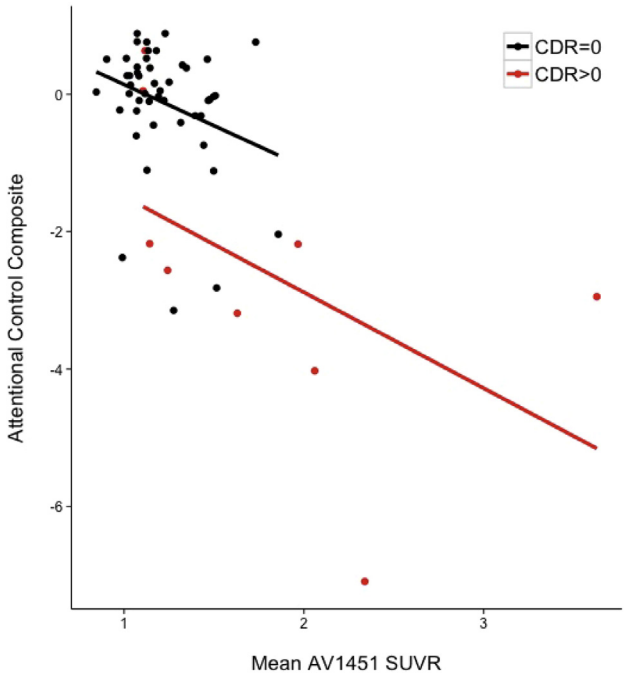

Figure 2c. Relationship between mean AV-1451 SUVR and attentional control

PET Tau deposition that is sensitive to early amyloid PET deposition and early cognitive change. In these regions a cut-off SUVR of 1.23 marks the transition between PET tau positive and negative in CNs.

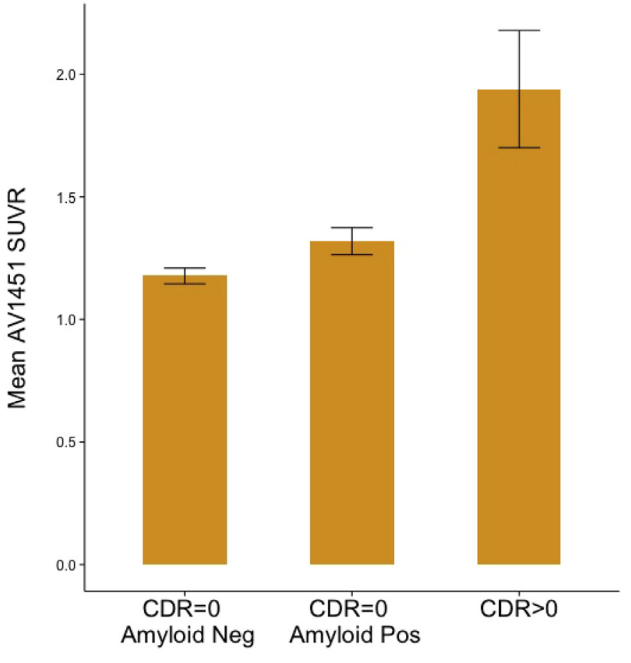

Figure 3. Mean AV1451 SUVR in PET Amyloid Positive vs. Negative Participants

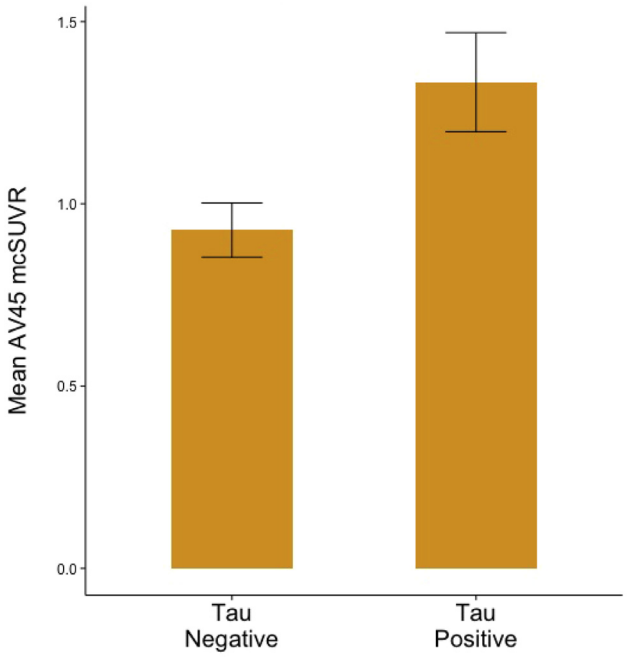

Figure 4. Difference in AV45 mcSUVR in Tau Positive vs. Tau Negative CN Participants

IC-01-04

^{18}F-AV1451 PET DETECTS TAU PATHOLOGY IN *MAPT* MUTATION CARRIERS AND CORRELATES STRONGLY WITH IMMUNOHISTOCHEMISTRY OF TAU AGGREGATES

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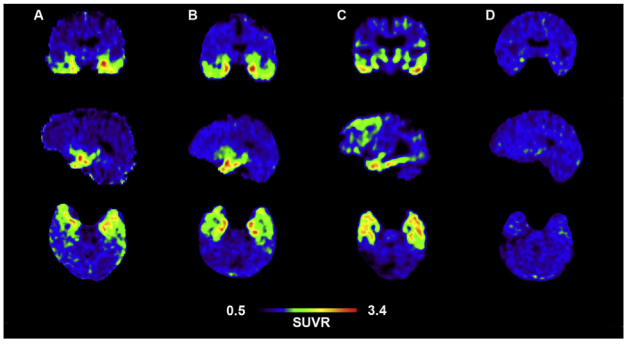
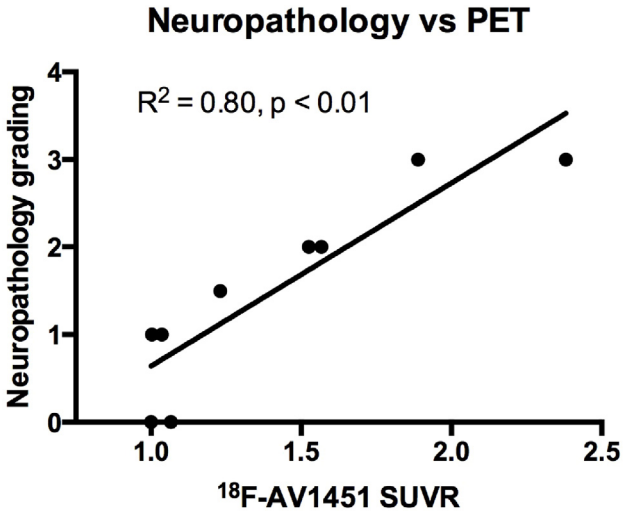
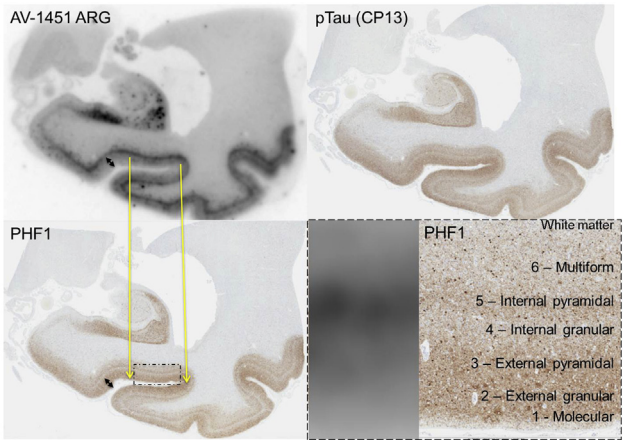
Background: The Tau PET ligand ^{18}F-AV1451 has been shown to reliably detect paired helical filaments of tau in Alzheimer's disease, but it is not yet known whether it binds to the tau aggregates present in patients with mutations in the gene (*MAPT*) coding for the tau protein. Further, no study has yet compared the cerebral retention of ^{18}F -AV1451 with the tau aggregates revealed using neuropathology. **Methods:** Three patients from a Swedish family carrying the R406W mutation of *MAPT* were assessed with cognitive tests and subjects underwent ^{18}F-AV1451 and ^{18}F-Flutemetamol PET scans. Further one of younger subjects also underwent an ^{18}F-FDG PET scan. The oldest subject died two weeks after the scan and the brain was processed for neuropathology. Tau immunohistochemistry was performed on brain sections from affected and unaffected brain regions. **Results:** Two mutation carriers, aged 56 and 60 years, had disease durations of 5-10 years and still only exhibited mild-moderate episodic memory impairment and no clear behavioural deficits. The MRI revealed only slight cortical atrophy and ^{18}F-AV1451 PET imaging showed uptake in the hippocampus and the temporal lobes, especially in the inferior and anterior parts (Fig 1A, B). The uptake of ^{18}F -AV1451 correlated well with hypometabolism revealed with FGD PET in one of the subjects. The third case, 76 years, had a disease duration of >20 years and exhibited clear cognitive impairment, behavioural disturbances, mutism and dysphagia. The CT

scan showed generalised cortical atrophy with a pronounced temporal lobe atrophy and ^{18}F -AV1451 PET imaging revealed uptake in the temporal and frontal lobes, as well as in the basal ganglia (Fig 1 C). The regional uptake of ^{18}F -AV1451 correlated strongly with the tau aggregates revealed using immunohistochemistry ($R^2 = 0.80$, $P < 0.01$; Fig 2). All cases exhibited negative amyloid (^{18}F -flutemetamol) PET scans. **Conclusions:** The *in vivo* uptake of ^{18}F-AV1451 reflects the regional amount of tau aggregates revealed by neuropathological examination. Further, tau pathology in *MAPT* mutation carriers is accurately detected with ^{18}F -AV1451 PET, which consequently can be used to track the effects of anti-tau therapies in this patient group.







IC-01-05 NEUROPATHOLOGIC FEATURES OF AV1451 TAU PET AUTORADIOGRAPHY IN DEMENTIA

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Background: It is essential to determine specificity of AV-1451 PET by using neuropathologic comparisons. We performed autoradiography in autopsy-confirmed Alzheimer's disease (AD) and other neurodegenerative disorders to evaluate the specificity of AV-1451 binding for tau aggregates. **Methods:** Tissue samples were selected that had a variety of dementia-related neuropathologies (n=37). Brain tissue sections were stained for tau, TDP-43, and α-synuclein and compared to adjacent sections processed for AV-1451 autoradiography. **Results:** In AD, AV-1451 preferentially localized to neurofibrillary tangles, with less binding to areas enriched in neuritic pathology. The strength of AV-1451 binding with respect to tau isoforms that preferentially accumulate in various neurodegenerative disorders was as follows: 3R+4R tau (e.g., AD) > 3R tau (e.g., Pick's disease) > 4R tau. Only modest binding of AV-1451 to TDP-43 was detected. No binding of AV-1451 to α-synuclein was detected. "Off-target" binding was seen in vasculature, iron-associated regions, substantia nigra, calcifications in the choroid plexus, and leptomeningeal melanin. **Conclusions:** Reduced AV-1451 binding in AD neuritic pathology compared to neurofibrillary tangles suggests complexity in AV-1451 binding. Maturity of neurofibrillary tangle pathology may play a role. Poor association of AV-1451 with tauopathies that have preferential accumulation of 4R tau or 3R tau suggests that it may have limited clinical utility in detecting these pathologies. In contrast, for disorders associated with 3R+4R tau, such as AD, AV-1451 binds tau avidly but does not reflect completely tau progression suggested by Braak neurofibrillary tangle staging. AV-1451 binding to TDP-43 pathology can be weakly positive in syndromes associated with TDP-43 proteinopathies. Clinical use of AV-1451 will require a familiarity with distinct types of "off-target" binding.

SATURDAY, JULY 23, 2016
ALZHEIMER'S IMAGING CONSORTIUM (AIC)
IC-02
IMAGING GENETICS

IC-02-01 THE EFFECTS OF THE TOP 20 ALZHEIMER'S DISEASE RISK GENES ON BRAIN ATROPHY

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Background: Genome-wide association studies (GWAS) have identified over 20 Alzheimer's disease (AD) risk genes. The mechanism