specifically targeted for hippocampal subfield morphometry. The strong relationship between AV1451 tau uptake and CA1 atrophy in Aβ negative individuals suggests that AV1451 PET may be sensitive to the tau pathology of PART, which, in turn, drives MTL neurodegeneration and perhaps the cognitive symptoms of those in this group with MCI/AD designations.

IC-P-203 JOINT DEBLURRING OF LONGITUDINAL DIFFERENTIAL PET IMAGES OF TAU

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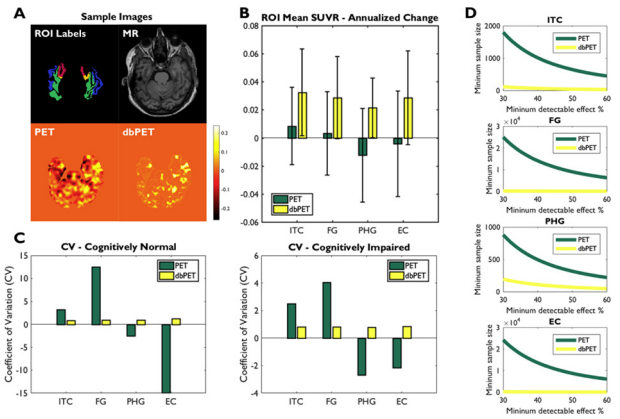
Background: Differential measurement of tau aggregates in the brain using serial PET imaging is of great significance in image-based biomarker development for aging and Alzheimer's disease. However, partial volume effects arising from the limited spatial resolution of PET pose a challenge to quantitation. We have developed an image deblurring technique that utilizes high-resolution anatomical information to correct for partial volume effects in differential images of tau based on serial [18F]Flortaucipir PET datasets. **Methods:** The deblurring technique is based on 1) deconvolution of co-registered difference images using the point spread function of the scanner measured in the image space and 2) minimization of the joint entropy between the PET difference image and a co-registered T1-weighted MPRAGE MR image. Serial [^{18}F]Flortaucipir ([^{18}F]AV1451) PET data was acquired from an elderly cohort (63-90 years) consisting of 96 Harvard Aging Brain Study participants. The time gap between baseline and follow-up scans was 0.6-3.6 years. **Results:** As shown in Fig. A, deblurring led to successfully recovery of structural details in the PET difference images while suppressing spurious negative values due to noise. Annualized rates of change based on standardized uptake value ratio (SUVR) differences across the two timepoints were computed corresponding to the following 4 clinically relevant regions-of-interest (ROIs): inferior temporal cortex (ITC), fusiform gyrus (FG), parahippocampal gyrus (PHG), and entorhinal cortex (EC), as shown in Fig. B. We used the coefficient of variation (CV) or relative standard deviation as a measure of biomarker reliability. As shown in Fig. C, deblurring led to prominent reductions in CV for all ROIs for both cognitively normal and impaired cohorts. Importantly, this translated to much smaller samples needed to detect an effect of given size as illustrated in Fig. D. **Conclusions:** Joint deblurring of serial datasets led to reduced CV levels and smaller sample size requirements. This finding is particularly critical in the context of drug development as it indicates lower sample sizes required to detect a drug-induced lowering of tau pathology. Thus, our deblurring approach shows promise in the development of novel tau-based quantitative biomarkers for aging and Alzheimer's disease.



A. Sample Images: Transverse slices from a subject showing the ROI labels, the high-resolution TI MR image, the uncorrected PET SUVR difference image, and the jointly deblurred PET (dbPET) SUVR difference image. The ROI labels include inferior temporal cortex (ITC), fusiform gyrus (FG), parahippocampal gyrus (PHG), and entorhinal cortex (EC).
B. ROI Mean SUVR - Annualized Change: dbPET led to non-negative measures with reduced standard deviation relative to the original PET difference images.
C. Coefficient of Variation: dbPET generated reduced coefficients of variation (CV) for both cognitively normal and impaired cohorts.
D. Minimum Sample Size: The reduction in CV translates to a dramatic reduction in the minimum required sample size for a given effect size.

IC-P-204 THE RELATIONSHIP BETWEEN TAU PET AND OTHER AD BIOMARKERS IN AUTOSOMAL DOMINANT ALZHEIMER DISEASE

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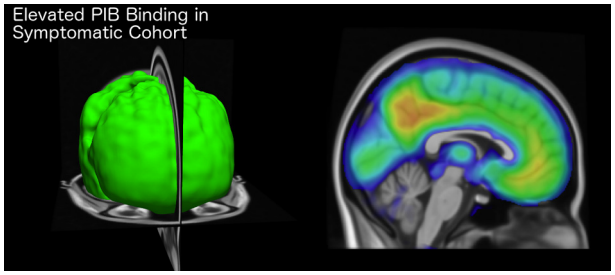
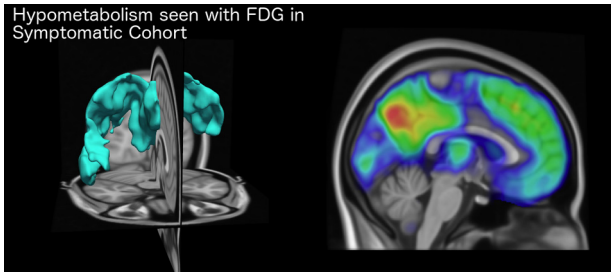
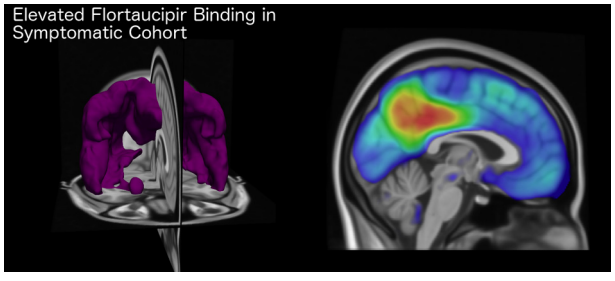
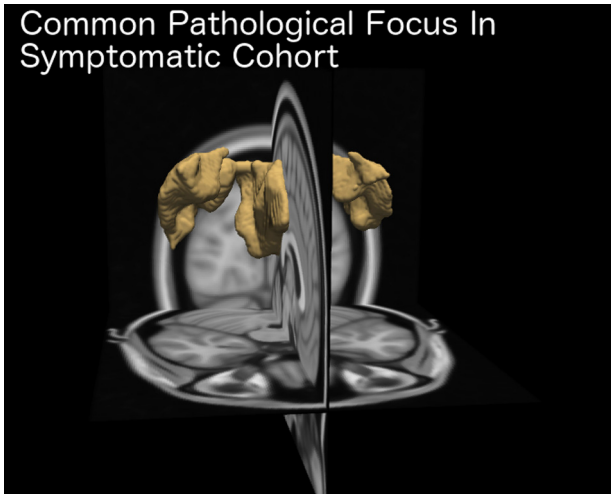
Background: In autosomal dominant Alzheimer disease (ADAD), there is a conservation of age of symptom onset within families. This consistency allows participants to be staged according to their estimated years to symptom onset (EYO). This provides an elegant model to study the emergence of AD biomarkers during the transition from preclinical to clinical stages of the disease. ADAD cohorts also provide robust populations of mutation carriers with preclinical and clinical AD as well as familial controls that are mutation non-carriers. **Methods:** ADAD participants were drawn from families known to have mutations in presenilin 1, presenilin 2, and amyloid precursor protein genes. The cohort consisted of 16 mutation non-carriers (NC), 20 asymptomatic carriers (aMC, CDR=0), and 15 symptomatic carriers (sMC: 13 CDR 0.5, 1 CDR=1, 1 CDR=3). Participants had tau (flortaucipir), beta-amyloid (PiB), and metabolic imaging (FDG) PET imaging as well as structural MRI. Voxel-wise PET data were nonlinearly aligned to the MNI152 atlas using a two-stage registration. Voxel-wise statistics were performed comparing groups using permutation testing. Data were additionally analyzed using regions of interest derived from Freesurfer. Primary comparisons were between NC, aMC, and sMC groups. **Results:** All four modalities showed significant group effects, with worse AD pathology in the sMC individuals relative to both the aMC and NC groups (Figures 1-4). There was a clear spatial overlap in what regions of the brain were affected by pathology, with a common focus in the precuneus and lateral parietal regions. There was a prominent cross-modal relationship between tau and the other three biomarkers. For the entire sample there was a significant correlation between precuneus tau and PiB (r=0.73, p=0.000000004), FDG (r=-0.63, p=0.002), and cortical thickness (r=-0.69, p=0.00000003). The strength of these

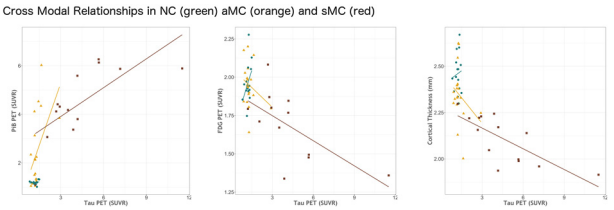








relationships varied by group (Figure 5) but were particularly prominent in the sMCs. **Conclusions:** We found overlapping spatial patterns of biomarker change in ADAD, with pathological changes consistently located in the precuneus and lateral parietal regions across all four biomarkers. The degree of beta-amyloid, hypometabolism, and cortical thinning were all strongly correlated with tau pathology measured with flortaucipir.



IC-P-205 LONGITUDINAL TAU-PET AND ATROPHY IN HEALTHY OLDER ADULTS AND THOSE WITH ALZHEIMER'S DISEASE

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Background: Tau accumulation is associated with normal aging and with Alzheimer's disease (AD). The rate of tau accumulation in healthy older adults and patients with AD is not well described, nor is the relationship of tau accumulation to cortical atrophy. **Methods:** We used AV1451-PET to interrogate tau accumulation over time in healthy older adults (OA; n=34) and patients with probable AD (n=12; Table 1). AV1451 images were normalized by cerebral white matter and preprocessed using a longitudinal pipeline. ROI analyses were also performed using partial volume correction (PVC; Rousset method) and annual percent change (APC) was calculated for mean PVC SUVR values in regions corresponding to Braak stages. Linear mixed effects models were used to predict AV1451 change in Braak regions. Structural MRI scans were processed for longitudinal VBM. PiB-PET scans were used to determine amyloid burden. **Results:** One sample t-tests on AV1451-APC in OA showed significant increases at follow-up in each Braak stage (Braak I/II mean AV1451-APC=2.37%; Braak III/IV AV1451-APC=2.82%; Braak V/VI AV1451-APC=2.79%, all $p<0.001$; Fig.1). There were no differences in AV1451-APC or in rate of AV1451 change based on PiB status in OA. Mixed effects models showed significant differences in AV1451 change over time between AD and OA in Braak III/IV (mean AD