normal older adults using: (1) a reference group of young adults, (2) Gaussian mixture modeling (GMM), (3) cluster analyses and (4) voxel-wise analyses. All analyses used DVR and SUVR data with a cerebellar gray reference ROI. For voxel-wise analyses, subjects were ranked based on their global DVR status. To track when and where amyloid starts accumulating we compared a group of 22 subjects with a mean DVR of 1 (control group) to the next 22 subjects (group of interest) and iteratively increased the mean DVR of the group of interest by dropping the subject with the lowest value and adding the subject with the next higher value. This procedure was repeated until the subject with the highest DVR was included in the group of interest. **Results:** The threshold 2 SD above the young subjects was a DVR of 1.07 (SUVR = 1.19). Both the GMM and the cluster-derived thresholds were 1.09 (SUVR 1.22). The Figure shows that amyloid starts accumulating in the medial frontal cortex (mean DVR = 1.07, SUVR = 1.19), then spreads to the precuneus, the lateral frontal and parietal lobes, and finally the temporal lobe. **Conclusions:** Amyloid starts to accumulate long before individuals reach the widely used SUVR cutoffs of 1.4 and 1.5. These results support an SUVR cutoff of 1.21 (DVR = 1.08) to capture early amyloid accumulation. This cutoff was confirmed by an autopsy study of 43 dementia cases (Rabinovici et al., submitted).

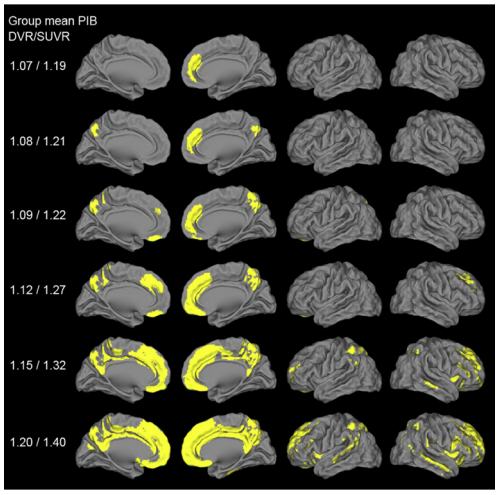

Figure. Pattern of amyloid accumulation in cognitively older adults. Each row of images reflects a voxel-wise contrast of 22 subjects with the mean value for global DVR/SUVR listed at left compared to a reference group (N=22) with a global DVR=1. Significant voxels first appeared when the group mean was DVR=1.07. Threshold at $p < .05$ after family-wise error correction, $k > 150$.

IC-02-04 EARLY, BUT NOT ADVANCED, NEUROFIBRILLARY TANGLE PATHOLOGY OR AMYLOID-B PATHOLOGY SIGNIFICANTLY ASSOCIATES WITH ABNORMAL HIPPOCAMPAL SIZE IN COGNITIVELY NORMAL ELDERLY

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Background: Hippocampal volume (HCV) is a surrogate measure of underlying neurodegenerative disease. Tau pathology is known to associate with hippocampal volume, but what is unclear is the extent to which early versus advanced neurofibrillary tangle (NFT) pathology contributes to hippocampal volume in nondemented patients. Early neuritic, pretangle and mature NFT pathology (measurable by hyperphosphorylated tau [pTau] antibodies) precedes the formation of advanced mature and extracellular NFTs (measurable by a NFT conformational epitope [cNFT]). The purpose of this study was to examine the relationship between hippocampal volume and neuropathologic measures of early pTau, advanced cNFT, and amyloid- β pathology in nondemented elderly participants. **Methods:** We selected Mayo Clinic Study of Aging autopsied participants who had available 3T antemortem MRI and were nondemented within 2.0 years of death (14 women and 27 men, aged 73-101). FreeSurfer v4.5 was used to measure HCV and adjusted based on regression modeling that measures how different the expected volume (based on TIV) is to the actual volume. Using a 90% sensitivity in clinically diagnosed ADs, the cut-point was -0.69. Serial sections of posterior hippocampus were analyzed using digital microscopy (Aperio technologies) to measure % burden of early pTau (CP13-antibody), advanced cNFT (Ab39-antibody), and amyloid- β (33.1.1- antibody). An H&E stain was used to quantify pyramidal neuron density. **Results:** Of the 41 nondemented participants who met selection criteria, 18 (44%, median=-1.25) were below the abnormal HCV cutpoint and 23 (56%, median=-0.0389) were above the cutpoint. Four multiple linear regression models predicting HCV were adjusted for age at MRI, gender, and time from MRI to death. Smaller HCV was significantly associated with higher early pTau burden ($p=0.017$), but not advanced cNFT ($p=0.299$) nor amyloid-β burden ($p=0.199$). A lower density of pyramidal neurons was also associated with smaller HCV ($p=0.012$). **Conclusions:** Our data supports previous work describing associations between HCV and hippocampal tau pathology, but adds new information relative to the maturity of neurofibrillary tangle pathology in the hippocampus. Early pTau pathology was found to significantly associate with hippocampal volumes in nondemented persons, suggesting that there are distinct mechanisms involved in NFT accumulation that may have different pathophysiologic bases relevant to structural MRI.

IC-02-05 CEREBRAL MICROBLEEDS ARE ASSOCIATED WITH CEREBRAL BLOOD FLOW AND METABOLISM BUT NOT AMYLOID BURDEN OR BRAIN ATROPHY IN COGNITIVELY NORMAL ELDERLY

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Background: Cerebral microbleeds (CMBs) are commonly seen in magnetic resonance (MR) images of elderly individuals and are related to small vessel disease from cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis. We hypothesized that CMBs are associated with decreased cerebral blood flow (CBF), decreased cerebral metabolism, and cognitive deficits in very elderly individuals. **Methods:** Fifty-five normal controls (NC) (86.8 $\pm$ 2.7 years; 22 female) were recruited from the Pittsburgh Ginkgo Evaluation of Memory Study (GEMS). MR imaging for each subject was performed on a Siemens 3T Trio scanner with a Siemens GRE or syngo SWI protocol for CMB identification, structural MPRAGE sequence for hippocampal volume and region-of-interest determination, and an arterial spin labeling (ASL) sequence for CBF measures. PET imaging was performed using a Siemens/CTI ECAT HR+ PET scanner and [11 C]PiB and [18 F]FDG to determine Aβ burden and metabolism, respectively. A single reader performed all CMB identifications, designating subjects as CMB(-) (no CMB found) or CMB(+) (one or more CMBs found). Hippocampal volumes were computed using FSL software (FIRST algorithm). Regional sampling of the ASL, [11 C]PiB, and [18 F]FDG images yielded regional values of ASL CBF (mL/100g/min), [11 C]PiB Aβ burden (SUVR), and [18 F]FDG metabolism (SUVR). SUVR values were computed using cerebellum as reference. Cognitive and functional status was assessed with a battery of neuropsychiatric tests and the Clinical Dementia Rating (CDR) scale. **Results:** CMBs were found in 21 of the 55 subjects. Both the presence and number of CMBs showed significant associations with reduced regional CBF ($p<0.05$).