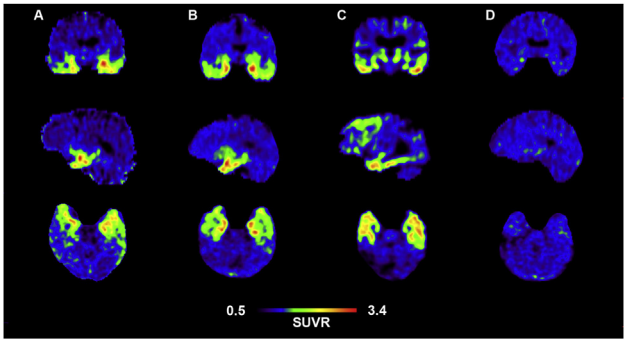
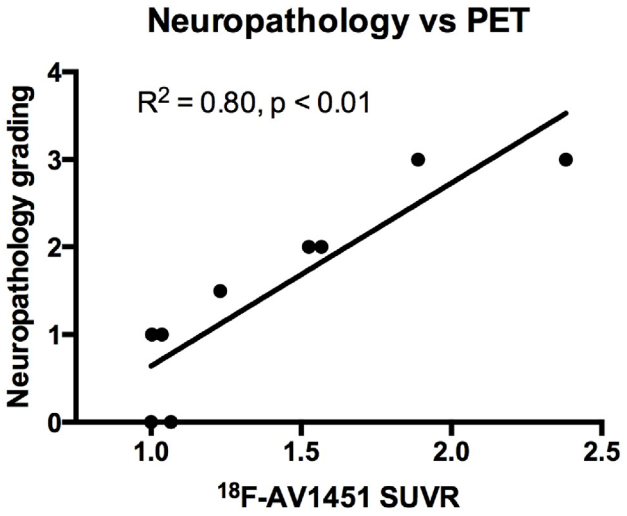
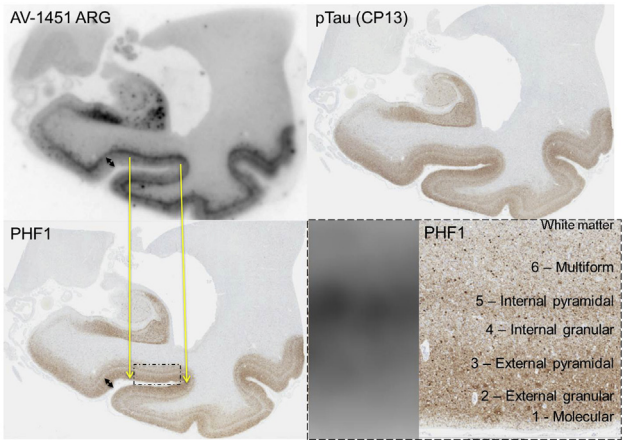
scan showed generalised cortical atrophy with a pronounced temporal lobe atrophy and ^{18}F -AV1451 PET imaging revealed uptake in the temporal and frontal lobes, as well as in the basal ganglia (Fig 1 C). The regional uptake of ^{18}F -AV1451 correlated strongly with the tau aggregates revealed using 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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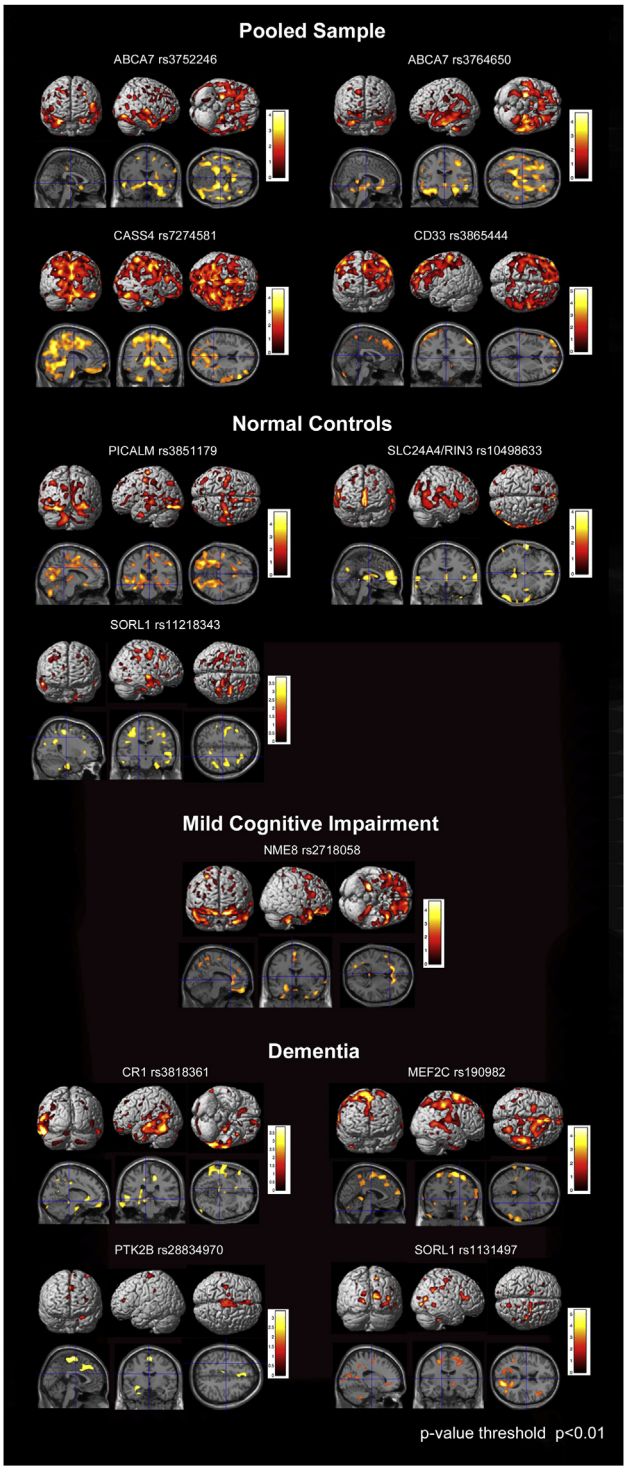
Background: Genome-wide association studies (GWAS) have identified over 20 Alzheimer's disease (AD) risk genes. The mechanism

through which these genes exert their effect remains unknown. Here we report a comprehensive analysis of the effects of the top 20 genes on brain atrophy. **Methods:** Our sample consisted of 305 cognitively normal (CN), 474 mild cognitive impairment (MCI) and 150 AD subjects from the Alzheimer's disease Neuroimaging Initiative (ADNI-GO/2) cohort. 795 subjects received 3T and the remainder 1.5T MRI. We focused on the variants of the top 20 AD genes discovered and validated in large GWAS studies. When linkage disequilibrium (LD) was present one variant from each LD block was chosen by yielding a total of 27 variants. We ran multivariate stepwise linear regression models with hippocampal volume, entorhinal, medial temporal and lateral parietal thickness obtained with Freesurfer v5.1 as outcome variables and all 27 variants as predictors while controlling for age, gender, APOE4 status and magnetic field strength in the pooled sample. Variants retained in the regression models, age, gender, APOE4 and magnetic field strength were included as predictors in 3D voxelwise multiple linear regression models in SPM8 with a cluster threshold of 50 voxels. **Results:** Results are shown in the Figure. ABCA7 rs3752246 and rs3764650, CASS4 rs7274581 and CD33 rs3865444 showed strong associations with brain atrophy across most disease stages (results shown are for the pooled sample). SLC24A4/RIN3 rs10498633 and SORL1 rs112118343 showed associations with neurodegeneration in the NC stage only, while PICALM rs3851179 demonstrated effects in both the NC (see Figure) and to some extent also the MCI stage (not shown). NME8 rs2718058 showed an association with neurodegeneration restricted to the MCI stage, while CR1 rs3818361, MEF2C rs190982, PTK2B rs28834970 and SORL1 rs1131497 showed associations in the dementia stage only. **Conclusions:** While ABCA7, CASS4, CD33, CR1, MEF2C, NME8, PICALM, PTK2B SLC24A4/RIN3 and SORL1 all show significant independent associations with brain atrophy, these associations are often confined to specific disease stage. Time- and stage-constrained genetic influences on AD pathology might be one of the reasons for the missing heritability in AD and need to be subject of further exploration.



IC-02-02 GENOME-WIDE POLYGENIC RISK FOR ALZHEIMER'S DISEASE IS ASSOCIATED WITH RATE OF METABOLIC DECLINE BUT NOT WITH RATE OF AMYLOID DEPOSITION

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Background: Genome-wide polygenic scores (GPS) summarize a person's genetic risk for a disease or trait in a single score. While there is strong evidence for an association of the GPS for Alzheimer's disease (AD) with AD diagnosis, little is known about the effect of polygenic risk on AD biomarkers. In this work we investigated the link between the AD-GPS and brain metabolism and amyloid deposition using fluorodeoxyglucose (FDG) positron emission tomography (PET) and florbetapir (AV45) PET, respectively. **Methods:** For computing the AD-GPS we relied on the results of the International Genomics of Alzheimer's Project (IGAP) genome wide association study (GWAS) comprising 54,162 subjects. We computed the AD-GPS for white, non-Hispanic subjects from the AD Neuroimaging Initiative (ADNI) database, who did not contribute to the IGAP GWAS. To include single nucleotide polymorphisms (SNPs) into the score we applied different P-value cutoffs ranging from 1e-5 to 0.95. SNPs in the extended APOE locus were excluded from the GPS. We obtained longitudinal measures for FDG PET in five ROIs (posterior cingulate cortex; left and right temporal pole; left and right angular gyrus) for 831 subjects and longitudinal measures for AV45 PET in a whole brain ROI for 742 subjects from the ADNI website. Linear mixed effects models were used to model the effect of the AD-GPS on longitudinal changes in both biomarkers. Models were corrected for age, sex,