SUPPLEMENTARY MATERIAL

S1. Testing for Partial Volume Effects

Linear mixed effects models were used to test for evidence of partial volume effects in the PET binding estimates. The first model investigated whether region of interest volume was a significant predictor of MK-6240 SUVR. The second model added global PiB DVR as a covariate since cases that were high in PiB also tended to be high in MK-6240 likely due to more advanced disease pathophysiology. These models were tested in the entorhinal cortex and hippocampus regions of interest. In all regions and models, the region of interest volume was not a significant predictor of MK-6240 SUVR (Supplementary Table S3). The lack of association between region volume and MK-6240 SUVR suggests partial volume effects were not influencing PET binding estimates.

S2. Influence of Entorhinal Cortex T+/- Threshold on Primary Model

To investigate the influence of the T+/- threshold in the entorhinal cortex on the main model outcomes, the analysis was repeated using thresholds that were 0.5, 1.0, and 1.5 standard deviations above the mean MK-6240 SUVR in the entorhinal cortex for defining T+/- status. Summaries of group membership and statistical outcomes are shown below in Supplementary Table S1 with the threshold and distributions of global PiB DVR and Entorhinal Cortex MK-6240 SUVR shown in Supplementary Figure S1. Regardless of threshold used to define T+/-, the results were consistent with the primary analysis suggesting a robust finding regarding the influence of elevated amyloid and tau affecting retrospective cognition.

S3. Influence of Using the Hippocampus for T+/- on Primary Model

Additional sensitivity analyses of the main model were performed to determine if using the hippocampus to define T+/- would affect the primary model outcomes. Similar to the analysis in S1, T+/- thresholds of 0.5, 1.0, 1.5, and 2.0 standard deviations above the mean MK-6240 SUVR in the hippocampus were used to define T+/- status, and the primary model was run for each biomarker stratified set. Summaries of group membership and statistical outcomes are shown below in Supplementary Table S2 with the threshold and distributions of global PiB DVR and Hippocampus MK-6240 SUVR shown in Supplementary Figure S2. Regardless of threshold used to define T+/-, the results

were consistent with the primary analysis suggesting a robust finding regarding the influence of elevated amyloid and tau affecting retrospective cognition.

Supplementary Tables

Supplementary Table S1: Association between regions of interest volume and MK-6240 SUVR

Entorhinal Cortex: MK-6240 SUVR ~ ROI Volume + intercept		
Parameter	**β (SE)**	**p**
Intercept	1.27 (0.17)	<0.001
ROI Volume	-0.04 (0.03)	0.25
Entorhinal Cortex: MK-6240 SUVR ~ ROI Volume + PiB DVR + intercept		
Intercept	0.07 (0.16)	0.69
ROI Volume	-0.005 (0.024)	0.85
PiB DVR	0.89 (0.08)	<0.001
Hippocampus: MK-6240 SUVR ~ ROI Volume + intercept		
Intercept	1.16 (0.15)	<0.001
ROI Volume	-0.03 (0.02)	0.11
Hippocampus: MK-6240 SUVR ~ ROI Volume + PiB DVR + intercept		
Intercept	0.28 (0.14)	0.05
ROI Volume	-0.009 (0.016)	0.59
PiB DVR	0.61 (0.06)	<0.001

Linear regression outcomes for models investigating potential partial volume effects. Region, regression model, parameter estimates, standard errors (SE) and significance are reported for all regions and models tested. No models indicated a relationships between region of interest (ROI) volume and MK-6240 SUVR suggesting partial volume effects were not impacting MK-6240 SUVR estimates.

Supplementary Table S2: Entorhinal Cortex Tau Threshold Primary Model Sensitivity Analysis

ERC T+/- Threshold (SD above A- mean)	1.07 SUVR (0.5)	1.13 SUVR (1.0)	1.20 SUVR (1.5)	1.27 SUVR (2.0)
Group Membership				
A-T- n(%)	90 (53.9%)	111 (66.5%)	119 (71.3%)	124 (74.3%)
A-T+ n(%)	39 (23.4%)	18 (10.8%)	10 (6.0%)	5 (3.0%)
A+T- n(%)	17 (10.2%)	18 (10.8%)	18 (10.8%)	23 (13.8%)
A+T+ n(%)	21 (12.6%)	20 (12.0%)	20 (12.0%)	15 (9.0%)
Main Model Outcomes (Effect p-value)				
Sex	<0.0001	<0.0001	<0.0001	<0.0001
WRAT-III	<0.0001	<0.0001	<0.0001	<0.0001
Practice	0.0016	0.0003	0.0004	0.0009
Age	<0.0001	<0.0001	<0.0001	<0.0001
Group	0.57	0.47	0.69	0.24
GroupXAge	<0.0001	<0.0001	<0.0001	<0.0001
Simple PACC-3 Slopes [β (standard error)]				
A-T-	-0.032 (0.008)	-0.031 (0.008)	-0.32 (0.008)	-0.032 (0.008)
A-T+	-0.035 (0.009)	-0.050 (0.012)	-0.044 (0.015)	-0.041 (0.021)
A+T-	-0.030 (0.014)	-0.027 (0.013)	-0.027 (0.013)	-0.041 (0.012)
A+T+	-0.120 (0.013)	-0.130 (0.013)	-0.129 (0.013)	-0.140 (0.015)
Group Contrasts Between PACC-3 Slopes (p-value)				
A-T- minus A-T+	1.00	0.36	0.85	0.97
A-T- minus A+T-	1.00	0.98	0.96	0.83
A-T- minus A+T+	<0.0001	<0.0001	<0.0001	<0.0001
A-T+ minus A+T-	0.99	0.41	0.76	1.00
A-T+ minus A+T+	<0.0001	<0.0001	<0.0001	0.0002
A+T- minus A+T+	<0.0001	<0.0001	<0.0001	<0.0001

Primary model outcomes and interaction details for sensitivity analyses investigating the influence of the T+/- threshold in the entorhinal cortex (ERC) on the primary model. Standard deviations (SD) above the mean MK-6240 SUVR in the entorhinal cortex of the A- group are shown at the top of the table with each column corresponding to group membership and model outcomes using that threshold.

Supplementary Table S3: Hippocampus Tau Threshold Primary Model Sensitivity Analysis

HC T+/- Threshold (SD above A- mean)	SUVR (0.5)	SUVR (1.0)	SUVR (1.5)	SUVR** (2.0)
Group Membership				
A-T-	57 (52.1%)	106 (63.5%)	120 (71.9%)	128 (76.6%)
A-T+	42 (25.1%)	23 (13.8%)	9 (5.4%)	1 (0.6%)
A+T-	17 (10.2%)	20 (12.0%)	22 (13.2%)	24 (14.4%)
A+T+	21 (12.6%)	18 (10.8%)	16 (9.6%)	14 (8.4%)
Main Model Sensitivity Analysis Outcomes (Effect p-value)				
Sex	<0.0001	<0.0001	<0.0001	<0.0001
WRAT-III	<0.0001	<0.0001	<0.0001	<0.0001
Practice	0.0031	0.0037	0.0021	0.0007
Age	<0.0001	<0.0001	<0.0001	<0.0001
Group	0.28	0.13	0.35	0.08
GroupXAge	<0.0001	<0.0001	<0.0001	<0.0001
Simple PACC-3 Slopes [β (standard error)]				
A-T-	-0.036 (0.008)	-0.036 (0.008)	-0.034 (0.008)	-0.033 (0.007)
A-T+	-0.030 (0.010)	-0.024 (0.012)	-0.033 (0.018)	-
A+T-	-0.037 (0.014)	-0.044 (0.013)	-0.045 (0.012)	-0.041 (0.012)
A+T+	-0.113 (0.013)	-0.118 (0.014)	-0.130 (0.015)	-0.145 (0.015)
Group Contrasts Between PACC-3 Slopes (p-value)				
A-T- minus A-T+	0.90	0.71	1.00	-
A-T- minus A+T-	1.00	0.91	0.77	0.69
A-T- minus A+T+	<0.0001	<0.0001	<0.0001	<0.0001
A-T+ minus A+T-	0.96	0.53	0.94	-
A-T+ minus A+T+	<0.0001	<0.0001	<0.0001	-
A+T- minus A+T+	<0.0001	<0.0001	<0.0001	<0.0001

Primary model outcomes and interaction details for sensitivity analyses investigating the influence of using the hippocampus with various thresholds for T+/- on the primary model. Standard deviations (SD) above the mean MK-6240 SUVR in the hippocampus of the A- group are shown at the top of the table with each column corresponding to outcomes using that threshold. **For the threshold using two standard deviations above the MK-6240 mean in A- people only one person remained in the A-T+ group. This person was grouped in the A-T- group and the analysis only had three groups.

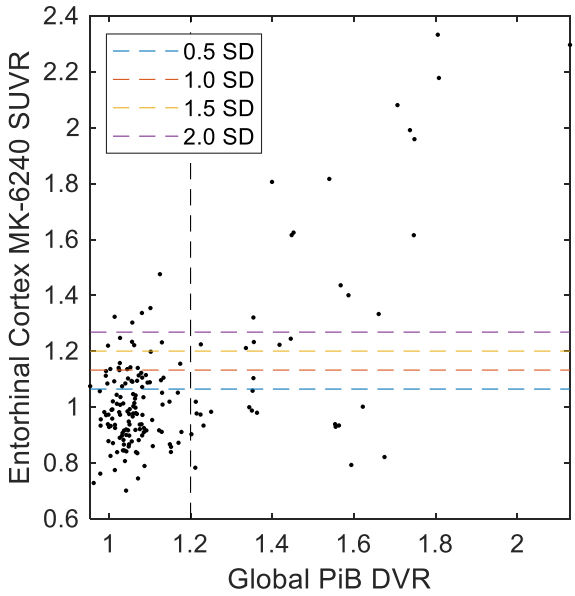
Supplementary Table S4: MK-6240 and Age Associations in PiB(-)

Region	R^2
Braak I Region	**0.02**
Braak II Region	**0.01**
Braak III Region	**0.00**
Braak IV Region	**0.00**
Braak V Region	**0.00**
Braak VI Region	**0.00**
Amygdala	**0.02**
Posterior Cingulate	**0.00**
Precuneus	**0.00**
Lingual Gyrus	**0.01**
Caudate	**0.00**
Putamen	**0.07**

Pearson Coefficient of Determination (R^2) for the association between age and MK-6240 SUVR in various regions in only amyloid negative individuals (n=129). For all regions, minimal to no associations were observed between MK-6240 SUVR and age in persons that were amyloid negative at the time of their MK-6240 PET scan.

Supplementary Figures

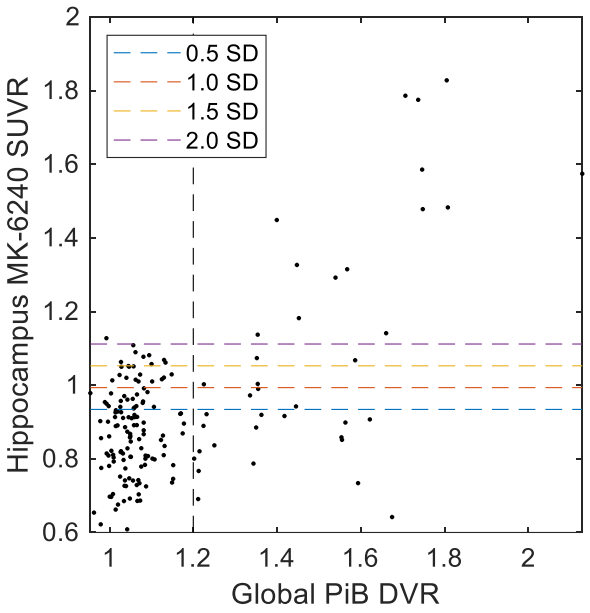
Supplementary FIG. 1 Entorhinal Cortex Thresholds for Sensitivity Analysis S1



Scatter plot showing the distribution of entorhinal cortex MK-6240 and global PiB DVR with various thresholds used for defining T+/- status for sensitivity analyses in supplemental section S1. Thresholds correspond to the number of standard deviations above the mean MK-6240 SUVR of the A- group in the entorhinal cortex.

SD = standard deviation, SUVR = standard uptake value ratio, PiB DVR = Pittsburgh Compound B distribution volume ratio

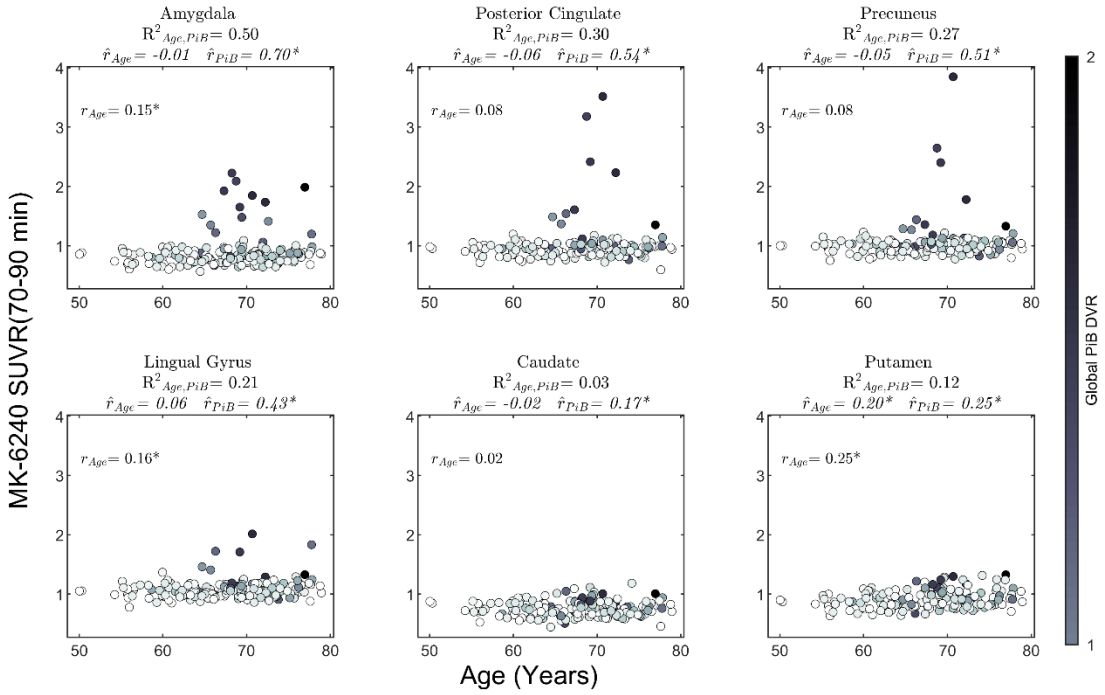
Supplementary FIG. 2 Hippocampus Thresholds for Sensitivity Analysis S1



Scatter plot showing the distribution of hippocampus MK-6240 and global PiB DVR with various thresholds used for defining T+/- status for sensitivity analyses in supplemental section S2. Thresholds correspond to the number of standard deviations above the mean MK-6240 SUVR of the A- group in the hippocampus.

SD = standard deviation, SUVR = standard uptake value ratio, PiB DVR = Pittsburgh Compound B distribution volume ratio

Supplementary FIG. 3 Associations between MK-6240, age and PiB in exploratory regions.



Pearson correlations between MK-6240 SUVR, global PiB DVR and age in exploratory regions. The percentage of variance in MK-6240 explained by both global PiB DVR and age ($R^2_{Age,PiB}$) is shown under the region name with the partial correlation between MK-6240 and age ($\hat{r}_{Age}$, global PiB partialed out) and the partial correlation between MK-6240 and global PiB DVR ($\hat{r}_{PiB}$, age partialed out) adjusted for age shown in the bottom of the title. The simple Pearson correlation between MK-6240 and age not adjusted for global PiB is shown in the top left corner of each plot.

*indicates $p<0.05$, unadjusted for multiple comparisons.