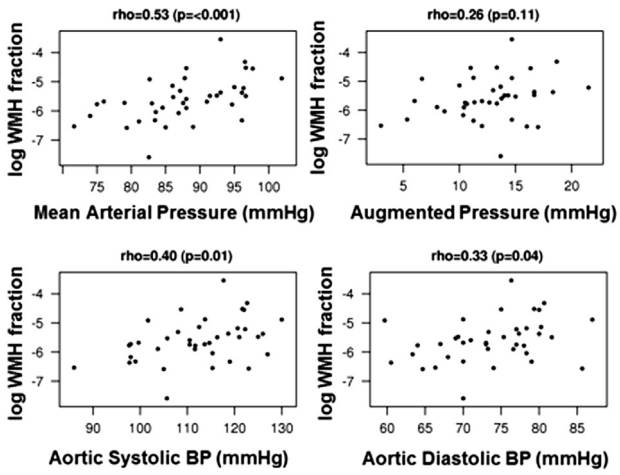

SATURDAY, JULY 12, 2014
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-02
PRECLINICAL ALZHEIMER'S DISEASE AND BIOMARKERS

IC-02-01 GREATER SUBJECTIVE COGNITIVE CONCERNS CORRESPOND WITH ADVANCING STAGES OF PRECLINICAL AD

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Background: Emerging evidence suggests that subjective cognitive concerns (SCC) may herald initial cognitive decline at the preclinical stage of Alzheimer's disease (AD). While previous studies have investigated the relationship between SCC and amyloid (A b) burden and neurodegeneration (ND) separately, it remains unclear if increased SCC correlates with successive stages of preclinical AD. **Methods:** We studied 186 CN individuals from the Harvard Aging Brain Study (Clinical Dementia Rating Scale = 0, Geriatric Depression Scale <11). A b status was determined with PIB-PET imaging and ND was measured using two a priori imaging markers: hippocampus volume and glucose metabolism extracted from AD-vulnerable regions. A subjective cognitive concerns composite was calculated using subscales from three questionnaires. Linear regression models with A b and ND status as simultaneous predictors were used to predict SCC, controlling for age, education, and gender. A secondary analysis included APOE ε4 carrier status as a predictor. SCC were also examined across groups based on joint A b and ND status (Stage 0: A b -/ND-; Stage 1: A b +/ND-, Stage 2: A b +/ND+, and SNAP: A b -/ND+). **Results:** SCC was not related to age, gender or education. Both A b (p=0.002) and ND (p=0.036) were independently associated with greater SCC. APOE ε4 carrier status was not related to SCC and did not impact results from the initial model. Examination across groups revealed that SCC was greater in stage 2 compared to stage 0 (p<0.001), stage 1 (p=0.20) and SNAP (p=0.03). Furthermore, Stage 0 had lower SCC than both SNAP (p = 0.07) and stage 1 (p=0.03). There was no difference between Stage 1 and SNAP (p=0.45). **Conclusions:** We demonstrate independent and additive contribution of A b and ND status in predicting SCC, unaffected by APOE ε4 carrier status, such that individuals who are positive on both biomarkers show the greatest SCC, while individuals positive for a single biomarker show intermediate levels of SCC. This pattern is consistent with the hypothesis that the combination of A b and ND markers increases likelihood of cognitive decline.

IC-02-02 THE USE OF NEUROIMAGING BIOMARKERS IN PRECLINICAL ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is a major public health issue. Atrophy assessed with structural MRI, hypometabolism and amyloid load have been recently proposed as neuroimaging biomarkers for the preclinical diagnosis of the disease, consistently with the amyloid cascade hypothesis. However the meaning and the relevance of each neuroimaging biomarker remain not completely understood. Our objective was to characterize populations defined according to each neuroimaging biomarker (i.e. positive vs negative cases) to further our understanding of their use in the preclinical diagnosis of AD. **Methods:** We prospectively included 54 healthy controls (HC) over 50 years old who all performed structural MRI, FDG-PET and Florbetapir-PET in the same neuroimaging center. All HC were then dichotomized into positive or negative independently for each of the three biomarkers considering the regions of greatest changes in AD. Then, demographic, neuropsychological and neuroimaging data were compared between positive and negative cases classified from MRI, FDG-PET or Florbetapir PET data. **Results:** Amongst the 54 HC, 12 (22%), 12 (22%) and 8 (15%) individuals were positive for atrophy, hypometabolism and amyloid deposition, respectively. Demographic and neuropsychological data were not statistically different between the positive and the negative subgroups, except for age that was higher in the amyloid positive versus negative subgroup. Interestingly, the atrophy positive subgroup showed both hippocampal and frontal atrophy, and posterior cingulate, temporoparietal and frontal hypometabolism compared to the atrophy negative subgroup. There was no difference in amyloid load between atrophy or hypometabolism positive versus negative subgroups and the amyloid positive group didn't differ from the amyloid negative in terms of grey matter atrophy or hypometabolism. However, when considering individuals with atrophy and/or hypometabolism together, there seems to be an inverse relationships between amyloid and neurodegenerative biomarkers such that those with more neurodegeneration tend to show lower amyloid deposition and reversely. **Conclusions:** The atrophy biomarker is associated with a mixed pattern of AD-like and frontal. The three biomarkers provide independent rather than redundant information. Our findings show that individuals tend to have either neurodegeneration or amyloid load but not both, suggesting additive rather than sequential/causative links between the current neuroimaging biomarkers in the pathological process of AD.

IC-02-03 EXISTING THRESHOLDS FOR PIB POSITIVITY ARE TOO HIGH

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Background: There is no consensus among researchers about the thresholds that define amyloid positivity and there is little known about the earliest phases of amyloid accumulation in older adults. The present study had two goals: first, to derive a cutoff that captures early accumulation using both DVR and SUVR data from our subjects and, secondly, to examine their pattern of amyloid accumulation. **Methods:** Amyloid accumulation was investigated in 152 cognitively

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).

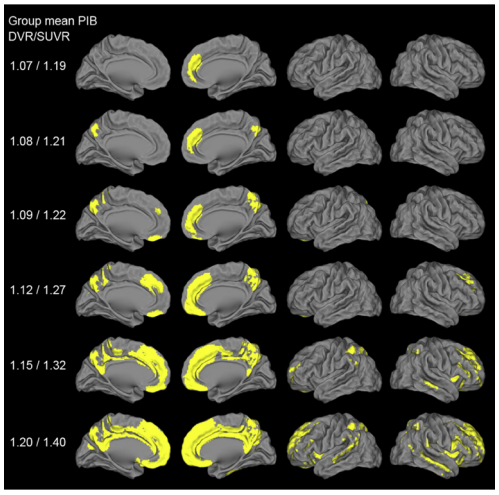

Figure. Pattern of amyloid accumulation in cognitively older adults. Each row of images reflects a voxel-wise contrast of 22 subjects with the mean value for global DVR/SUVR listed at left compared to a reference group (N=22) with a global DVR=1. Significant voxels first appeared when the group mean 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 ($p<0.05$).