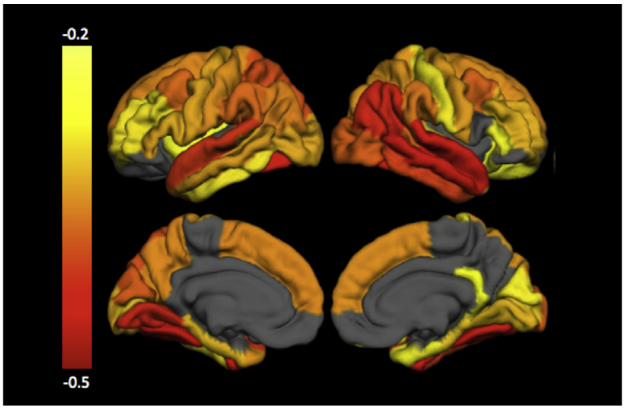

Figure 1. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age and gender in cognitively normal and AD participants.

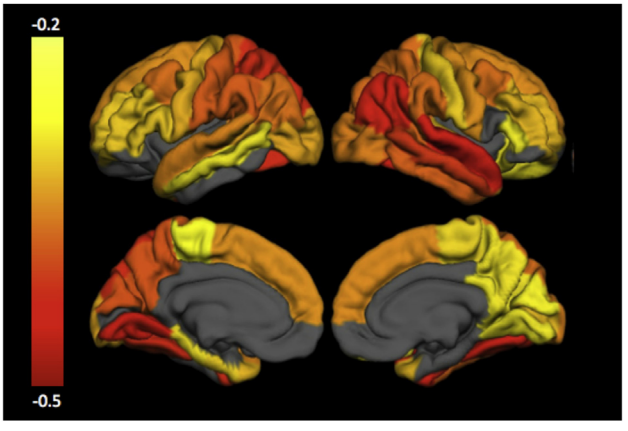

Figure 2. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age, gender, and current florbetapir mean cortical SUVR in cognitively normal and AD participants.

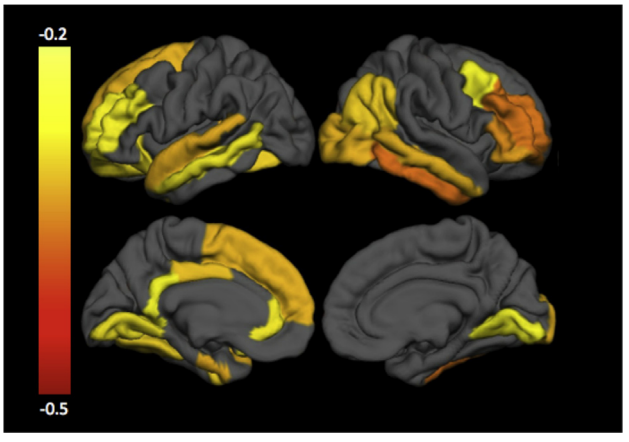

Figure 3. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age and gender in cognitively normal participants.

cognitively normal (with CDR=0) and 14 cognitively impaired (CDR> 0, 9 CDR 0.5, 3 CDR 1, and 2 CDR 2) participants were drawn from studies on aging at Washington University in St. Louis. Participants had one or more MRI sessions preceding a visit where they acquired both a MRI scan and underwent PET imaging with AV-1451, with mean follow-up from first MRI of 5.3 (sd 2.3) yrs. A subset (n = 93) also underwent florbetapir beta-amyloid imaging. MRIs were processed using FreeSurfer to generate mean cortical thickness in each region of interest (ROI). PET data was converted to standardized uptake value ratios (SUVRs) normalized to the cerebellum and partial volume corrected. Global tau burden was estimated by the mean SUVR from entorhinal cortex, amygdala, inferior temporal cortex, and lateral occipital cortex ROIs. For each person, a slope estimating structural atrophy in each ROI was quantified by fitting all longitudinal MRI measurements in a generalized linear model (GLM). These slope estimates were then used to predict tau burden in a GLM while controlling for baseline age and gender. Participants who also had beta-amyloid imaging were fit into a second GLM, with an additional covariate of florbetapir mean cortical SUVR. Multiple comparisons were controlled using a false discovery rate. **Results:** Antecedent cortical thinning was significantly associated with tau deposition throughout the cortex in the entire cohort (Figure 1). The effects were most prominent in the lateral temporal lobe and inferior parietal areas. These associations remained even after controlling for florbetapir levels (Figure 2) and were evident even in cognitively normal cohorts alone (Figure 3). **Conclusions:** Antecedent cortical thinning predicts current PET Tau in preclinical AD and symptomatic AD. This relationship holds in AD even after controlling for PET beta-amyloid burden. This may be useful for participant selection for tau PET imaging or clinical trials.

IC-02-03 TAU AND HIPPOCAMPAL VOLUME REFLECT DISTINCT PROCESSES IN PRECLINICAL ALZHEIMER'S DISEASE

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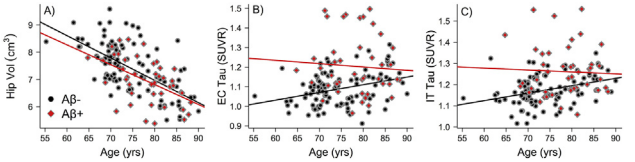
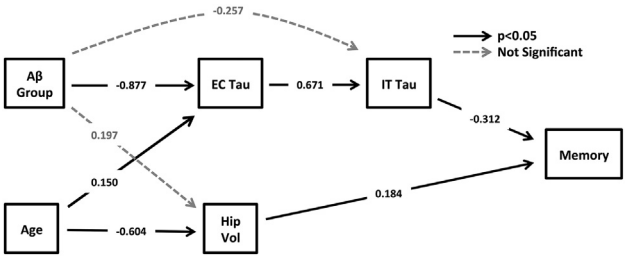
Background: To explore Tau and hippocampal volume as a function of age and beta-amyloid, as well as the contributions of these biomarkers to memory among older clinically normal (CN) participants. **Methods:** We examined 143 CN participants from the Harvard Aging Brain Study that underwent PIB/AV1451 PET, structural MRI, and neuropsychological testing (mean age=75.5±6.9, age range=55-90). Effects related to age and Aβ status were compared for Tau in entorhinal cortex (EC) and inferior temporal (IT), as well as hippocampal volume. Hierarchical regression and path analysis was used to assess associations among Aβ, Tau, hippocampal volume, age, and cross-sectional memory performance. **Results:** Age was related to hippocampal volume, regardless of Aβ status (within Aβ-: r= -0.63; within Aβ+: r= -0.52) (Figure 1A). Aβ+ showed significantly higher Tau than Aβ- in both EC (r= 0.44) and IT (r= 0.42); age was related to Tau in Aβ- (EC: r=0.32, IT: r= 0.35) but not within Aβ+ (EC: r=0.07, IT: r= 0.04)(Figure





1B-C). Although Tau was related to hippocampal volume among Aβ+ (EC: r= -0.28, IT: r= -0.29), the strength of these relationships were smaller than the association between age and hippocampal volume in Aβ+ (r= -0.52). Among Aβ-, 5.3% of the total variance in memory was explained by age, EC Tau, IT Tau, and hippocampal volume, with age accounting for the most unique variance (ΔR^2= 1.7%). Among Aβ+, 32.5% of the total variance in memory was explained by age, EC Tau, IT Tau, and hippocampal volume, with IT Tau accounting for the most unique variance (ΔR^2= 17.8%). Path analysis provided support for a model in which both EC and IT Tau are related to Aβ whereas hippocampal volume is related to age. Furthermore, EC Tau is more proximal to Aβ and IT Tau is more proximal to memory (Figure 2). **Conclusions:** These results suggest that hippocampal volume largely reflects non-Aβ age-related etiologies whereas Tau is more specific for early AD processes during the asymptomatic stage of AD. Our results are consistent with a model by which Aβ exacerbates Tau in entorhinal cortex and catalyzes the spread of Tau into adjacent neocortex, which subsequently results in subtle memory impairment.

IC-02-04 AXONAL DENSITY IS ASSOCIATED WITH SUBJECTIVE COGNITIVE DECLINE (SCD) IN OLDER ADULTS ASSESSED USING THE COGNITIVE CHANGE INDEX

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Background: Converging evidence suggests that the pathophysiologic processes in the brains of Alzheimer's disease (AD) patients begin decades before symptoms occur[1-3]. Individuals in the preclinical stages of AD often report self-perceived decline in cognitive functions. The self-perception of cognitive decline can be assessed via the cognitive change index (CCI)[4,5], a recently proposed measure of perceived neuropsychological function focusing on the memory, executive, and language domains from both self and informant perspectives. In this study, we examine the association of CCI with a novel diffusion metric for axonal density. The axonal density metric is derived via a three-compartmental model, Neurite Orientation Distribution and Density Imaging (NODDI)[6]. **Methods:** Sixty-one participants with cognitively normal (CN, N=21), subjective cognitive decline (SCD, N=23) and mild cognitive impairment (MCI, N=17) underwent Hybrid Diffusion Imaging (HYDI)[7,8] that consists of five b-value shells. Diffusion images were corrected for motion, eddy and geometric distortion[9] prior to nonlinear transformation to standard MNI space using ANTS registration[10]. Median values of diffusion metrics including DTI, NODDI, and q-space analysis were extracted from skeletonized 48 white matter (WM) ROIs provided in the JHU atlas[11]. General linear regression analyses were performed to test associations between diffusion metrics and CCI scores adjusted for age, sex, and education. For comparisons of demographic and cognitive variables, ANOVAs were employed with Tukey's tests followed by post-hoc t-tests. **Results:** The three groups did not differ significantly in age, sex, and education distribution (Table 1). Strong associations ($p<0.001$) between CCI and diffusion metrics were found in ROIs belonging to the limbic system. Specifically, fractional anisotropy (FA) of DTI in the right stria terminalis had negative correlation with CCI-12 (i.e., episodic memory) ($p<0.001$, Figure 1).

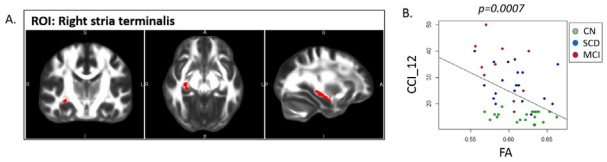

Figure 1. ROI map and scatter plot of CCI score and fractional anisotropy (FA). A. The ROI in red denotes the right stria terminalis. B. FA of diffusion tensor imaging (DTI) negatively correlated with CCI-12 (episodic memory) with p=0.0007. Age, sex and education were adjusted in the linear regression analysis. Green dots denote cognitively normal (CN); blue dots denote subjective cognitive decline (SCD); red dots denote mild cognitive impairment (MCI); and the black solid line denotes the regression line.

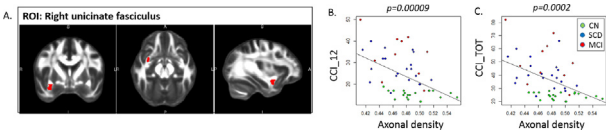

Figure 2. ROI map and scatter plot of CCI score and axonal density. A. The ROI in red denotes the right uncinate fasciculus. B. Axonal density negatively correlated with both CCI-12 (episodic memory) with p=0.00009 and CCI-TOT (20 items) with p=0.0002. Age, sex and education were adjusted in the linear regression analysis. Green dots denote cognitively normal (CN); blue dots denote subjective cognitive decline (SCD); red dots denote mild cognitive impairment (MCI); and the black solid line denotes the regression line.

Table 1
Demographic and cognitive comparisons of the three cohorts' characteristics

	CN	MCI	SCD	F/χ^2	p value	SCD-CN	MCI-CN	MCI-SCD
Age (yrs)	68.1 (5.8)	67.9 (10)	69.7 (10.3)	0.236	0.79	1	0.84	0.8
Sex (M:F)	6:15	9:14	7:10	0.384	0.68	0.76	0.71	0.99
Education (yrs)	17 (2.2)	16.5 (2.6)	16.1 (2.9)	0.505	0.61	0.82	0.58	0.9
CCI_12	15.3 (1.9)	27.6 (6.8)	33.6 (10.3)	33.471	$p<1\times10^{-5}$	$p<1\times10^{-5}$	$p<1\times10^{-5}$	p<0.05
CCI_TOT	24.3 (2.6)	41 (11)	51 (17.6)	24.682	$p<1\times10^{-5}$	$p<1\times10^{-5}$	$p<1\times10^{-5}$	p<0.05
CCI_INF12	15.6 (6)	16.1 (5.7)	32.7 (11.3)	22.029	$p<1\times10^{-5}$	0.97	$p<1\times10^{-5}$	$p<1\times10^{-5}$
CCI_INFTOT	25.7 (10.1)	25.7 (8.8)	53.3 (19.4)	21.3	$p<1\times10^{-5}$	1	$p<1\times10^{-5}$	$p<1\times10^{-5}$