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).

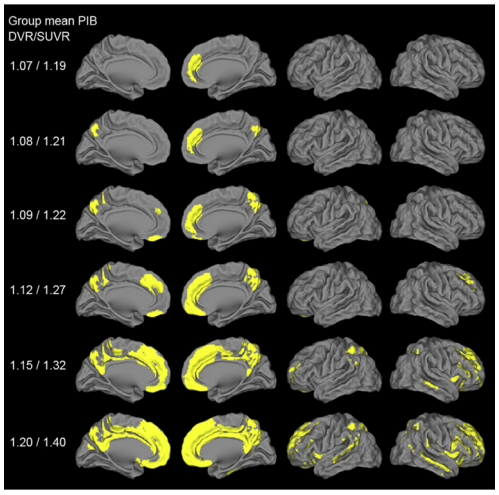

Figure. Pattern of amyloid accumulation in cognitively older adults. Each row of images reflects a voxel-wise contrast of 22 subjects with the mean value for global DVR/SUVR listed at left compared to a reference group (N=22) with a global DVR=1. Significant voxels first appeared when the group mean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

Melissa Erin Murray[1], Amanda M. Liesinger[1], Scott A. Przybelski[2], Jeffrey L. Gunter[3], Matthew L. Senjem[2], Mekala R. Raman[4], Ronald Carl Petersen[3], Dennis W. Dickson[1], Clifford R. Jack[2], David S. Knopman[2], *[1]Mayo Clinic, Jacksonville, Florida, United States; [2]Mayo Clinic, Rochester, Minnesota, United States; [3]Mayo Clinic Rochester, Rochester, Minnesota, United States; [4]Mayo Graduate School, Rochester, Minnesota, United States. Contact e-mail: murray.melissa@mayo.edu*

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

Davneet Singh Minhas[1], Nicholas M. Gregg[2], Albert E. Kim[3], Mahmut E. Gurol[4], Oscar L. Lopez[1], Howard J. Aizenstein[1], Julie C. Price[1], Chester A. Mathis[1], Jeffrey A. James[1], Beth E. Snitz[1], Ann D. Cohen[1], Ilyas Kamboh[1], Lisa A. Weissfeld[1], Erica L. Tamburo[1], William E. Klunk[1], *[1]University of Pittsburgh, Pittsburgh, Pennsylvania, United States; [2]UPMC Shadyside Hospital, Pittsburgh, Pennsylvania, United States; [3]Medical College of Georgia, Augusta, Georgia, United States; [4]Massachusetts General Hospital, Boston, Massachusetts, United States. Contact e-mail: minhasd@upmc.edu*

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 ($p<0.05$).

The number of CMBs in CMB(+) subjects also correlated significantly with reduced metabolism in the medial temporal lobe ($p<0.05$). Subjects with CMBs were significantly more likely to have deficits on the Clinical Dementia Rating scale (χ 2 p-value = 0.0015). Neither the presence nor number of CMBs was found to be significantly associated with [11 C]PiB SUVR or hippocampal volume. **Conclusions:** In this cohort of very elderly NCs, CMBs are associated with reduced cerebral blood flow, reduced cerebral metabolism, and mild deficits on the CDR scale. Our findings suggest that the small vessel disease associated with CMBs can independently contribute to impaired cognition and functional status, a process likely mediated by chronic hypoperfusion and hypometabolism.

IC-02-06 LONGITUDINAL CHANGES IN BRAIN MRI AND NEUROPSYCHOLOGICAL MEASURES IN ASYMPTOMATIC AND SYMPTOMATIC FAMILIAL FRONTOTEMPORAL LOBAR DEGENERATION WITH MUTATIONS IN MAPT

David Thomas Jones[1], Stephen Weigand[1], Scott Przybelski[1], Jonathan Graff-Radford[1], Senjem Mathew[2], Jeffrey Gunter[3], Jennifer Louise Whitwell[1], David S. Knopman[1], Neill R. Graff-Radford[4], Kieth Josephs[2], Zbigniew Wszolek[4], Prashanthi Vemuri[5], Julie A. Fields[6], Mary M. Machulda[1], Tanis J. Ferman[7], John Lucas[2], Val J. Lowe[3], Ralitza Gavrilova[2], Karen Kuntz[1], Mariely DeJesus Hernandez[2], Matthew Baker[8], Rosa Rademakers[8], Ronald Carl Petersen[3], Kejal Kantarci[1], Clifford Jack, Jr,[1], Bradley F. Boeve[1], *[1]Mayo Clinic, Rochester, Minnesota, United States; [2]Mayo Clinic, Rochester, Minnesota, United States; [3]Mayo Clinic Rochester, Rochester, Minnesota, United States; [4]Mayo Clinic, Jacksonville, Jacksonville, Florida, United States; [5]Mayo Clinic, Rochester, Minnesota, United States; [6]Mayo Clinic College of Medicine, Rochester, Minnesota, United States; [7]Mayo Clinic, Jacksonville, Florida, United States; [8]Mayo Clinic, Jacksonville, Florida, United States. Contact e-mail: Jones.David@mayo.edu*

Background: As disease modifying therapies for familial frontotemporal lobar degenerations (f-FTLD) move into both the symptomatic and asymptomatic patient populations, it will be necessary to develop robust biomarkers that are sensitive to disease progression in both of these populations. In this study we investigated the longitudinal change in brain MRI and neuropsychological measures in asymptomatic and symptomatic carriers of microtubule associated protein tau (MAPT) mutations. **Methods:** All available neuroimaging and neuropsychological data on MAPT mutation carriers (symptomatic = +m CDR≥0.5 and asymptomatic = +m CDR=0) evaluated at Mayo Clinic were analyzed; non-mutation carrier family members (-m CDR=0) were used as controls (Table 1). Longitudinal structural brain MRI scans for each subject were processed using the Symmetric Diffeomorphic Image Normalization method for normalization of serial scans to obtain Tensor Based Morphometry (TBM-SyN) maps. We also compared baseline and longitudinal data on the Controlled Oral Word Association Test (COWAT), Trailmaking Test B (TMT B), Boston Naming Test (BNT) and Category Fluency (Cat Fl). We used linear mixed models with random slopes and intercepts to analyze longitudinal clinical and imaging data with years from baseline as the time scale. **Results:** The +m CDR≥0.5 subjects had non-zero rates of decline in annual % change in all regions analyzed with TBM-SyN. These rates were significantly different from both +m CDR=0 and -m CDR=0 family members (Figure 1a). The +m CDR=0 subjects had a non-zero rate of decline in the temporal ROI ($p = 0.009$) and trends in the composite frontotemporal region ($p = 0.08$) and the ventricular volume ($p = 0.08$). There was no significant difference when comparing the rates between +m CDR=0 and -m CDR=0. A similar pattern was also observed for all neuropsychological measures without any evidence for non-zero rates of change in +m CDR=0 (Figure 1b). **Conclusions:** Regional brain MRI volumes and neuropsychological measures longitudinally decline in +m CDR≥0.5 subjects and may be useful as biomarkers in this phase of the disease. TBM-SyN analysis of +m CDR=0 subjects identified a non-zero rate of temporal lobe change in this relatively young group, which may indicate that brain MRI is a suitable biomarker in the asymptomatic phase of the disease.

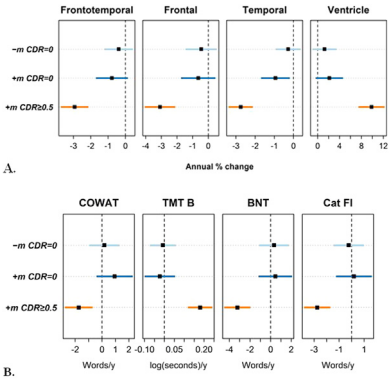

Figure 1. Mean and 95% confidence intervals of annual change in a) frontotemporal regions of interest and ventricular volume and b) neuropsychological measures per group.

Table 1Demographics table of asymptomatic and symptomatic familial FTLD subjects with mutations of MAPT.

	Non-carrier MAPT family members n = 11	Asymptomatic MAPT mutation carriers n = 9	Symptomatic MAPT carriers n = 21
No. of males (%)	4 (36%)	2 (22%)	12 (57%)
Age (y)	39 (9)	35.0 (6.9)	50 (12)
Education (y)	15 (2)	15 (2)	14 (2)
No. of ε4 carriers (%)	3 (27%)	4 (44%)	4 (19%)
Scan interval (y)	4.2 (1.7)	5.2 (2.1)	5.3 (4.0)

Mean (SD) for continuous variables
Count (%) for categorical variable

SATURDAY, JULY 12, 2014
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-03
NEW DEVELOPMENTS

IC-03-01 IMAGING OF TAU PATHOLOGY IN PATIENTS WITH NON-ALZHEIMER'S DISEASE TAUOPATHIES BY [11C]PBB3-PET

Hitoshi Shinotoh[1], Hitoshi Shimada[2], Shigeki Hirano[3], Shogo Furukawa[3], Yoko Eguchi[4], Keisuke Takahata[4], Yasuyuki Kimura[2], Harumasa Takano[5], Makiko Yamada[4], Satoshi Kuwabara[6], Hiroshi Ito[4], Tetsuya Suhara[4], Makoto Higuchi[4], *[1]National Institute of Radiological Sciences, Chiba, Japan; [2]National Institute of Radiological Sciences, Chiba-shi, Japan; [3]Chiba University School of Medicine, Chiba, Japan; [4]National Institute of Radiological Sciences, Chiba, Japan; [5]National Institute of Radiological Sciences, Chiba, Japan; [6]Chiba University, Chiba, Japan. Contact e-mail: hitoshi.shinoto@nifty.com*

Background: [11 C]PBB3 has been recently developed as a tau imaging PET ligand.The preclinical studies showed high affinity and selectivity of this ligand for tau deposits. Our initial PET study with [11 C]PBB3 demonstrated high [11 C]PBB3 binding in the cerebral cortex including medial temporal lobes in patients with Alzheimer's disease (AD) compared with age-matched controls. The aim of this study is to test the hypothesis that [11 C]PBB3 PET is a sensitive in vivo imaging method for detecting tau lesions in non-AD tauopathies such as progressive supranuclar palsy (PSP) and corticobasal degeneration (CBD). **Methods:** Ten patients with PSP, five patients with corticobasal syndrome (CBS), and 18 age-matched healthy controls (HCs) participated in this study. Sequential PET scans were performed for 70 min following intravenous injection of [11 C]PBB3. PET images were anatomically normalized to the Montreal Neurological Institute space using T1 weighted MRI, and standardized uptake value ratio (SUVR) was calculated using the cerebellar cortex as reference region. One-way ANOVA test was performed among PSP, CBS patients, and HCs using statistical parametric mapping software (SPM 8). Statistical threshold was set to 0.01 with extent threshold of 50 voxels without correction for multiple comparisons. Cerebral beta-amyloid depositions were also estimated using