injection of 18F-PI-2620. Venous blood is obtained to characterize the kinetics of parent compound and metabolites. **Results:** Initial imaging data shows robust brain uptake and fast wash-out in non-target regions with peak SUV = 4-4.5. There was no increased uptake seen in choroid plexus, striatum, amygdala, or other regions noted in first generation tau agents. In AD, focal asymmetric uptake was evident in temporal and parietal lobes, precuneus, and cingulate. SUVr time curves demonstrate a plateau at 90-100 min post injection with resultant SUVrs of 2.5-2.8.in abnormal regions, whilst HV demonstrated shorter time to secular equilibrium (60-70 min) and lower SUVrs (1.0-1.2) in comparable brain regions. Finally, PSP subjects demonstrated focal and symmetric increased uptake in the globus (SUVr=1.99-2.11) and midbrain (SUVr=2.41-2.58). Blood data confirmed fast kinetics with 20% of parent compound present at 60 min and the presence of polar metabolites. **Conclusions:** Initial PI-2620 PET first-in-human studies demonstrate excellent brain penetrance, favorable kinetics, and high target specificity with low nonspecific binding and high signal in regions of expected tau pathology.

SATURDAY, JULY 15, 2017
ALZHEIMER'S IMAGING CONSORTIUM
IC-02
PRECLINICAL AD

IC-02-01 THE RELATIONSHIP OF ELEVATED MEDIAL TEMPORAL LOBE AND DIFFUSE BRAIN TAU-PET SIGNAL IN CLINICALLY NORMAL PARTICIPANTS

Val Lowe, *Mayo Clinic College of Medicine, Rochester, MN, USA. Contact e-mail: vlowe@mayo.edu*

Background: Medial temporal lobe (MTL) uptake on tau-PET is seen in AD dementia but also in the aging population. Some AD dementia patients have much less MTL tau-PET signal compared to other isocortical signal. The relationship of these findings to the development of AD dementia needs to be better understood. **Methods:** Tau-PET with AV-1451 was performed on 439 cognitively normal (CN) participants ages 50-94. For each cortical region we defined abnormal tau-PET as cortical to cerebellar crus grey matter ratio (SUVr) greater than the 95th percentile among 71 CN participants ages 30-49. We included entorhinal cortex, parahippocampal gyrus, and hippocampus as MTL regions. All other cortical regions were considered extra-MTL regions. Off-target regions, such as pallidum, were excluded. The number of CNs with and without abnormal MTL regions and those with or without extra-MTL abnormalities were determined. We characterized the age, PiB and *APOE* status of the groups. **Results:** Of CN participants, 37% (163/439) had MTL abnormalities. Of those with MTL findings, 95% (155/163) had extra-MTL abnormality with most having more than one (Figure 1). Of the 276 without an MTL abnormality, 29% (81/276) had extra-MTL abnormalities (Figure 2). Participants having MTL abnormalities tended to be older ($p<0.001$) and have elevated amyloid ($p<0.001$). Among those having MTL abnormalities, no age or PIB differences were seen between those with or without extra-temporal abnormalities. There were no significant differences in the percentage of *APOE* e4 carriers. **Conclusions:** MTL tau-PET signal is often associated with abnormal extra-MTL tau-PET signal in CN participants and likely represents neurofibrillary tangle development in participants likely to develop AD dementia. Tau-PET signal exclusively outside of the MTL is seen in 29% of CN participants and could be the initial finding in a unique subset of participants in the AD dementia pathway. These findings need to be evaluated with longitudinal data.

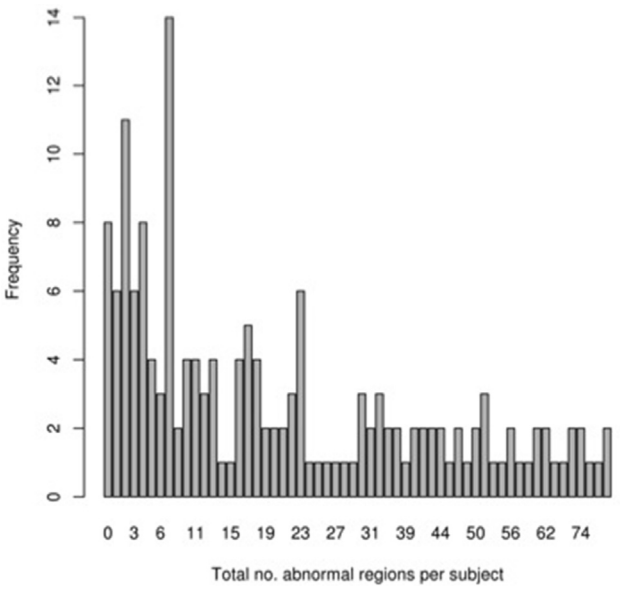

Figure 1. Numeric distribution of regional abnormalities outside medial temporal lobe (MTL) among those having any MTL abnormality.

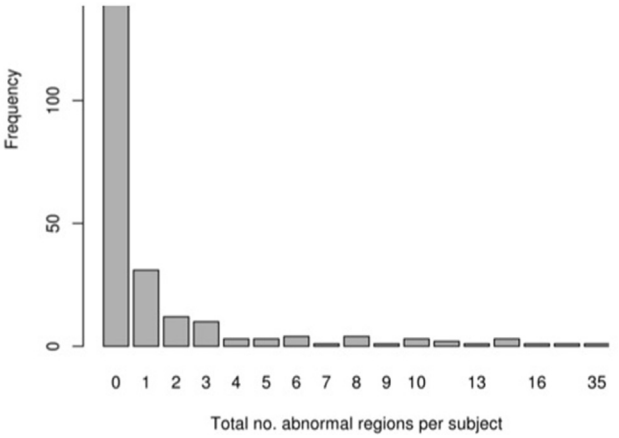

Figure 2. Numeric distribution of regional abnormalities outside medial temporal lobe (MTL) among those having any MTL abnormality.

IC-02-02 RELATIONSHIP BETWEEN TAU POSITRON EMISSION TOMOGRAPHY WITH [18F]-AV-1451 AND LONGITUDINAL CORTICAL ATROPHY IN ALZHEIMER DISEASE

Shruti Mishra[1], Brian A. Gordon[1,2], Tyler Blazey[1], Yi Su[1,2], Jon Christensen[1], Kelley Jackson[1], Russ C. Hornbeck[1], John C. Morris[1,2,3], Beau M. Ances[1,2], Tammie L. S. Benzinger[1,2], *[1]Washington University School of Medicine, St. Louis, MO, USA; [2]Knight Alzheimer's Disease Research Center, St. Louis, MO, USA; [3]Hope Center for Neurological Disorders, St. Louis, MO, USA. Contact e-mail: shruti.mishra@wustl.edu*

Background: Neurofibrillary tau pathology is a marker of neurodegeneration and can be evaluated using the PET tracer [18F]-AV-1451 (flortaucipir, T807). Many studies have added tau imaging to ongoing longitudinal cohorts. We wanted to evaluate whether longitudinal MRI scans could predict tau PET positivity in preclinical and symptomatic Alzheimer disease (AD). **Methods:** 87

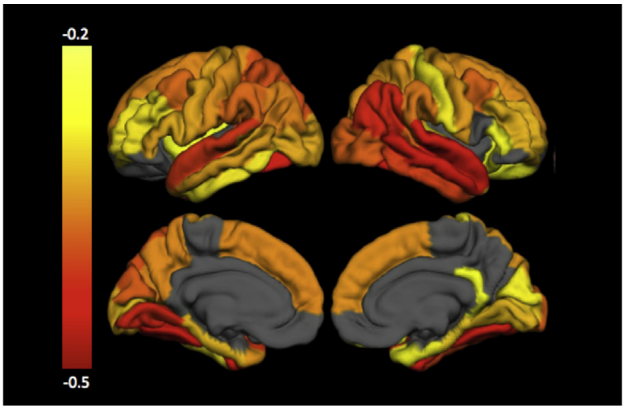

Figure 1. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age and gender in cognitively normal and AD participants.

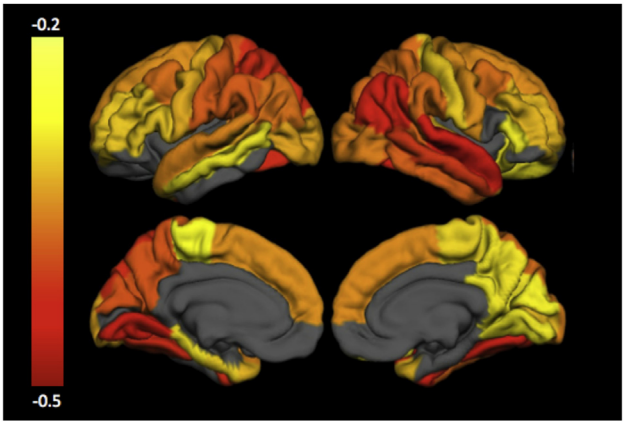

Figure 2. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age, gender, and current florbetapir mean cortical SUVR in cognitively normal and AD participants.

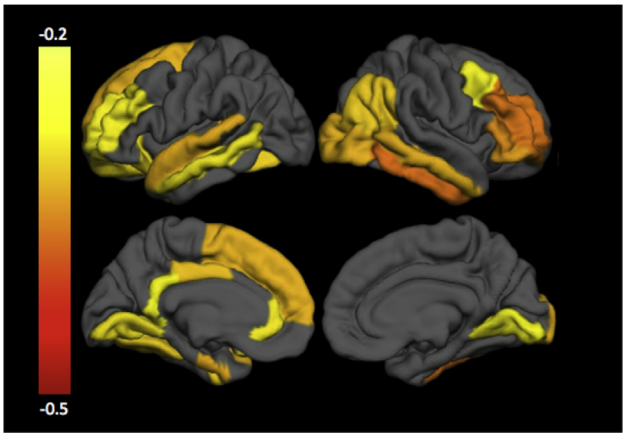

Figure 3. Relationship between antecedent cortical atrophy and current PET Tau, controlling for baseline age and gender in cognitively normal participants.

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

Beth C. Mormino[1], Aaron P. Schultz[2], Kate V. Papp[3], Molly R. LaPoint[4], Bernard J. Hanseeuw[5], Trey Hedden[2], Dorene M. Rentz[4], Reisa A. Sperling[3], Keith Johnson[6], *[1]Stanford University School of Medicine, Palo Alto, CA, USA; [2]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; [3]Brigham and Women's Hospital, Boston, MA, USA; [4]Massachusetts General Hospital, Charlestown, MA, USA; [5]Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium; [6]Massachusetts General Hospital, Boston, MA, USA. Contact e-mail: bmormino@stanford.edu*

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