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ALZHEIMER'S IMAGING CONSORTIUM
IC-01
TAU PET

IC-01-01 AV1451-PET CORTICAL UPTAKE AND REGIONAL DISTRIBUTION PREDICTS LONGITUDINAL ATROPHY IN ALZHEIMER'S DISEASE

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Background: We aimed to assess whether β-amyloid (PIB) and tau (AV1451) PET predict longitudinal atrophy in patients with AD. **Methods:** A group of 10 patients fulfilling NIA-AA criteria for AD dementia likely due to AD were included (age = 63 ± 9, MMSE = 24 ± 4 at baseline). All patients underwent i) a baseline visit with structural MRI and PET imaging with both AV1451 and PIB, ii) a follow-up structural MRI (time between MRIs = 1.06 ± 0.15 years). Structural images were preprocessed using SPM12's longitudinal registration pipeline to obtain voxelwise maps of atrophy showing areas of local contractions and expansions (i.e. Jacobians, see figure 1A). Relationships between baseline PET data (Standardized Uptake Value Ratio (SUVR) images normalized to cerebellar gray matter) and subsequent atrophy were assessed in two complementary ways. First, a global cortical value was extracted for each patient and each modality (figure 1B) and correlations were computed at the group level. Second, we computed voxelwise correlations at the individual patient level to evaluate the similarity between baseline maps of PET uptake and the subsequent atrophy map (figure 1C). **Results:** Using global cortical measures (figure 2A), a significant association was observed between steeper cortical atrophy (lower Jacobians) and higher baseline AV1451 cortical SUVR (rho = -0.76, p = 0.02) but not PIB-SUVR (rho = 0.13, p = 0.73), see Fig 2a. Similarly, voxelwise correlation analyses revealed that maps of atrophy resembled baseline AV1451-PET images (median rho = -0.57), i.e. voxels of higher baseline AV1451-uptake showed a steeper rate of atrophy. Correlation between PIB and atrophy maps were minimal (median rho = -0.14) and significantly different from the correlations with AV1451 (Wilcoxon signed-rank test: p=0.004, Figure 2B). **Conclusions:** These results support the hypothesis that neurodegeneration is more closely related to tau than to β-amyloid pathology, and further suggests that tau pathology precedes and drives neurodegeneration locally. Our results further suggest a potential prognostic role for AV1451 in predicting individual patient longitudinal trajectories. From a clinical perspective, our results suggest that AV1451-PET could have a major clinical utility to predict short-term outcomes in patients.

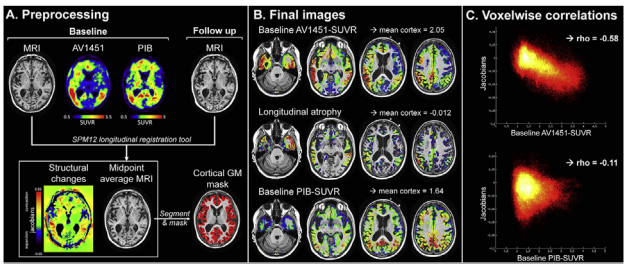

Figure 1. Study design, image preprocessing, and analyses (All images & values are from a representative patient with close to median values).

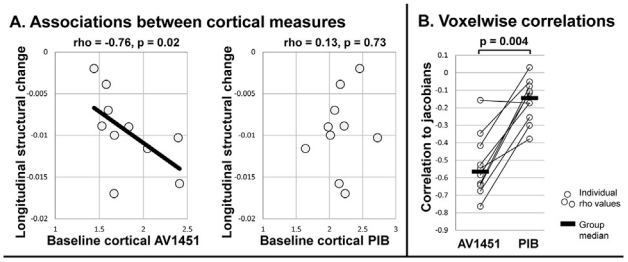

Figure 2. Results of the correlation analyses.

IC-01-02 WHITE MATTER INTEGRITY REFLECTS TAU ACCUMULATION IN AD-DEFINED REGIONS

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Background: Axonal loss and demyelination are pathological changes that co-occur in Alzheimer disease (AD). Diffusion tensor imaging (DTI) is sensitive at detecting white matter degeneration in AD with changes more pronounced at later stages of the disease.

Table 1

B-amyloid Regions	Mean Diffusivity	Axial Diffusivity	Radial Diffusivity	Fractional Anisotropy
Gyrus Rectus	0.0669	0.0378	0.0803	-0.1245
(R-value)	0.5877	0.7598	0.5150	0.3118
(P-Value)				
Occipital	0.4029	0.4369	0.3773	-0.1574
	0.0014**	0.0004**	0.003**	0.2
Prefrontal	0.0892	0.0582	0.1011	-0.1113
	0.4692	0.6371	0.4119	0.3663
Temporal	0.4526	0.5356	0.3972	-0.0366
	0.0004**	0.00008**	0.003**	0.7672

* p<0.05.
** p<0.01.

The association for the β-amyloid regions between regional tau and DTI metrics in the β-amyloid positive subjects.

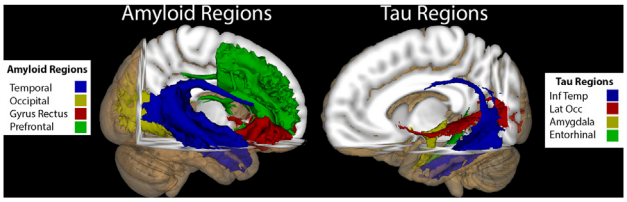
Table 2

Tau Regions	Mean Diffusivity	Axial Diffusivity	Radial Diffusivity	Fractional Anisotropy
Amygdala	0.6497	0.5991	0.6681	-0.6476
(R-value)	0.0026**	0.0067**	0.0018**	0.0027**
(P-Value)				
Entorhinal	0.5345	0.5101	0.5456	-0.6747
	0.0184*	0.0256*	0.0157*	0.0054**
Inferior	0.7878	0.7806	0.7716	-0.5229
Temporal	0.0004**	0.0004**	0.0004**	0.0288*
Lateral	0.660	0.5995	0.6583	-0.3163
Occipital	0.0019**	0.0067**	0.0022**	0.1871

* $p<0.05$

** $p<0.01$

The association for the tau regions between regional tau and DTI metrics in the β-amyloid positive subjects.



Deposition of tau in gray matter (GM) is associated with atrophy and cognitive impairment. However, the relationship between tau accumulation and white matter integrity has not been well characterized. We sought to correlate β-amyloid and tau deposition in predefined regions of interest (ROIs) with corresponding white matter (WM) projections from these ROIs. **Methods:** Sixty-nine participants underwent DTI, β-amyloid (florbetapir) and tau ([18F]AV-1451 (T807, flortaucipir)) positron emission tomography imaging. Twenty-one were β-amyloid positive, including 8 persons who were CDR>0. DTI metrics were processed in FMRIB software library, and GM regions were obtained with Freesurfer 5.3. Two sets of four AD-defined regions were evaluated based on either β-amyloid (Table 1) or tau (Table 2) accumulation. Probabilistic tractography projections were created for these predefined ROIs using ten cognitively normal individuals from the Human Connectome Project (Figure 1). The projections were applied to each participant's diffusion maps and average values calculated. Values were adjusted by age for partial correlations with either regional tau or β-amyloid. Correction for multiple comparisons was performed with false discovery rate correction (FDR). **Results:** Within β-amyloid defied regions, no association was seen between β-amyloid and diffusion metrics after FDR correction. With tau defined ROIs, Diffusion values within the occipital and temporal projections were associated with tau in β-amyloid positive individuals (Table 1). For the tau defined regions, β-amyloid did not associate with any diffusion metric. Significant associations were seen in all tau-defined regions for tau and absolute diffusion metrics in β-amyloid positive individuals (Table 2). No relationship was present between tau and diffusion metrics in the β-amyloid negative subjects. **Conclusions:** Tau and not β-amyloid accumulation was associated with changes in WM integrity. Observed changes were primarily seen in occipital and temporal projections. These results suggest that tau mediated changes primarily occur within posterior or temporal regions of the brain and are mediated by the presence of β-amyloid.

IC-01-03 RELATIONSHIP AMONG TAU, AMYLOID BURDEN AND BRAIN ATROPHY IN EARLY-ONSET ALZHEIMER'S DISEASE AND LATE-ONSET ALZHEIMER'S DISEASE

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Background: We investigated the relationship among 18F-THK 5351 PET tau retention, amyloid burden and brain atrophy in early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). **Methods:** We included 158 participants including 54 patients with EOAD (onset age < 65), 41 patients with LOAD (onset age ≥ 65), 8 young participants (age < 50) and 55 elderly participants (age ≥ 50) with normal cognition, who completed 18F-THK5351 PET scans, 18F-flutemetamol (FMM) PET scans and 3T MRI. Brain atrophy was evaluated with cortical thickness and hippocampal volume. To investigate the distinct features of inter-regional correlation of THK and FMM retention, connectivity matrices were calculated in EOAD and LOAD, respectively. **Results:** Ninety-eight percent (53/54) of patients with EOAD were positive for FMM retention, whereas 82.9 % (34/41) of patients with LOAD were found as FMM positive. LOAD showed significant positive correlation between global FMM retention and global THK retention, cortical THK retention, and THK retention in the lateral temporal cortex. Meanwhile, EOAD did not show any significant correlation between global FMM retention and THK retention. On the contrary, only EOAD patients had significant negative correlation between mean cortical thickness or hippocampal volume and global THK retention, cortical THK retention, or THK retention in the lateral temporal cortex. THK retention in the mesial temporal areas did not have significant correlation with mean cortical thickness or hippocampal volume in any groups. There was no significant