

Fluorodeoxyglucose Metabolism Associated With Tau-Amyloid Interaction Predicts Memory Decline

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Objective: The aim of this article was to evaluate in normal older adults and preclinical Alzheimer's disease (AD) the impact of amyloid and regional tauopathy on cerebral glucose metabolism and subsequent memory decline.

Methods: We acquired positron emission tomography using F18 flortaucipir (tau), C11 Pittsburgh compound B (amyloid), and F18 fluorodeoxyglucose (FDG) in 90 clinically normal elderly of the Harvard Aging Brain Study.

Results: Posterior cingulate metabolism decreased when both amyloid and neocortical tau were high and predicted subsequent memory decline in a larger sample of normal elderly. In contrast, frontal hypometabolism related to the common age-related entorhinal tauopathy, but this dysfunction was independent of amyloid, and did not predict significant memory decline. Neocortical tauopathy was positively associated with metabolism in individuals with sub-threshold amyloid, suggesting that glucose metabolism increases before decreasing in the course of preclinical AD.

Interpretation: Our study identified a synergistic effect of amyloid and tau deposits and demonstrated, for the first time, in normal elderly its link to AD-like hypometabolism and to AD-like memory decline. The amyloid effect was observed with tau in neocortex, but not with tau in entorhinal cortex, which is the common site of age-related tauopathy. Entorhinal tau was associated with frontal hypometabolism, but this dysfunction was not associated with memory loss.

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Alzheimer's disease (AD) is a neurodegenerative disorder expressed clinically by a progressive memory decline leading to dementia in which brain amyloid-beta ($A\beta$) plaques and tau neurofibrillary tangles slowly accumulate as the cardinal pathologic features.^{1,2} Autopsy studies suggest that tau pathology appears in the medial temporal lobe before the appearance of $A\beta$ pathology in neocortex,³ and that both pathologies appear before cognitive decline, defining a preclinical, asymptomatic stage of AD^{3,4} that may progress to the symptomatic stage, AD dementia.⁵ Neural dysfunction and cell death are thought

to result from the interaction of the two pathologies, but our ability to assess the linkage between early pathology and dysfunction during life has been quite limited. Furthermore, cognitive symptoms correlate best with autopsy evidence of tau deposition that has expanded from medial temporal lobe to neocortex,¹ but the differential association of medial temporal and neocortical tau depositions with in vivo brain function has not been evaluated.

The development of in vivo imaging of tau pathology followed the introduction of the selective tau ligand, ¹⁸F flortaucipir (FTP; also known as AV1451 or T807), used with

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TABLE 1. Demographics, Genetics, and Cognitive Data

	Whole Sample	Low-PiB Participants	High-PiB Participants
Sample 1: participants with ¹⁸ F FDG, ¹¹ C PiB, and ¹⁸ F FTP			
N	90	57	33
Age, years	75.6 (6.3)	74.2 (6.1)**	77.8 (5.9)**
Education, years	15.8 (3.1)	15.7 (3.2)	15.9 (2.9)
Female, % (N)	55.6 (50)	54.5 (31)	57.6 (19)
E4 carriers, % (N)	30.0 (27)	14.0 (8)**	57.6 (19)**
MMSE (/30)	29.2 (1.0)	29.3 (0.9)	29.0 (1.2)
Logical Memory (/25)	15.2 (4.0)	15.3 (3.9)	15.0 (4.2)
Sample 2: participants with ¹⁸ F FDG, ¹¹ C PiB, and memory follow-up			
N	277	198	79
Age, years	73.5 (6.1)	73.0 (6.2)**	74.9 (5.5)**
Education, years	15.8 (3.1)	15.6 (3.2)	16.3 (2.9)
Female, % (N)	59.2 (164)	57.6 (114)	64.6 (51)
E4 carriers, % (N)	26.4 (73)	15.2 (30)**	54.4 (43)**
MMSE (/30)	29.0 (1.0)	29.1 (1.0)*	28.7 (1.0)*
Logical memory (/25)	13.7 (3.3)	13.6 (3.4)	13.9 (3.0)
Age and cognitive data are given at the closest time of ¹⁸ F FTP imaging in sample 1 and at baseline in sample 2. Significant differences between low- and high-PiB participants are highlighted: two-sided * <i>p</i> < 0.050; ** <i>p</i> < 0.010. FDG = fluorodeoxyglucose; FTP = flortaucipir; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B.			

positron emission tomography (PET).^{6–11} Tau-PET permits for the first time a regional assessment of tau pathology in relation to age, amyloidosis, and brain functional integrity, measured with ¹⁸F fluorodeoxyglucose (FDG-PET). We sought to determine whether the anatomic pattern of association cortex dysfunction typically associated with AD^{12–14} was related to brain amyloidosis and tau deposition detected in clinically normal elderly. Second, we aimed to determine whether A β - and tau-associated hypometabolism related to subsequent memory decline, using thus A β - and tau-PET imaging to identify brain regions in which glucose metabolism predicts future memory decline in older adults with normal memory at baseline. Our results indicate that the interaction of AD pathological hallmarks, A β and neocortical tau, relates to posterior cingulate hypometabolism, which, in turn, predicts memory deterioration.

Patients and Methods

Participants

Participants included in this report were recruited from the Harvard Aging Brain Study (HABS), a longitudinal study of aging and preclinical AD (Table 1). They were all clinically

normal older adults at the time of FTP imaging: Mini-Mental State Examination (MMSE) was $\geq 26/30$, and Logical Memory II subscale (Delayed Paragraph Recall) was normal for education: $\geq 9/25$ if education ≥ 16 years, $\geq 6/25$ otherwise. Ninety participants with FTP (tau), Pittsburgh compound B (PiB; A β), and FDG (glucose metabolism) PET examinations conducted over the same year were included in a first study sample. Two hundred seventy-seven participants with longitudinal memory assessments, Pittsburgh compound B (PiB), and FDG-PET examinations were included in a second sample. All participants underwent a comprehensive medical and neurological evaluation and none had serious medical or neurological conditions, history of alcoholism, drug abuse, or family history of dominant AD. None were clinically depressed when entering the study (Geriatric Depression Scale $< 11/30$) or had other psychiatric illnesses. Participants provided informed consent and were studied under protocols approved by the Partners Human Research Committee at the Massachusetts General Hospital.

Neuropsychological Assessment

We evaluated changes in memory performance using the Free and Cued Selective Reminding Test (FCSRT).¹⁵ The FCSRT is a 16-item verbal memory test, selectively reminding items that

have been forgotten over three successive trials. In the encoding phase, each item is presented with a semantic cue. Every four items, an immediate cued recall controls that encoding has been adequately performed. In the delayed recall phase, participants are first asked to freely recall as many items as possible; next, categorical cueing is provided for those items that were not spontaneously retrieved. We used the total free recall (/48) and the total cued recall (/48) performance over the three trials. HABS participants undergo annual cognitive testing, including the FCSRT. All together, the 277 HABS participants included in this study had 1,230 FCSRT evaluations, on average: 4.4 ± 1.2 per participant (minimum, 2; maximum, 6 evaluations). The average follow-up duration was 3.6 ± 1.3 years (minimum, 0.9; maximum, 5.6).

Brain Imaging Procedures

Magnetic resonance imaging (MRI) was performed on a Siemens 3 Tesla Tim Trio (Siemens, Erlangen, Germany) and included a three-dimensional (3D) structural T₁-weighted scan using a repetition time = 6,400ms, echo time = 2.8ms, flip angle = 8 degrees, and a voxel size = $1 \times 1 \times 1.2$ mm. Images were processed with Freesurfer software (v5.1; <http://surfer.nmr.mgh.harvard.edu>), to identify gray, white, and pial surfaces to permit region of interest (ROI) parcellation based on the Desikan-Killiany atlas.

¹⁸F-FTP, ¹⁸F-FDG, and ¹¹C-PiB were prepared and acquired according to previously published⁸ protocols. The mean \pm standard deviation (SD) lag time between PET examinations was 11.3 ± 12.3 weeks (maximum, 50.9). PET data were acquired on a Siemens ECAT HR+ scanner using a 3D mode; 63 image planes; 15.2-cm axial field of view; 5.6-mm transaxial resolution; and 2.4-mm slice interval. T807 was acquired from 80 to 100 minutes (min) after a 9.0- to 11.0-millicurie (mCi) bolus injection in 4×5 -min frames. FDG was acquired from 45 to 75 minutes after a 5- to 10-mCi bolus injection in 6×5 -min frames. PiB was acquired with an 8.5- to 15-mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12×15 seconds, 57×60 seconds). PET images were coregistered to the corresponding T₁ image for each subject using six degrees of freedom, rigid body registration, and structural ROIs, as determined by Freesurfer, were mapped into native PET space in SPM8. FTP and FDG were expressed as standard uptake volume ratios (SUVRs) and PiB as the distribution volume ratio (DVR) using the Logan graphical method, with slopes extracted from the 40- to 60-minute time frame. All PET data used the cerebellum as the reference region (gray matter only) and were corrected for partial volume effects using MRI-based methods (geometric transfer matrix^{16,17} for ROI and extended Müller-Gärtner^{17,18} for surface analyses). The point spread function for partial volume correction was estimated at 6mm.

PiB retention was assessed using a large neocortical aggregate that included superior frontal, rostral middle frontal, rostral anterior cingulate, medial orbitofrontal, inferior and middle temporal, inferior parietal, and precuneus (Freesurfer-defined FLR region). Specific analyses were conducted in low- and

high-PiB groups: A Gaussian mixture model defined the threshold for PiB positivity (DVR = 1.34) using the baseline PiB PET scans obtained from the 277 HABS participants, as previously described.¹⁹ FDG and FTP retention were assessed using vertex-wise surface mapping of the cortical ribbon (gray matter threshold: 0.25; smoothing kernel: 10mm) and using Freesurfer-defined ROIs.

Statistical Analyses

Mean and *t*-statistics maps were computed using the GLM Flex tools (mrtool.mgh.harvard.edu) implemented in Matlab 8.4 (R2014b; The MathWorks, Inc., Natick, MA). Threshold was selected by applying a correction for multiple comparisons using the false discovery rate (FDR; $q < 0.050$) in the local correlation map between tracers (Fig 1B, left). This correction was obtained for a $T = 2.65$, $p < 0.010$ and used for all subsequent analyses. For ROI analyses, Lilliefors tests confirmed that FDG data were close to normal distribution ($K < 0.069$ for each FDG ROI, $p > 0.360$; criterion for 90 subjects: 0.094). We therefore used linear regressions to assess the correlations between FTP and FDG ROIs, with and without adjusting for covariates. We used linear mixed models with a random intercept per subject to relate FDG ROI data to changes in memory.

Results

Temporal Tau Deposition Is Associated With Local FDG Hypometabolism

We first asked whether tau deposits were associated with locally altered glucose metabolism. We computed a mean FTP and a mean FDG map, averaging SUVR values in each vertex across all participants of sample 1. In widespread portions of the temporal and inferior frontal lobes, the average FTP signal was high whereas the average FDG signal was low (Fig 1A). In contrast, in the primary cortices, the average FTP signal was low and the average FDG signal high. Each FTP vertex was then correlated with its corresponding FDG vertex to evaluate local associations between tracers, adjusting for age. Greater local FTP binding was associated with lower FDG metabolism in the temporal lobe, specifically in the entorhinal and inferior temporal cortices (Fig 1B, left: arrow indicates the peak p value = 4×10^{-5} , minimal *t*-statistic = -4.3). We next inquired whether A β burden increased the association between tau and brain dysfunction: We evaluated at each vertex the association between the FDG-PET signal and the statistical interaction between the corresponding local FTP signal and a global continuous measure of PiB DVR binding. The local negative correlation between FTP and FDG increased with increasing levels of PiB binding (Fig 1B, right: peak $p = 9 \times 10^{-6}$, $t = -4.7$). High-PiB participants had significant temporal hypometabolism locally associated with tau-PET signal (Fig 1C, right: peak $p = 4 \times 10^{-5}$, $t = -4.8$)

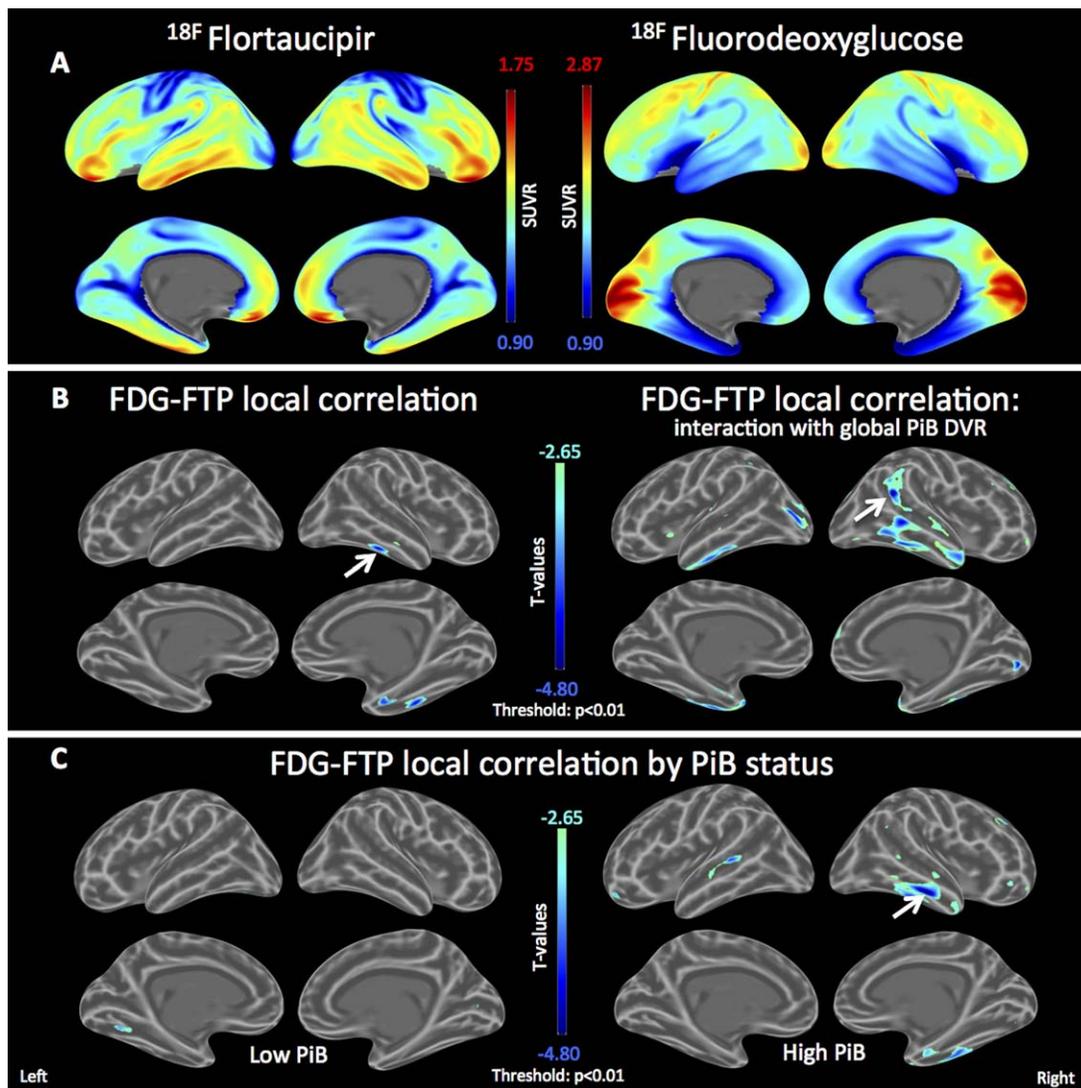


FIGURE 1: Tau deposition locally associated with hypometabolism in the temporal lobe. (A) Mean SUVR maps for flortaucipir (FTP) and fluorodeoxyglucose (FDG) across the 90 study participants. (B) Left: local correlation map between FTP and FDG, adjusting for age. Temporal tau deposition is locally associated with FDG hypometabolism. Right: interaction effect of global continuous PiB on the local FTP-FDG association, adjusting for age. FTP-associated temporal hypometabolism is dependent on PiB levels. (C) Local FTP-associated hypometabolism is only observed in the high-PiB participants. Scale: Cold colors represent hypometabolism. Threshold: $T < -2.65$; $p < 0.010$. Arrows indicate peak statistics. DVR = distribution volume ratio; PiB = Pittsburgh compound B; SUVR = standard uptake value ratio.

whereas the association in low-PiB participants was very low or absent (Fig 1C, left: peak $p = 0.001$, $t = -3.6$).

Temporal Neocortical Tau Is Associated With Distant, $A\beta$ -Dependent, FDG Hypometabolism

We then asked whether tau deposition in specific regions, where tau was locally associated with hypometabolism, also related to altered metabolism in distant cortical regions. We extracted the FTP signal from two bilateral ROIs: entorhinal and inferior temporal, defined anatomically using Freesurfer, and regressed the FTP signal from these ROIs into the vertex-wise FDG data, adjusting for age. We found that, in addition to the local association,

entorhinal FTP was associated with hypometabolism in nearby temporal regions and in inferior frontal, insular, and cingulate gyri (Fig 2A, left: peak $p = 2 \times 10^{-6}$, $t = -5.1$). In contrast, FTP binding in the inferior temporal neocortex was not associated with hypometabolism, except in very small nearby areas (Fig 2A, right: peak $p = 2 \times 10^{-4}$; $t = -3.9$). When correlating global PiB binding to vertex-wise FDG, virtually no effects were observed (peak $p > 0.001$). Thus, neither inferior temporal (ie, neocortical) tau nor $A\beta$ had major metabolic impact in our sample of normal older adults.

We hypothesized that the observed absence of an effect of either neocortical tau or $A\beta$ on glucose metabolism

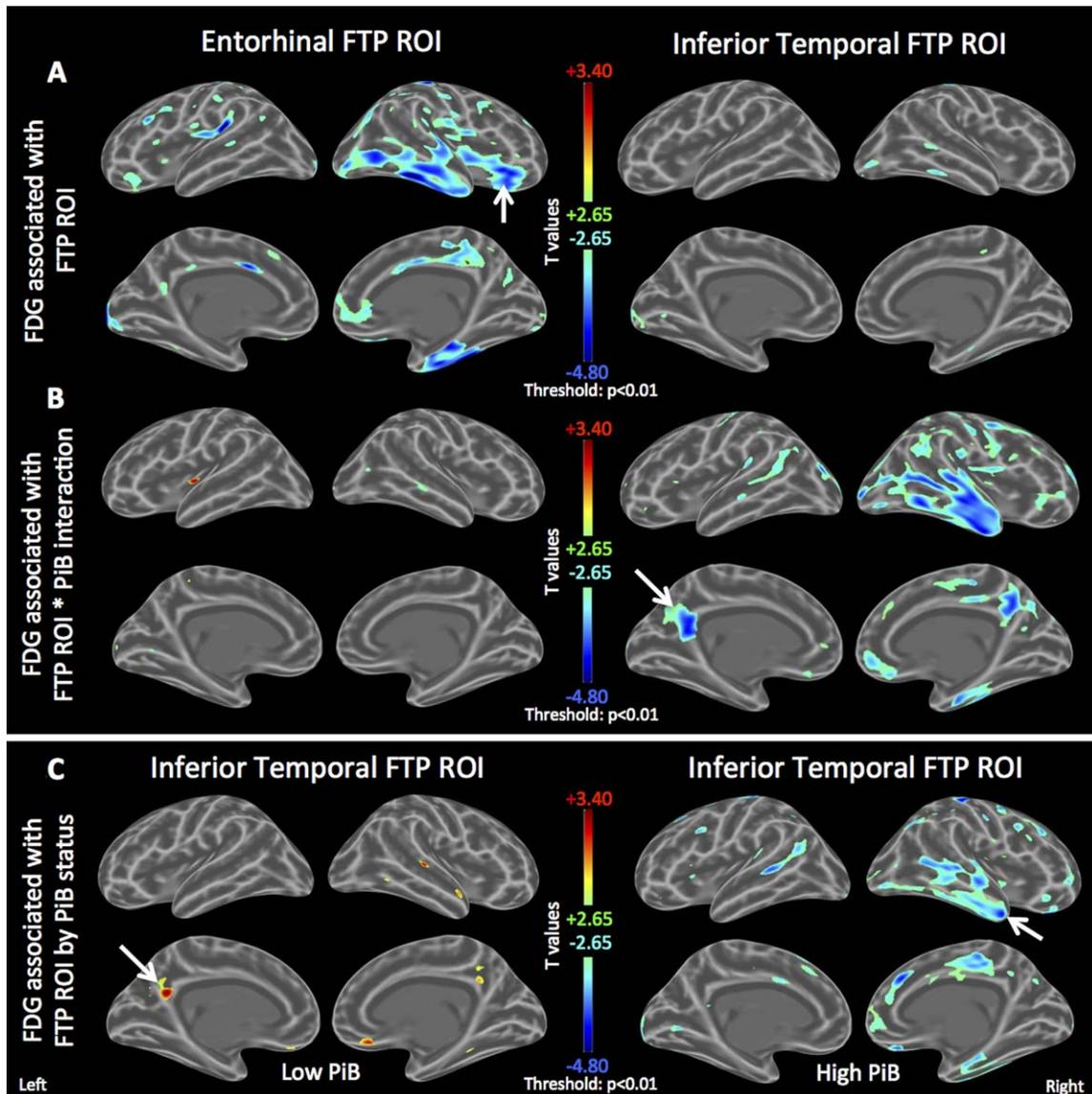


FIGURE 2: Tau deposition in the inferior temporal neocortex associated with amyloid-dependent hypometabolism. Age-adjusted FDG maps showing the association between the FDG-PET signal in each vertex and FTP (tau-PET) signal in two regions of interest (ROIs): entorhinal versus inferior temporal. (A) Left: Entorhinal FTP-associated FDG hypometabolism includes inferior frontal, insular, and cingulate gyri. Right: Inferior temporal FTP-associated FDG hypometabolism is restricted to the temporal lobe. (B) Interaction effect of global continuous PiB and FTP ROIs on FDG, adjusting for main effects and age. Entorhinal FTP-associated hypometabolism is not PiB dependent (left) whereas inferior temporal FTP is associated with PiB-dependent temporoparietal FDG hypometabolism (right). Inferior temporal FTP is associated with FDG hypermetabolism in the subset of low-PiB individuals (left), but FDG hypometabolism in the subset of high-PiB individuals (right). See Figure Sup1 for entorhinal FTP. (C) Scale: Cold colors represent hypometabolism. Threshold: $T > \pm 2.65$; $p < 0.010$. Arrows indicate peak statistics. FDG = fluorodeoxyglucose; FTP = flortaucipir; PET = positron emission tomography; PiB = Pittsburgh compound B.

might be attributed to differential tau relationships between those with high- and low- $A\beta$ burden. We assessed the joint association of global $A\beta$ burden and regional tau and found a highly significant interaction between global PiB and inferior temporal FTP predicting FDG metabolism in the bilateral posterior cingulate areas, unilaterally in right anterior temporal and, to a lesser extent, in other temporoparietal areas (Fig 2B, right: peak $p = e-5$; $t = -4.6$). High-PiB participants had hypometabolism (Fig 2C, right: peak $p =$

9×10^{-5} ; $t = -4.5$) whereas, in contrast, low-PiB participants had *increased* metabolism associated with higher levels of inferior temporal tau (Fig 2C, left: peak $p = 0.001$; $t = +3.4$). Unlike inferior temporal FTP, the interaction between PiB and entorhinal FTP was not associated with FDG metabolism (Fig 2B, left; see Fig 3 for separate PiB subsets).

In summary, surface analyses indicated that hypometabolism associated with entorhinal tau was not driven

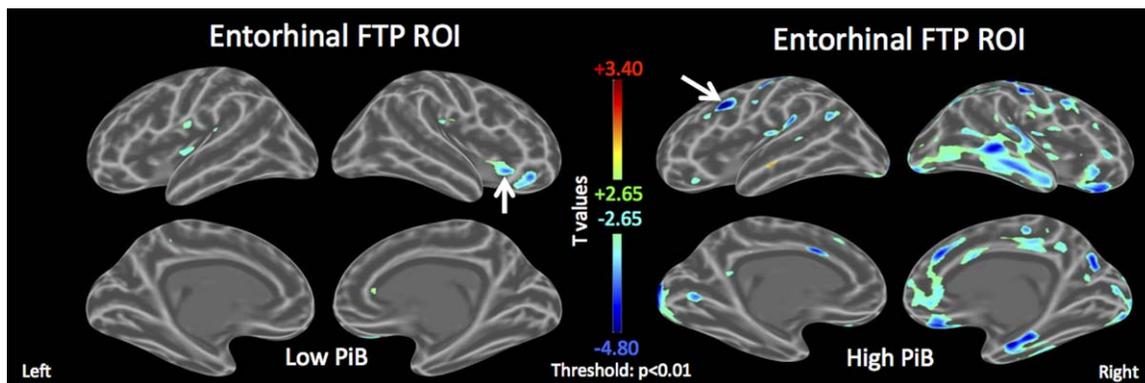


FIGURE 3: Tau deposition in the entorhinal cortex associated with amyloid-independent inferior frontal and insular hypometabolism. Age-adjusted FDG maps in the subsets of low- and high-PiB individuals showing the association between the FDG-PET signal in each vertex and entorhinal FTP (tau-PET) signal. **Left:** In the low-PiB individuals, entorhinal FTP is associated with inferior frontal and insular hypometabolism (arrow indicates peak p value = 3×10^{-4} , minimal $t = -3.9$). **Right:** In the high-PiB individuals, entorhinal FTP is associated with widespread temporoparietal hypometabolism, including locally in the entorhinal cortex (arrow indicates peak p value = 4×10^{-6} , minimal $t = -5.6$). Scale: Cold colors represent hypometabolism. Threshold: $T \geq \pm 2.65$, $p < 0.010$. Arrows indicate peak statistics. PET = positron emission tomography; PiB = Pittsburgh compound B; ROI = region of interest.

by $A\beta$ burden and did not match the regional anatomy typically associated with AD, whereas FDG associated with inferior temporal tau was driven by $A\beta$ and primarily involved the temporal and parietal lobes, in a set of regions where metabolism is associated with AD, defined clinically¹⁴ or pathologically.²⁰

ROI ANALYSES. We aimed to confirm and further control our vertex-wise findings using FDG ROIs to assess the effects of covariates on the association between tau and metabolism: age, sex, education, $A\beta$, and apolipoprotein E (APOE) $\epsilon 4$ status. We investigated the associations between entorhinal and inferior temporal FTP and four bilateral Freesurfer-defined FDG ROIs. Entorhinal and inferior temporal FDG ROIs were selected to assess the local association with the corresponding FTP ROIs. We also selected the regions that included the maximal association with entorhinal or inferior temporal FTP in the vertex-wise maps: inferior frontal and posterior cingulate, respectively, labeled “pars triangularis” and “isthmus cingulate” in Freesurfer. ROI results are summarized in Table 2 and illustrated in Figure 4.

We first predicted FDG signal in ROIs with PiB or FTP ROIs without adjusting for any covariate (Table 2, box 1): PiB did not significantly predict FDG-PET signal in any ROI. Entorhinal FTP, in contrast, was significantly associated with low metabolism in all FDG ROIs. Inferior temporal FTP was only associated with hypometabolism locally, in the inferior temporal, and in the nearby entorhinal cortex.

We next introduced age, sex, education, PiB, and $\epsilon 4$ status as covariates in the FTP-FDG models (box 2): The associations between entorhinal FTP and FDG

ROIs remained close to significance after all adjustments, but inferior temporal FTP did not relate to any FDG ROI. To assess the relative strength of these associations, we conducted backward selection models for each FDG ROI with FTP ROIs, PiB, and covariates as predictors. Entorhinal FTP consistently remained in the models whereas inferior temporal FTP and PiB were excluded.

Prediction of signal in FDG ROIs by the interaction between PiB status and FTP ROIs confirmed our vertex-wise findings (box 3A): An interaction between PiB status and inferior temporal FTP, but not entorhinal FTP, was associated with hypometabolism in the posterior cingulate (Fig 4, right). Results were driven by significant hypometabolism in the high-PiB participants and by a positive association of marginal significance (Table 2, box 3B; $p = 0.121$) in the low-PiB participants.

This latter result suggested the hypothesis that neocortical tau deposition may be associated with increased metabolism at $A\beta$ levels below our PiB-PET threshold. To further explore this possibility, we evaluated in the low-PiB participants the association between FDG and the interaction between a continuous PiB measure and inferior temporal FTP. We observed that posterior cingulate FDG increased with the PiB by FTP interaction, demonstrating that the positive FTP-FDG association was driven by individuals with subthreshold levels of PiB binding. In contrast, in the high-PiB subset, the PiB by FTP interaction related to decreased posterior cingulate FDG, confirming that among high- $A\beta$ individuals, FDG decreases with increasing levels of tau and $A\beta$ burden (box 3C).

To test whether the aforementioned impact of PiB status on the FTP-FDG associations was driven by

TABLE 2. Amyloid- and Tau-Associated Regional Hypometabolism

FDG Regions: (N = 90 normal elderly)	Posterior Cingulate ¹⁸F FDG	Inferior Frontal ¹⁸F FDG	Entorhinal Cortex ¹⁸F FDG	Inferior Temporal ¹⁸F FDG
1. Unadjusted				
¹¹ C PiB	-0.013 (0.041); <i>p</i> = 0.741	-0.027 (0.035); <i>p</i> = 0.436	-0.015 (0.020); <i>p</i> = 0.434	-0.042 (0.023); <i>p</i> = 0.066
Entorhinal ¹⁸ F FTP	-0.184 (0.074); <i>p</i> = 0.014	-0.131 (0.064); <i>p</i> = 0.042	-0.080 (0.036); <i>p</i> = 0.028	-0.151 (0.040); <i>p</i> = 0.0003
Inferior temporal ¹⁸ F FTP	-0.173 (0.130); <i>p</i> = 0.189	-0.109 (0.112); <i>p</i> = 0.331	-0.135 (0.062); <i>p</i> = 0.032	-0.190 (0.071); <i>p</i> = 0.009
2. Multiple regressions adjusting for age, sex, education, ¹¹ C PiB, and APOE ε4 status				
Entorhinal ¹⁸ F FTP	-0.197 (0.087); <i>p</i> = 0.026	-0.139 (0.079); <i>p</i> = 0.082	-0.068 (0.060); <i>p</i> = 0.117	-0.133 (0.046); <i>p</i> = 0.005
Inferior temporal ¹⁸ F FTP	-0.053 (0.158); <i>p</i> = 0.739	-0.069 (0.141); <i>p</i> = 0.626	-0.089 (0.076); <i>p</i> = 0.244	-0.105 (0.084); <i>p</i> = 0.217
Backward selection: Entorhinal ¹⁸ F FTP	-0.134 (0.074)^b; <i>p</i> = 0.073	-0.131 (0.064)^a; <i>p</i> = 0.042	-0.080 (0.036)^a; <i>p</i> = 0.028	-0.104 (0.041)^c; <i>p</i> = 0.012
3.A. ¹⁸ F FTP interactions with PiB status, age adjusted ^d				
Entorhinal ¹⁸ F FTP * PiB status	-0.044 (0.169); <i>p</i> = 0.793	-0.067 (0.152); <i>p</i> = 0.660	-0.132 (0.083); <i>p</i> = 0.116	-0.056 (0.093); <i>p</i> = 0.547
Inferior temporal ¹⁸ F FTP * PiB status	-0.866 (0.306); <i>p</i> = 0.006	-0.285 (0.283); <i>p</i> = 0.318	-0.206 (0.155); <i>p</i> = 0.188	-0.443 (0.171); <i>p</i> = 0.011
3.B. Low PiB participants, age adjusted (N = 57)				
Inferior temporal ¹⁸ F FTP	+0.524 (0.331); <i>p</i> = 0.121	+0.058 (0.299); <i>p</i> = 0.848	-0.016 (0.144); <i>p</i> = 0.913	+0.196 (0.164); <i>p</i> = 0.239
Inferior temporal ¹⁸ F FTP * ¹¹ C PiB	+9.41 (3.38); <i>p</i> = 0.007	-4.89 (3.27); <i>p</i> = 0.141	-1.89 (1.58); <i>p</i> = 0.239	-0.590 (1.77); <i>p</i> = 0.740
3.C. High PiB participants, age-adjusted (N = 33)				
Inferior temporal ¹⁸ F FTP	-0.258 (0.108); <i>p</i> = 0.023	-0.114 (0.111); <i>p</i> = 0.311	-0.158 (0.083); <i>p</i> = 0.067	-0.215 (0.087); <i>p</i> = 0.020
Inferior temporal ¹⁸ F FTP * ¹¹ C PiB	-0.467 (0.262); <i>p</i> = 0.086	-0.297 (0.266); <i>p</i> = 0.274	-0.202 (0.210); <i>p</i> = 0.345	-0.234 (0.219); <i>p</i> = 0.294
4. ¹⁸ F FTP interactions with APOE ε4 status, age adjusted ^d				
Entorhinal ¹⁸ F FTP * PiB status	+0.115 (0.148); <i>p</i> = 0.442	+0.106 (0.133); <i>p</i> = 0.428	-0.035 (0.074); <i>p</i> = 0.641	-0.011 (0.079); <i>p</i> = 0.885
Inferior temporal ¹⁸ F FTP * ε4 status	+0.108 (0.270); <i>p</i> = 0.688	+0.110 (0.241); <i>p</i> = 0.649	-0.152 (0.131); <i>p</i> = 0.249	-0.109 (0.144); <i>p</i> = 0.448

Unstandardized estimates (SD)—results significant at two-sided *p* < 0.100 are highlighted in bold. Subgroup results are only given if the FTP by PiB interaction is significant at *p* < 0.100 (in gray otherwise).

^aEntorhinal FTP was the only predictor left in the models predicting inferior frontal and entorhinal FDG.

^bEntorhinal FTP and age remained in the model predicting posterior cingulate FDG.

^cEntorhinal FTP, age, and APOE ε4 status remained in the model predicting inferior temporal FDG.

^dEstimates are given for the interaction term, adjusting for the main effects and age.

APOE = apolipoprotein E; FDG = fluorodeoxyglucose; FTP = flortaucipir; SD = standard deviation.

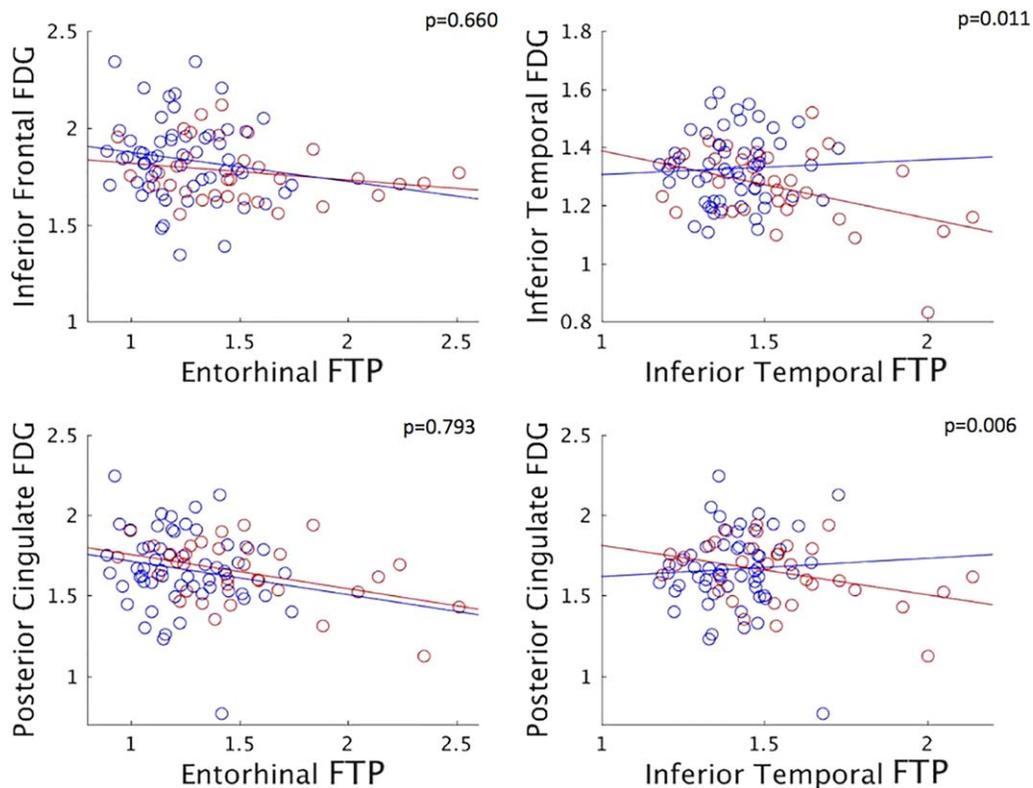


FIGURE 4: PiB status only has an effect on hypometabolism associated with inferior temporal tau, not with entorhinal tau. Scatter plots of FTP (tau-PET) against FDG SUVR signals in selected ROIs. *p* values in the right-upper corners indicate the significance of the interaction effect between FTP and PiB status on FDG (see Table 2, box 3.A). Dots are categorized by PiB status (blue: low-PiB [*n* = 57]; red: high-PiB [*n* = 33]). Entorhinal and inferior temporal FTP have different impact on posterior cingulate FDG in low-PiB, but similar in high-PiB, participants. FDG = fluorodeoxyglucose; FTP = flortaucipir; PET = positron emission tomography; PiB = Pittsburgh compound B; ROI = region of interest; SUVR = standard uptake value ratio.

APOE $\epsilon 4$ status, we verified that the associations between FTP and FDG were not different according to $\epsilon 4$ status (box 4). We also tested these interactions between $\epsilon 4$ and FTP in the low- and high-PiB participants separately, to investigate whether $\epsilon 4$ status played a role in the positive and negative associations observed between inferior temporal FTP and posterior cingulate FDG. In the low-PiB participants, the positive FTP-FDG association was stronger in the $\epsilon 4$ carriers than in the noncarriers (age-adjusted estimate for the $\epsilon 4$ by FTP interaction term: $+1.68 \pm 0.63$; $p = 0.010$; $n = 8$ carriers), although the low-PiB $\epsilon 4$ carriers were a small group. In contrast, in the high-PiB participants, the negative FTP-FDG association was not different according to $\epsilon 4$ status (estimate: -0.06 ± 0.26 ; $p = 0.825$; $n = 19$ carriers).

In summary, ROI analyses confirmed that the interaction (ie, the multiplicative association) of inferior temporal tauopathy and $A\beta$ burden specifically correlates with temporoparietal hypometabolism. When $A\beta$ is high, inferior temporal tau is associated with hypometabolism, and the association tends to be more pronounced with increasing levels of $A\beta$, regardless of $\epsilon 4$ status. When $A\beta$ is low, inferior temporal tau is positively associated with

glucose metabolism, specifically in those individuals with subthreshold levels of $A\beta$ or carrying an $\epsilon 4$ allele. Our findings suggest that tau-associated hypermetabolism may be an earlier sign of brain dysfunction associated with AD pathology than decreased metabolism.

Associations Between FDG Metabolism and Memory Decline

We next tested whether the brain regions in which we identified brain dysfunction associated with tau deposition would also be associated with memory decline. For this purpose, we studied a larger cohort (sample 2, $n = 277$) of normal older adults including the previously described participants, but also others who did not have FTP-PET imaging. We analyzed prospective longitudinal memory performances over a mean 4-year period following baseline FDG-PET (1–6 years). We used the four FDG ROIs previously described, hypothesizing that posterior cingulate would best predict future memory decline. Our proxy measure of memory decline was the FCSRT,¹⁵ a highly predictive indicator of progression to AD dementia²¹ and of AD pathology in the cerebrospinal fluid (CSF).²² Demographics of sample 2 participants

TABLE 3. Associations Between Longitudinal Free and Cued Recall Memory and Regional FDG Hypometabolism

FDG Regions: (N = 277 normal elderly)	Posterior Cingulate ¹⁸ F FDG	Inferior Frontal ¹⁸ F FDG	Entorhinal Cortex ¹⁸ F FDG	Inferior Temporal ¹⁸ F FDG
1. ¹⁸ F FDG main effect ^a				
Longitudinal free recall	1.08 (0.39); <i>p</i> = 0.006	0.67 (0.39); <i>p</i> = 0.086	0.84 (0.68); <i>p</i> = 0.217	0.90 (0.66); <i>p</i> = 0.173
Longitudinal cued recall	0.29 (0.15); <i>p</i> = 0.045	-0.12 (0.15); <i>p</i> = 0.407	0.66 (0.25); <i>p</i> = 0.010	-0.04 (0.25); <i>p</i> = 0.872
¹⁸ F FDG interaction				
with PiB status ^b				
Longitudinal free recall	2.43 (0.85); <i>p</i> = 0.004	0.39 (0.81); <i>p</i> = 0.630	2.97 (1.54); <i>p</i> = 0.054	1.34 (1.82); <i>p</i> = 0.556
Longitudinal cued recall	0.73 (0.32); <i>p</i> = 0.023	-0.33 (0.31); <i>p</i> = 0.282	1.57 (0.58); <i>p</i> = 0.007	-0.27 (0.51); <i>p</i> = 0.600
Low PiB participants (N = 198) ^c				
Longitudinal free recall	0.55 (0.42); <i>p</i> = 0.193	0.53 (0.45); <i>p</i> = 0.238	0.21 (0.75); <i>p</i> = 0.783	0.70 (0.77); <i>p</i> = 0.363
Longitudinal cued recall	0.11 (0.12); <i>p</i> = 0.391	-0.05 (0.13); <i>p</i> = 0.732	0.35 (0.22); <i>p</i> = 0.110	-0.01 (0.23); <i>p</i> = 0.986
High PiB participants (N = 79)				
Longitudinal free recall	2.57 (0.87); <i>p</i> = 0.004	0.51 (0.74); <i>p</i> = 0.494	3.13 (1.47); <i>p</i> = 0.034	0.73 (1.22); <i>p</i> = 0.547
Longitudinal cued recall	0.76 (0.43); <i>p</i> = 0.079	-0.55 (0.36); <i>p</i> = 0.128	2.12 (0.71); <i>p</i> = 0.003	-0.46 (0.59); <i>p</i> = 0.435

^aResults of linear mixed-effects models predicting memory change with FDG, adjusted for age, sex, and education. Separate models were run for the four FDG ROIs and for free and cued recalls resulting in eight models. Unstandardized estimates (SD) and two-sided *p* values (**bold if significant at *p* < 0.100**) are given for the FDG by time interaction term (ie, how FDG predicts change in memory over time).

^bSimilar models than in (a), but including an FDG by PiB status by time interaction term to investigate whether the impact of FDG on memory decline would be different in low- and high-PiB participants.

^cSubgroup results are only given if the FDG by PiB by time interaction is significant at *p* < 0.100 (in gray otherwise).

FDG = fluorodeoxyglucose; PiB = Pittsburgh compound B; SD = standard deviation.

are given in Table 1. Memory results are summarized in Table 3 and illustrated in Figure 5.

Posterior cingulate hypometabolism was associated with subsequent decline in both free and cued recall memory, while adjusting for demographics. Adjusting for PiB did not change this result. However, PiB retention strongly interacted with FDG, and when the high and low-PiB subsets were tested separately, posterior cingulate FDG only predicted memory deterioration in the participants with high PiB (Fig 5 right). Thus, memory decline on a measure highly sensitive to AD was associated with FDG metabolism in the brain area that had the greatest hypometabolism predicted by the tau-*Aβ* interaction.

Because entorhinal cortex is the earliest site of tau deposition and entorhinal tau was linked to inferior frontal hypometabolism, including in the low-*Aβ* participants (Fig 3, left), we evaluated the association of inferior frontal FDG and memory decline. We found that inferior frontal hypometabolism was associated with a modest decline in free recall that was independent of *Aβ* and marginally significant (estimate: 0.72 ± 0.38; *p* = 0.061, adjusting for PiB and demographics). There was no interaction with PiB and no effect on cued recall. The result was similar without PiB in the model (Table 3; *p* = 0.086).

We finally tested the association of entorhinal FDG and inferior temporal FDG with memory decline because

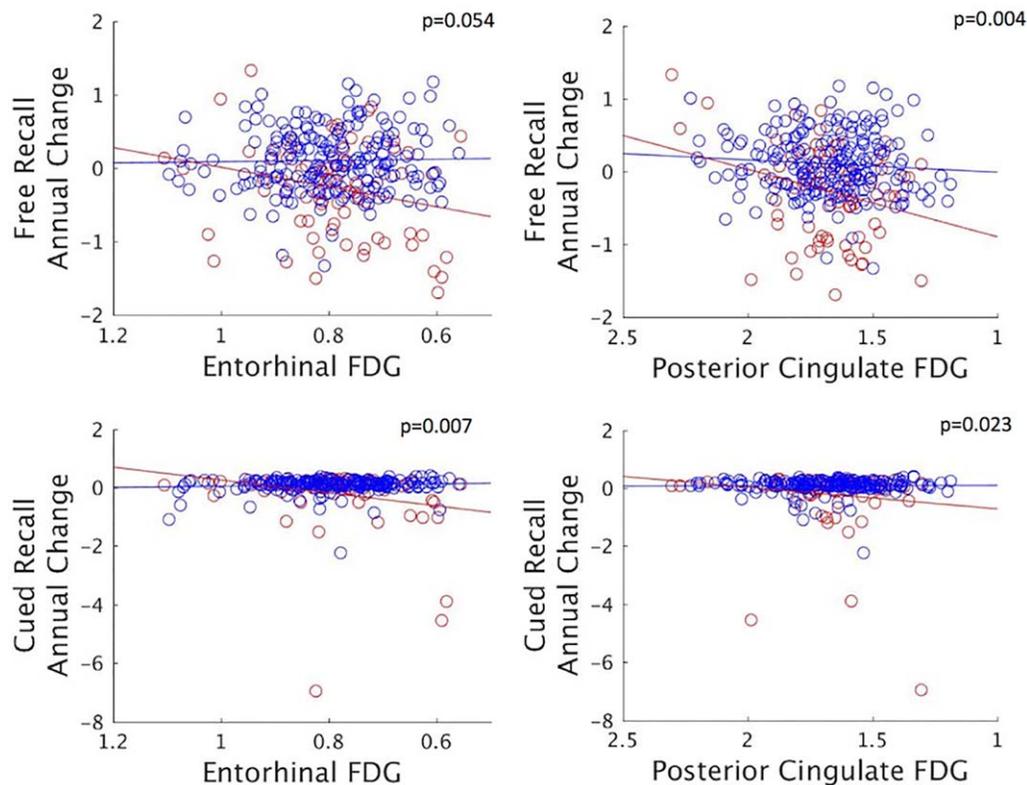


FIGURE 5: FDG hypometabolism predicts subsequent memory decline in high-PiB participants only. Scatter plots showing annual change in memory scores against FDG metabolism (SUVR) in selected ROIs. Memory and FDG data were residualized for age, sex, and education. *p* values indicate the significance of the interaction effect between FDG and PiB status on memory changes (see Table 3). Dots are categorized by PiB status (blue: low-PiB [*n* = 198]; red: high-PiB [*n* = 79]). FDG = fluoro-deoxyglucose; PiB = Pittsburgh compound B; ROI = region of interest; SUVR = standard uptake value ratio.

these were the regions where tau deposition had local effects. Interestingly, entorhinal FDG was also associated with subsequent memory decline, specifically in cued recall performance, and PiB interacted with FDG in this region (Fig 5, left), similar to the finding that tau associates with entorhinal hypometabolism in the high—but not in the low—PiB participants (Figs 1C and 3). In contrast, inferior temporal FDG did not relate to memory decline. APOE *e4* status did not affect these associations.

Posterior Cingulate FDG Mediates the Effect of Neocortical Tau on Memory in Preclinical AD

Using the 33 high-PiB participants with FTP data, we tested the hypothesis that memory decline is more closely associated with posterior cingulate FDG than with inferior temporal FTP. When both predictors were simultaneously entered in a mixed-model predicting free recall, FDG (estimate: 3.51 ± 1.21 ; $p = 0.004$) was associated with decline, but FTP was not (Estimate: -1.11 ± 0.92 ; $p = 0.231$). A mediation test formally demonstrated that the tauopathy effect on memory decline was mediated by posterior cingulate hypometabolism (Sobel test: -1.79 ; $p = 0.037$).

Discussion

We acquired PET biomarker measures of the principal pathological deposits of AD, $A\beta$ and tau, and related them in normal older persons to FDG PET, a biomarker of glucose metabolism that indicates synaptic activity. We found that the anatomy of glucose hypometabolism, first reported more than 30 years ago in AD, directly correlated with the interaction of both AD pathological hallmarks, $A\beta$ and neocortical tau. In patients with symptomatic AD,^{23,24} hypometabolic patterns had been previously observed in relation to $A\beta$ and tau measured in the CSF; however, the multiplicative effect was not reported. In addition, associations between CSF tau and FDG metabolism have not been found in normal elderly.^{25,26} The development of tau-PET imaging allowed us to isolate the metabolic signatures of entorhinal and neocortical tauopathy, and to demonstrate that AD-like hypometabolism was specifically associated with neocortical tau. Furthermore, previous studies did not find significant associations between FDG metabolism and memory decline in normal older adults.^{27,28} Using tau-PET to identify FDG ROIs, we demonstrated that FDG metabolism is predictive of memory decline in normal

individuals with various levels of $A\beta$. More broadly, our finding raises the possibility that AD therapeutic strategies could potentially be successful when either pathology is the target, and that a combination of both strategies and/or therapies targeting the tau- $A\beta$ interaction may be most successful.

Neocortical Tau Deposition and Memory Decline Point to the Same FDG Region as AD Vulnerable

We found that tau pathology was better correlated with FDG metabolism than $A\beta$, in line with previous neuropathology²⁹ and CSF³⁰ studies, but also found that the location of the tau deposition determines the location of tau-related hypometabolism as well as the impact of $A\beta$ on metabolic activity. The strongest predictor of cortical hypometabolism was the neocortical tau- $A\beta$ interaction, and the anatomy of the predicted hypometabolism included predominantly parietal and temporal lobes (Fig 2B, right). These limbic and association cortices have long been noted to undergo progressive deterioration in FDG metabolism along the AD trajectory.³¹ Moreover, we found that the area of greatest hypometabolism, the posterior cingulate, predicted subsequent memory decline, which confirmed that the FDG signal we identified related both to AD pathology and to evidence of progressive amnesia. These findings integrate two anatomically distinct phenomena in AD pathophysiology, temporal lobe tauopathy and parietal physiological change, and relate these processes to progressive memory loss in normal elderly.

Tau-Associated Hypometabolism Is Both Local and Distant and Both $A\beta$ Dependent and $A\beta$ Independent

To detect signs of a local synaptic toxicity associated with tau deposition, we related FDG and FTP each measured in the same cortical vertex or region. We found local tau effects confined to entorhinal and inferior temporal cortices (Fig 1B, left), perhaps reflecting the known association at autopsy of tauopathy and local synaptic loss.⁴ As elaborated below, these local effects were not evident in low- $A\beta$ individuals. We did not observe a local effect of tau in the parietal lobe,¹¹ possibly because these normal participants did not have sufficient parietal tauopathy for a local effect to be observed. Additional areas of local negative correlation were evident at increasing $A\beta$ burdens, which is consistent with hypometabolism reported in high- $A\beta$ normal individuals³² or clinical AD¹² and with recent work that observed spatial concordance between tau and hypometabolism in AD.³³

In contrast, distant associations, that is, those between FDG and FTP-PET signals each measured in

different vertices or regions, were observed in widespread neocortical areas. These fell into two categories: those that were consistently attributed to an interaction of tau with $A\beta$ and another set of areas that were associated with tau deposition that was independent of $A\beta$ (Fig 2). The key differentiating feature was choice of tau-PET region: When neocortical temporal tau deposition predicted hypometabolism, it was attributed to an interaction with $A\beta$, whereas when entorhinal tau predicted hypometabolism, there was no $A\beta$ interaction.

Tau deposition in the temporal neocortex was associated with parietal hypometabolism, most strongly involving posterior cingulate. The association in these areas interacted with $A\beta$, such that FDG only decreased with neocortical tau when $A\beta$ was high. This observation is consistent with the view that $A\beta$ and tau potentiate the physiological consequences of each other. The mechanism or anatomic connection mediating such an interaction is uncertain; however, a direct disconnection is unlikely to underlie the observed association, because the known connectivity of the inferior temporal gyrus would not predict that the posterior cingulate would be directly affected. A more plausible explanation may simply be that the inferior temporal tau-PET signal is a better tau biomarker because it is amplified among individuals with $A\beta$ -related tauopathy, that is, it is a proxy measure of potentially more widespread propagating and $A\beta$ -interacting tauopathy.¹¹

Positive Associations Between Tau and FDG Metabolism

Among the low- $A\beta$ participants, FDG metabolism was greater with *higher* levels of inferior temporal FTP, and this positive association was greater according to $A\beta$ level within the low- $A\beta$ group. The association was thus driven by subthreshold $A\beta$ and was also greater in the small group of low- $A\beta$ e4 carriers. Metabolism did not increase with entorhinal tau. These findings raise the possibility that there is an antecedent period of aberrant tau-related hypermetabolism, consistent with data from preclinical autosomal-dominant AD³⁴ and sporadic AD.^{35,36} Here, we provide evidence that tau-associated AD pathophysiology is underway at $A\beta$ levels that are subthreshold using established cutpoints, arguing for an adjustment toward lower cutpoints. Above the $A\beta$ threshold, we found tau-associated hypometabolism in regions commonly used as FDG biomarker readouts for AD. Our finding of tau-related increasing metabolism in subjects with subthreshold $A\beta$ is consistent with postmortem-PET correlations showing that $A\beta$ is evident in a subset of individuals below typical PET thresholds.^{37,38}

Whether a putative hypermetabolic phase is a cause or consequence of amyloidosis and/or tauopathy remains uncertain. Tau pathology could be driving increased activity either as compensatory or aberrant activity, or it could be increased activity attributed to incipient amyloidosis. Whereas $A\beta$ has also been linked to hypermetabolism,^{35,36} there is also support for the notion of increased neuronal activity fostering tau propagation and hyperphosphorylation.³⁹ A mechanism related to cognitive reserve could account for higher metabolism in individuals with AD pathology,⁴⁰ and early compensatory responses to AD pathologies are possible, highlighting the need for repeated imaging measures beginning in younger individuals. But the present data do suggest that the link to metabolism may be more evidently tau associated than $A\beta$ associated.

$A\beta$ -Independent Entorhinal Tauopathy Relates to Frontal and Insular Hypometabolism

In contrast to neocortical, entorhinal tauopathy is very commonly observed in this age range at autopsy and is thought to begin before substantial $A\beta$ and cognitive impairment.^{41,42} Our entorhinal tau measures did not interact with $A\beta$ to predict metabolism. Rather, in those with low- $A\beta$, entorhinal tauopathy was associated most prominently with inferior frontal and insular hypometabolism (Fig 3). Glucose metabolism in these regions has been associated with aging,¹⁷ and while our data were age adjusted, evaluation of younger individuals will be required. Some entorhinal connectivity to these regions has been reported in rodents⁴³; however, medial temporal ablation in primates was not linked to FDG hypometabolism in these regions, but rather to hippocampal and cingulate hypometabolism.⁴⁴ We also observed an $A\beta$ -independent association between entorhinal tauopathy and cingulate metabolism. Nevertheless, the overall pattern of entorhinal tau-associated hypometabolism was distinct from the typical temporoparietal AD pattern. Longitudinal PET studies will help determine whether entorhinal tauopathy fosters additional pathology, but without PET detectable amyloidosis, our study suggests that older individuals with entorhinal tauopathy do not manifest the AD-metabolic endophenotype.

Associations Between Glucose Metabolism and Memory Decline

We found that memory progressively declined in individuals with posterior cingulate hypometabolism, the region most strongly linked to the tau- $A\beta$ interaction. Previous studies evaluating regional FDG predicted cognitive decline in mild cognitive impairment⁴⁵ and in normal subjects reporting subjective impairment.⁴⁶ However, in

normal elderly, association between FDG and memory decline had not been observed so far.²⁸

Here, we used a novel tau- $A\beta$ interaction assessment to identify a region of FDG hypometabolism and then demonstrated that FDG in this region predicts memory decline in a group of normal elderly with various levels of $A\beta$. Previous work showed that posterior cingulate is critically involved in encoding and retrieval memory processes,⁴⁷ likely accounting for the association of metabolism in this region and memory decline. We also found a strong association between memory and entorhinal hypometabolism, similarly driven by the high- $A\beta$ participants. These findings are consistent with the idea that episodic memory specifically decreases with temporolimbic damage.^{48,49} In contrast, the inferior temporal FDG region also identified by the tau- $A\beta$ interaction was not associated with memory decline, suggesting that not all hypometabolic regions indicated by the tau- $A\beta$ interaction are associated with memory decline.

In addition, we found a modest effect of inferior frontal FDG on free recall decline that was independent of $A\beta$, suggesting that retrieval-based memory inefficiencies prevalent in aging and less specific to AD may be more associated with frontal dysfunction.⁵⁰ Our finding that entorhinal tauopathy was strongly associated with inferior frontal hypometabolism, particularly in low- $A\beta$ subjects, raises the possibility that medial temporal tauopathy, highly prevalent in this age range, may affect free recall, mediated by frontal dysfunction. Pursuit of this hypothesis will require longer follow-up among those with earlier stages of tau deposition.

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Author Contributions

B.H., D.R., R.S., and K.J. were responsible for conception and design of the study. For data analyses, M.L., J.B., D.C., and A.S. were responsible for MRI and PET preprocessing and B.H., R.B., E.M., K.P., J.C., J.S., and A.S. were responsible for statistics. BH, KJ were responsible for drafting of the manuscript and figures.

Potential Conflicts of Interest

D.R., R.S., and K.J. have been consultants for Eli Lilly/Avid, which owns FTP, the tau tracer used in this study.

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