | -0.276~0.487        | -0.420~0.363         | -0.412~0.253          | -0.542~-0.029      | -0.560~-0.018          | -0.476~0.083           |
|                                                             |                                                                | <i>p</i>      | 0.587               | 0.887                | 0.640                 | <b>0.030</b>       | <b>0.038</b>           | 0.170                  |
|                                                             | <i>A<math>\beta</math>+Parahip. tau × KL-VS<sup>het</sup></i>  | $\beta_{std}$ | 0.141               | 0.050                | 0.016                 | -0.222             | -0.236                 | -0.139                 |
|                                                             |                                                                | 95% ci        | -0.303~0.585        | -0.386~0.486         | -0.355~0.387          | -0.482~0.038       | -0.520~0.048           | -0.433~0.156           |
|                                                             |                                                                | <i>p</i>      | 0.535               | 0.823                | 0.931                 | 0.096              | 0.106                  | 0.357                  |
|                                                             | <i>A<math>\beta</math>+Fusi. tau × KL-VS<sup>het</sup></i>     | $\beta_{std}$ | 0.035               | 0.0751               | 0.075                 | -0.100             | -0.136                 | 0.007                  |
|                                                             |                                                                | 95% ci        | -0.571~0.641        | -0.462~0.612         | -0.462~0.612          | -0.434~0.233       | -0.529~0.257           | -0.411~0.425           |
|                                                             |                                                                | <i>p</i>      | 0.910               | 0.784                | 0.784                 | 0.556              | 0.499                  | 0.974                  |
|                                                             | <i>A<math>\beta</math>+Inf-temp. tau × KL-VS<sup>het</sup></i> | $\beta_{std}$ | 0.390               | 0.162                | 0.227                 | -0.045             | 0.036                  | 0.209                  |
|                                                             |                                                                | 95% ci        | -0.254~1.035        | -0.473~0.797         | -0.326~0.780          | -0.397~0.307       | -0.333~0.406           | -0.189~0.607           |
|                                                             |                                                                | <i>p</i>      | 0.237               | 0.618                | 0.423                 | 0.804              | 0.847                  | 0.305                  |
|                                                             | <i>A<math>\beta</math>+Mid-temp. tau × KL-VS<sup>het</sup></i> | $\beta_{std}$ | 0.465               | 0.156                | 0.202                 | -0.062             | 0.028                  | 0.244                  |
|                                                             |                                                                | 95% ci        | -0.184~1.114        | -0.485~0.798         | -0.366~0.769          | -0.454~0.329       | -0.368~0.424           | -0.156~0.644           |
|                                                             |                                                                | <i>p</i>      | 0.162               | 0.634                | 0.487                 | 0.756              | 0.889                  | 0.234                  |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

Interaction term was marked in italic, and  $p < 0.05$  was indicated in bold.

## Sensitivity analysis

### Temporal-metaROI FTP SUVR threshold (1.27)



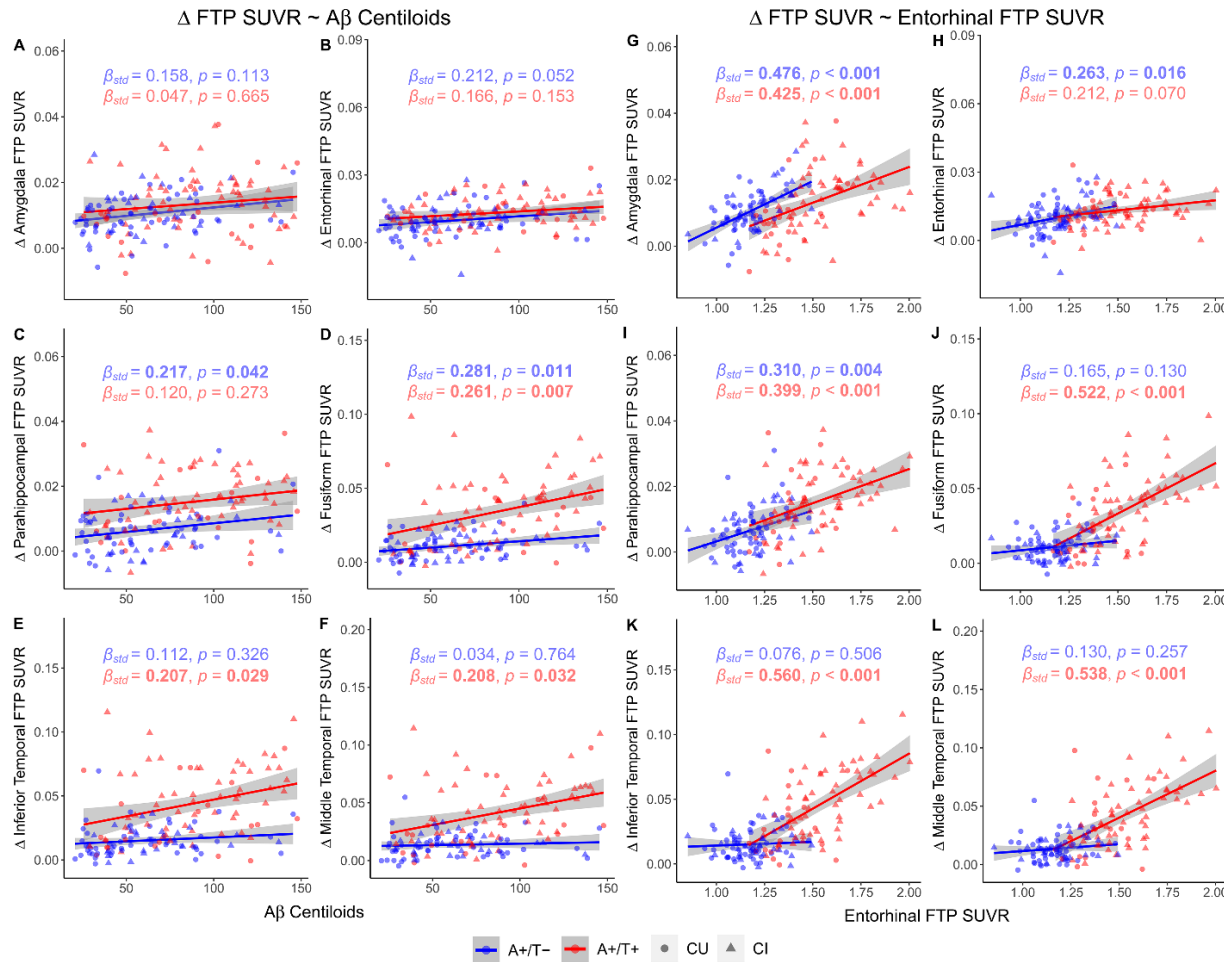
**Figure S13. Comparisons of baseline and slopes of tau PET in Temporal-metaROI region and 6 ROIs in this composite region among Ref, A+/T- and A+/T+ groups.** Comparisons of baseline and slopes of (A) A $\beta$  PET Centiloids, (B) tau PET in Temporal-metaROI region, (C) amygdala, (D) entorhinal, (E) parahippocampal, (F) fusiform, (G) inferior temporal and (H) middle temporal regions. The boxplot whiskers extended to the lowest and highest data points within 1.5 times the interquartile range from the lower to the upper quartiles. Ref, A+/T- and A+/T+ individuals were colored in green, blue and red respectively. Green dashed lines represented the median value of the Ref group.  $P < 0.05$  were marked in bold.

**Table S12. Comparisons of baseline and slopes of A $\beta$  Centiloids, regional tau PET of Temporal-metaROI**

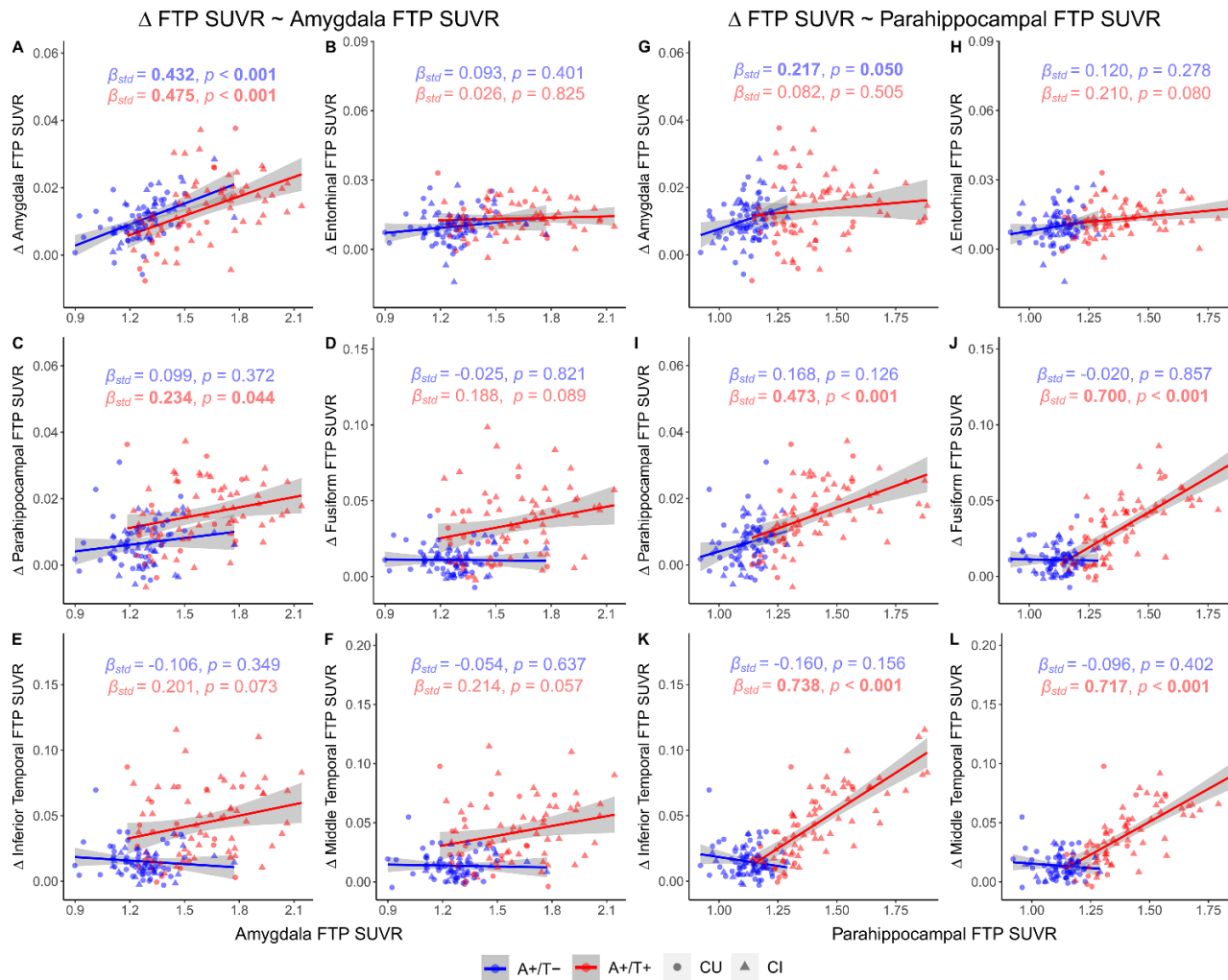
| Ref vs. A+/T-   Ref vs. A+/T+   A+/T- vs. A+/T+ |               |                |                |                | Ref vs. A+/T-   Ref vs. A+/T+   A+/T- vs. A+/T+ |               |              |                |                |
|-------------------------------------------------|---------------|----------------|----------------|----------------|-------------------------------------------------|---------------|--------------|----------------|----------------|
| A $\beta$                                       | $\beta_{std}$ | 1.091          | 1.839          | 0.748          | Parahip. tau                                    | $\beta_{std}$ | 0.199        | 1.713          | 1.515          |
|                                                 | 95% ci        | 0.947~1.235    | 1.697~1.981    | 0.611~0.884    |                                                 | 95% ci        | 0.049~0.349  | 1.566~1.861    | 1.373~1.657    |
|                                                 | <i>p</i>      | < <b>0.001</b> | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | <b>0.010</b> | < <b>0.001</b> | < <b>0.001</b> |
| $\Delta$ A $\beta$                              | $\beta_{std}$ | 0.8675         | 1.336          | 0.469          | $\Delta$ Parahip. tau                           | $\beta_{std}$ | 0.281        | 1.260          | 0.979          |
|                                                 | 95% ci        | 0.594~1.141    | 1.053~1.619    | 0.170~0.767    |                                                 | 95% ci        | -0.051~0.613 | 0.925~1.595    | 0.711~1.247    |
|                                                 | <i>p</i>      | < <b>0.001</b> | < <b>0.001</b> | <b>0.002</b>   |                                                 | <i>p</i>      | 0.099        | < <b>0.001</b> | < <b>0.001</b> |
| Temporal-metaROI tau                            | $\beta_{std}$ | 0.178          | 1.627          | 1.449          | Fusi. tau                                       | $\beta_{std}$ | 0.141        | 1.528          | 1.388          |
|                                                 | 95% ci        | 0.018~0.337    | 1.469~1.784    | 1.298~1.601    |                                                 | 95% ci        | -0.027~0.309 | 1.363~1.694    | 1.228~1.547    |
|                                                 | <i>p</i>      | <b>0.030</b>   | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | 0.101        | < <b>0.001</b> | < <b>0.001</b> |
| $\Delta$ Temporal-metaROI tau                   | $\beta_{std}$ | 0.194          | 1.419          | 1.224          | $\Delta$ Fusi. tau                              | $\beta_{std}$ | 0.152        | 1.3562         | 1.2047         |
|                                                 | 95% ci        | -0.109~0.498   | 1.112~1.725    | 0.979~1.470    |                                                 | 95% ci        | -0.157~0.460 | 1.044~1.668    | 0.955~1.454    |
|                                                 | <i>p</i>      | 0.211          | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | 0.337        | < <b>0.001</b> | < <b>0.001</b> |
| Amygd. tau                                      | $\beta_{std}$ | 0.316          | 1.699          | 1.384          | Inf-temp. tau                                   | $\beta_{std}$ | 0.156        | 1.568          | 1.413          |
|                                                 | 95% ci        | 0.161~0.471    | 1.547~1.852    | 1.237~1.530    |                                                 | 95% ci        | -0.009~0.321 | 1.406~1.731    | 1.26~1.569     |
|                                                 | <i>p</i>      | < <b>0.001</b> | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | 0.065        | < <b>0.001</b> | < <b>0.001</b> |
| $\Delta$ Amygd. tau                             | $\beta_{std}$ | 0.362          | 0.760          | 0.399          | $\Delta$ Inf-temp. tau                          | $\beta_{std}$ | 0.188        | 1.383          | 1.195          |
|                                                 | 95% ci        | -0.0141~0.737  | 0.381~1.140    | 0.095~0.703    |                                                 | 95% ci        | -0.120~0.497 | 1.072~1.695    | 0.9459~1.444   |
|                                                 | <i>p</i>      | 0.061          | < <b>0.001</b> | <b>0.011</b>   |                                                 | <i>p</i>      | 0.232        | < <b>0.001</b> | < <b>0.001</b> |
| Entorh. tau                                     | $\beta_{std}$ | 0.258          | 1.749          | 1.491          | Mid-temp. tau                                   | $\beta_{std}$ | 0.181        | 1.536          | 1.355          |
|                                                 | 95% ci        | 0.110~0.405    | 1.603~1.894    | 1.351~1.631    |                                                 | 95% ci        | 0.012~0.350  | 1.369~1.703    | 1.195~1.516    |
|                                                 | <i>p</i>      | < <b>0.001</b> | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | <b>0.037</b> | < <b>0.001</b> | < <b>0.001</b> |
| $\Delta$ Entorh. tau                            | $\beta_{std}$ | 0.347          | 0.879          | 0.532          | $\Delta$ Mid-temp. tau                          | $\beta_{std}$ | 0.1127       | 1.289          | 1.177          |
|                                                 | 95% ci        | -0.022~0.716   | 0.506~1.251    | 0.234~0.830    |                                                 | 95% ci        | -0.202~0.428 | 0.971~1.608    | 0.922~1.431    |
|                                                 | <i>p</i>      | 0.067          | < <b>0.001</b> | < <b>0.001</b> |                                                 | <i>p</i>      | 0.484        | < <b>0.001</b> | < <b>0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

*P* < 0.05 was indicated in bold.



**Figure S14. Prediction of longitudinal tau accumulations by baseline A $\beta$  Centiloids and entorhinal tau.** Models have been accounted for age and sex. Prediction of longitudinal FTP SUVR increases in (A) amygdala, (B) entorhinal, (C) parahippocampal, (D) fusiform, (E) inferior temporal and (F) middle temporal regions by baseline A $\beta$  Centiloids. Prediction of longitudinal FTP SUVR increase in (G) amygdala, (H) entorhinal, (I) parahippocampal, (J) fusiform, (K) inferior temporal and (L) middle temporal regions by baseline entorhinal FTP SUVR. Linear regression lines, each individual point,  $\beta_{std}$  and  $p$  values of A+/T- and A+/T+ groups were colored in blue and red, and CU and CI individuals were represented by circle and triangle respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.



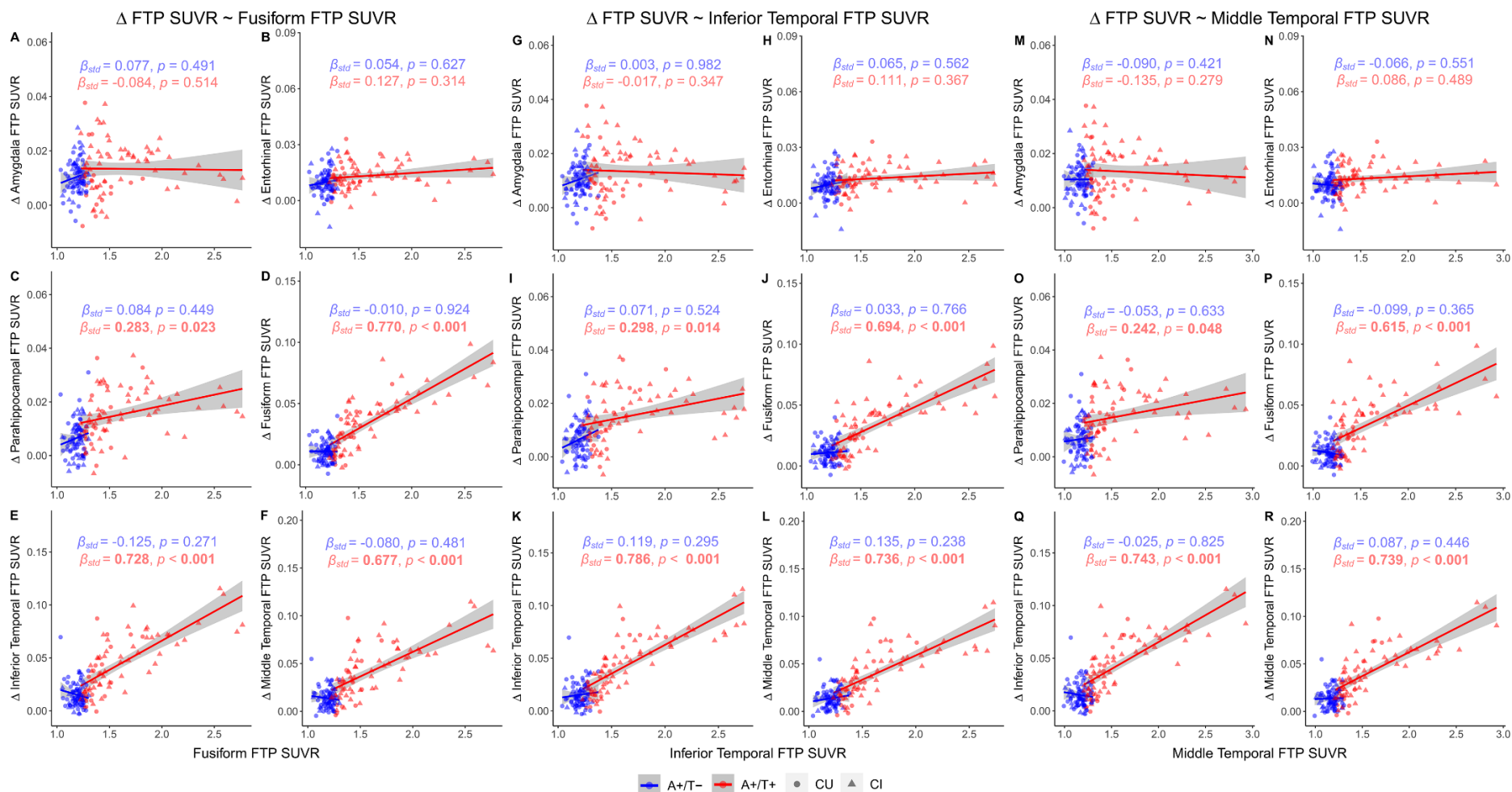
**Figure S15. Prediction of longitudinal tau accumulations by baseline tau in amygdala or parahippocampal.** Models have been accounted for age, sex and baseline A $\beta$ . Prediction of longitudinal FTP SUVR increases in (A) amygdala, (B) entorhinal, (C) parahippocampal, (D) fusiform, (E) inferior temporal and (F) middle temporal regions by baseline amygdala FTP SUVR. Prediction of longitudinal FTP SUVR increases in (G) amygdala, (H) entorhinal, (I) parahippocampal, (J) fusiform, (K) inferior temporal and (L) middle temporal regions by baseline parahippocampal FTP SUVR. Linear regression lines, each individual point,  $\beta_{std}$  and  $p$  values of A+/T- and A+/T+ groups were colored in blue and red, and CU and CI individuals were represented by circle and triangle respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.

**Table S13. Prediction of longitudinal tau accumulation by baseline amygdala tau or entorhinal tau adjusted for baseline A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Amygd. tau |                   |              |                   | A $\beta$ + Entorh. tau |                   |              |                   |
|------------------------|---------------|------------------------|-------------------|--------------|-------------------|-------------------------|-------------------|--------------|-------------------|
|                        |               | A+/-                   |                   | A+/T+        |                   | A+/-                    |                   | A+/T+        |                   |
|                        |               | A $\beta$              | Amygd. tau        | A $\beta$    | Amygd. tau        | A $\beta$               | Entorh. tau       | A $\beta$    | Entorh. tau       |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.194                  | 0.432             | 0.051        | 0.475             | 0.158                   | 0.476             | 0.047        | 0.425             |
|                        | 95% ci        | -0.002~0.390           | 0.235~0.628       | -0.155~0.256 | 0.270~0.680       | -0.035~0.350            | 0.283~0.668       | -0.165~0.260 | 0.212~0.637       |
|                        | $p$           | 0.056                  | <b>&lt; 0.001</b> | 0.631        | <b>&lt; 0.001</b> | 0.113                   | <b>&lt; 0.001</b> | 0.665        | <b>&lt; 0.001</b> |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.236                  | 0.093             | 0.206        | 0.026             | 0.212                   | 0.263             | 0.166        | 0.212             |
|                        | 95% ci        | 0.020~0.452            | -0.123~0.309      | -0.023~0.436 | -0.204~0.256      | 0.002~0.422             | 0.053~0.473       | -0.059~0.392 | -0.014~0.438      |
|                        | $p$           | <b>0.036</b>           | 0.401             | 0.082        | 0.825             | 0.052                   | <b>0.016</b>      | 0.153        | 0.070             |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.246                  | 0.099             | 0.161        | 0.234             | 0.217                   | 0.310             | 0.120        | 0.399             |
|                        | 95% ci        | 0.030~0.461            | -0.117~0.314      | -0.062~0.385 | 0.011~0.458       | 0.011~0.423             | 0.104~0.517       | -0.093~0.332 | 0.187~0.611       |
|                        | $p$           | <b>0.028</b>           | 0.372             | 0.162        | <b>0.044</b>      | <b>0.042</b>            | <b>0.004</b>      | 0.273        | <b>&lt; 0.001</b> |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.298                  | -0.025            | 0.337        | 0.188             | 0.281                   | 0.165             | 0.261        | 0.522             |
|                        | 95% ci        | 0.085~0.511            | -0.238~0.189      | 0.123~0.550  | -0.026~0.402      | 0.070~0.492             | -0.046~0.376      | 0.077~0.444  | 0.339~0.706       |
|                        | $p$           | <b>0.008</b>           | 0.821             | <b>0.003</b> | 0.089             | <b>0.011</b>            | 0.130             | <b>0.007</b> | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.123                  | -0.106            | 0.288        | 0.201             | 0.112                   | 0.076             | 0.207        | 0.560             |
|                        | 95% ci        | -0.098~0.343           | -0.327~0.115      | 0.071~0.506  | -0.016~0.419      | -0.110~0.334            | -0.146~0.298      | 0.025~0.390  | 0.377~0.742       |
|                        | $p$           | 0.280                  | 0.349             | <b>0.011</b> | 0.073             | 0.326                   | 0.506             | <b>0.029</b> | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.048                  | -0.054            | 0.282        | 0.214             | 0.034                   | 0.130             | 0.208        | 0.538             |
|                        | 95% ci        | -0.174~0.271           | -0.277~0.169      | 0.065~0.499  | -0.003~0.431      | -0.188~0.257            | -0.093~0.352      | 0.021~0.394  | 0.352~0.723       |
|                        | $p$           | 0.671                  | 0.637             | <b>0.013</b> | 0.057             | 0.764                   | 0.257             | <b>0.032</b> | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

$P < 0.05$  was indicated in bold.



**Figure S16. Prediction of longitudinal tau accumulation by baseline tau in fusiform, inferior temporal or middle temporal regions.** Models have been accounted for age, sex and baseline A $\beta$ . Prediction of longitudinal FTP SUVR increases in (A) amygdala, (B) entorhinal, (C) parahippocampal, (D) fusiform,

(E) inferior temporal and (F) middle temporal regions by baseline fusiform FTP SUVR. Prediction of longitudinal FTP SUVR increases in (G) amygdala, (H) entorhinal, (I) parahippocampal, (J) fusiform, (K) inferior temporal and (L) middle temporal regions by baseline inferior temporal FTP SUVR. Prediction of longitudinal FTP SUVR increases in (M) amygdala, (N) entorhinal, (O) parahippocampal, (P) fusiform, (Q) inferior temporal and (R) middle temporal regions by baseline middle temporal FTP SUVR. Linear regression lines, each individual point,  $\beta_{std}$  and  $p$  values of A+/T- and A+/T+ groups were colored in blue and red, and CU and CI individuals were represented by circle and triangle respectively. Linear model fits were indicated with 95% confidence intervals.  $P < 0.05$  and associated  $\beta_{std}$  were marked in bold.

**Table S14. Prediction of longitudinal tau accumulation by baseline parahippocampal tau or fusiform tau adjusted for A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Parahip. tau |              |              |                   | A $\beta$ + Fusi. tau |              |              |                   |
|------------------------|---------------|--------------------------|--------------|--------------|-------------------|-----------------------|--------------|--------------|-------------------|
|                        |               | A+/T-                    |              | A+/T+        |                   | A+/T-                 |              | A+/T+        |                   |
|                        |               | A $\beta$                | Parahip. tau | A $\beta$    | Parahip. tau      | A $\beta$             | Fusi. tau    | A $\beta$    | Fusi. tau         |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.205                    | 0.217        | 0.112        | 0.082             | 0.204                 | 0.077        | 0.170        | -0.084            |
|                        | 95% ci        | -0.008~0.418             | 0.004~0.430  | -0.127~0.351 | -0.157~0.321      | -0.014~0.422          | -0.141~0.295 | -0.080~0.420 | -0.333~0.166      |
|                        | <i>p</i>      | 0.063                    | <b>0.050</b> | 0.362        | 0.505             | 0.071                 | 0.491        | 0.186        | 0.514             |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.238                    | 0.120        | 0.148        | 0.210             | 0.237                 | 0.054        | 0.159        | 0.127             |
|                        | 95% ci        | 0.023~0.453              | -0.095~0.335 | -0.084~0.380 | -0.022~0.442      | 0.020~0.454           | -0.163~0.271 | -0.086~0.405 | -0.119~0.372      |
|                        | <i>p</i>      | <b>0.034</b>             | 0.278        | 0.215        | 0.080             | <b>0.035</b>          | 0.627        | 0.208        | 0.314             |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.248                    | 0.168        | 0.062        | 0.473             | 0.247                 | 0.084        | 0.088        | 0.283             |
|                        | 95% ci        | 0.035~0.461              | -0.045~0.382 | -0.149~0.272 | 0.263~0.683       | 0.031~0.462           | -0.132~0.299 | -0.151~0.327 | 0.044~0.522       |
|                        | <i>p</i>      | <b>0.025</b>             | 0.126        | 0.567        | <b>&lt; 0.001</b> | <b>0.028</b>          | 0.449        | 0.471        | <b>0.023</b>      |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.297                    | -0.020       | 0.161        | 0.700             | 0.298                 | -0.010       | 0.057        | 0.770             |
|                        | 95% ci        | 0.084~0.511              | -0.233~0.194 | 0.004~0.317  | 0.544~0.856       | 0.084~0.511           | -0.224~0.203 | -0.097~0.210 | 0.617~0.924       |
|                        | <i>p</i>      | <b>0.008</b>             | 0.857        | <b>0.048</b> | <b>&lt; 0.001</b> | <b>0.008</b>          | 0.924        | 0.470        | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.120                    | -0.160       | 0.104        | 0.738             | 0.122                 | -0.125       | 0.028        | 0.728             |
|                        | 95% ci        | -0.099~0.339             | -0.379~0.059 | -0.049~0.257 | 0.585~0.891       | -0.098~0.342          | -0.345~0.096 | -0.142~0.199 | 0.558~0.898       |
|                        | <i>p</i>      | 0.287                    | 0.156        | 0.188        | <b>&lt; 0.001</b> | 0.281                 | 0.271        | 0.744        | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.047                    | -0.096       | 0.106        | 0.717             | 0.048                 | -0.080       | 0.045        | 0.677             |
|                        | 95% ci        | -0.175~0.269             | -0.318~0.127 | -0.053~0.264 | 0.559~0.876       | -0.174~0.271          | -0.303~0.142 | -0.137~0.227 | 0.495~0.858       |
|                        | <i>p</i>      | 0.679                    | 0.402        | 0.196        | <b>&lt; 0.001</b> | 0.671                 | 0.481        | 0.629        | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

*P* < 0.05 was indicated in bold.

**Table S15. Prediction of longitudinal tau accumulation by baseline inferior temporal tau or middle temporal tau adjusted for A $\beta$  Centiloids.**

|                        |               | A $\beta$ + Inf-temp. tau |               |              |                   | A $\beta$ + Mid-temp. tau |               |              |                   |
|------------------------|---------------|---------------------------|---------------|--------------|-------------------|---------------------------|---------------|--------------|-------------------|
|                        |               | A+/-                      |               | A+/-         |                   | A+/-                      |               | A+/-         |                   |
|                        |               | A $\beta$                 | Inf-temp. tau | A $\beta$    | Inf-temp. tau     | A $\beta$                 | Mid-temp. tau | A $\beta$    | Mid-temp. tau     |
| $\Delta$ Amygd. tau    | $\beta_{std}$ | 0.112                     | 0.003         | 0.178        | -0.117            | 0.201                     | -0.090        | 0.185        | -0.135            |
|                        | 95% ci        | -0.015~0.424              | -0.217~0.222  | -0.065~0.421 | -0.360~0.126      | -0.017~0.419              | -0.308~0.128  | -0.058~0.428 | -0.378~0.108      |
|                        | $p$           | 0.071                     | 0.982         | 0.156        | 0.347             | 0.074                     | 0.421         | 0.141        | 0.279             |
| $\Delta$ Entorh. tau   | $\beta_{std}$ | 0.232                     | 0.065         | 0.172        | 0.111             | 0.235                     | -0.066        | 0.180        | 0.086             |
|                        | 95% ci        | 0.015~0.450               | -0.153~0.282  | -0.068~0.412 | -0.129~0.351      | 0.018~0.452               | -0.283~0.151  | -0.061~0.421 | -0.155~0.327      |
|                        | $p$           | <b>0.039</b>              | 0.562         | 0.164        | 0.367             | <b>0.037</b>              | 0.551         | 0.147        | 0.489             |
| $\Delta$ Parahip. tau  | $\beta_{std}$ | 0.242                     | 0.071         | 0.099        | 0.298             | 0.246                     | -0.053        | 0.117        | 0.242             |
|                        | 95% ci        | 0.026~0.459               | -0.146~0.287  | -0.133~0.330 | 0.066~0.529       | 0.030~0.462               | -0.269~0.163  | -0.119~0.352 | 0.007~0.478       |
|                        | $p$           | <b>0.031</b>              | 0.524         | 0.406        | <b>0.014</b>      | <b>0.029</b>              | 0.633         | 0.335        | <b>0.048</b>      |
| $\Delta$ Fusi. tau     | $\beta_{std}$ | 0.295                     | 0.033         | 0.127        | 0.694             | 0.293                     | -0.099        | 0.150        | 0.615             |
|                        | 95% ci        | 0.081~0.509               | -0.181~0.247  | -0.037~0.291 | 0.530~0.857       | 0.081~0.505               | -0.311~0.114  | -0.030~0.331 | 0.435~0.796       |
|                        | $p$           | <b>0.009</b>              | 0.766         | 0.135        | <b>&lt; 0.001</b> | <b>0.008</b>              | 0.365         | 0.107        | <b>&lt; 0.001</b> |
| $\Delta$ Inf-temp. tau | $\beta_{std}$ | 0.110                     | 0.119         | 0.049        | 0.786             | 0.119                     | -0.025        | 0.059        | 0.743             |
|                        | 95% ci        | -0.111~0.331              | -0.102~0.340  | -0.098~0.195 | 0.639~0.932       | -0.103~0.341              | -0.247~0.197  | -0.100~0.218 | 0.584~0.902       |
|                        | $p$           | 0.333                     | 0.295         | 0.518        | <b>&lt; 0.001</b> | 0.298                     | 0.825         | 0.468        | <b>&lt; 0.001</b> |
| $\Delta$ Mid-temp. tau | $\beta_{std}$ | 0.036                     | 0.135         | 0.062        | 0.736             | 0.051                     | 0.087         | 0.056        | 0.739             |
|                        | 95% ci        | -0.186~0.258              | -0.087~0.357  | -0.099~0.222 | 0.575~0.896       | -0.172~0.273              | -0.136~0.309  | -0.104~0.216 | 0.579~0.900       |
|                        | $p$           | 0.753                     | 0.238         | 0.453        | <b>&lt; 0.001</b> | 0.656                     | 0.446         | 0.496        | <b>&lt; 0.001</b> |

$\Delta$ : longitudinal tau increase; Amygd.: amygdala; Entorh.: entorhinal; Parahip.: parahippocampal; Fusi.: fusiform; Inf-temp.: inferior temporal; Mid-temp.: middle temporal.

$P < 0.05$  was indicated in bold.

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