lower brain volumes in the frontal and occipital lobes 2. We examined the influence of the obesity associated SNP rs17817449 in FTO on longitudinal changes in brain volume in non-demented older individuals within the Baltimore Longitudinal Study of Aging (BLSA). We hypothesized that obesity-associated risk allele carriers of the FTO gene would show faster rates of brain atrophy relative to non-carriers. **Methods:** Non-demented individuals (N=120; mean baseline age 70.5 years) received annual volumetric MRI (826 MRI scans in total) over a mean six-year interval and underwent genome-wide genotyping. Linear mixed effects models were used in a region of interest approach to examine differences in longitudinal rates of change in brain volumes between obesity-associated risk allele carriers and non-carriers of rs17817449. The analyses were adjusted for sex, age, APOE genotype and average body mass index (BMI) over the follow-up interval. **Results:** There were 72 individuals in the risk group and 48 in the non-risk group. The minor allele frequency was 0.41. There were no differences between the two groups in APOE ε 4 carrier status and average BMI. We did not observe any differences in global, lobar or regional brain volumes at baseline. Risk allele carriers showed significantly greater rates of decline in volume in the cuneus (one-tailed p=0.001; Bonferroni corrected p=0.038) relative to the non-risk group. **Conclusions:** Non-demented older individuals carrying one or more copies of the obesity-related SNP rs17817449 in the FTO gene show greater rates of brain atrophy within the cuneus of the occipital lobe. Together with previous cross-sectional findings of reduced occipital lobe volume in risk allele carriers, these results suggest that the FTO gene influences regional vulnerability to rates of brain atrophy during aging.1. J Alzheimers Dis. 2011; 23(3):461-9.2. Proc Natl Acad Sci U S A. 2010; 107(18):8404-9.

P1-281 ROLE OF GENETIC VARIATION ON LONGITUDINAL IMAGING MEASURES OF ALZHEIMER'S DISEASE IN THE ADNI COHORT

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Background: Our goal was to characterize the role of genetic variation in genes associated with Alzheimer's disease to longitudinal imaging and cognitive measures of disease progression. **Methods:** We completed an imaging genetics study on 398 ADNI participants (ND=120, MCI=116, AD=162) who had brain imaging data at baseline and two years. Candidate genes associated with AD risk were chosen from alzgene.org (APOE, BIN1, CLU, CR1, PICALM, MS4A6A, CD33, ABCA7 and MS4A4E). We used morphometric data processed with FreeSurfer, specifically hippocampal and whole brain volume (WBV), and rates of hippocampal atrophy and whole brain atrophy over two years, as well as ADAS-Cog as markers of AD. We used an ANCOVA within diagnosis groups to identify main effects of each SNP on chosen markers, controlling for baseline disease severity, age, gender and APOE. Finally, we did a VBM analysis in 138 ND subjects to characterize regionally specific relationships in those SNPs implicated in brain volume. **Results:** APOE was not associated with cognitive or imaging measures in the ND group. In MCI and AD groups, APOE was significantly associated with several imaging measures, namely baseline left ((Bonferroni corrected p value; effect size (partial eta-squared))(.003; .024)) and right (.018; .016) hippocampus, WBV atrophy (.025; .027), left (.003; .047) and right (.010; .036) hippocampal atrophy. In ND, PICALM was associated with cognitive decline (.045; .036), and baseline WBV (.006; .051). CR1 significantly impacted baseline hippocampal volumes (.001; .057). MS4A6A trended towards an association with whole brain atrophy over 2 years (.081; .049). In MCI and AD groups, CR1 (.048; .012) and ABCA7 (.041; .031) were associated with rate of cognitive decline. PICALM was strongly associated with baseline WBV (.006; .071), and BIN1 was associated with rate of atrophy in the hippocampus (.029; .027) as well as baseline cognition (.007; .019). Our VBM analysis was only significant in our analysis of PICALM, which was specifically related to parahippocampal gyrus, cuneus, and superior temporal gyrus volume. **Conclusions:** Our imaging-genetics analysis in a large dataset clarifies the individual and varied roles of several AD risk genes in Alzheimer disease (AD) progression and neurodegeneration.

P1-282 EFFECT OF APOE AND FAMILY HISTORY OF DEMENTIA ON ALZHEIMER'S DISEASE IMAGING BIOMARKERS IN COGNITIVELY NORMAL SUBJECTS

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Background: To investigate the effect of APOE and family history of dementia on biomarkers of AD pathophysiology in cognitively normal (CN) subjects. The biomarkers evaluated were brain beta-amyloid load via PIB-PET and neurodegeneration via FDG-PET and structural MRI. **Methods:** We analyzed 940 Mayo Clinic Study of Aging CN participants with PET or MRI, APOE, and self-reported parental medical history. For a subject to be classified as having no family history of dementia, both parents had to survive to at least age 65 and remain dementia free through life. We fit univariate and multivariate linear regression models to test for associations between APOE e4 status, family history, and the interaction of the two with the imaging outcome variables. **Results:** We found that amyloid load differed by APOE status ($p<0.001$) and family history ($p=0.002$) but FDG-PET and MRI did not ($p>0.1$). While there was no evidence of an interaction between APOE and family history in terms of amyloid load, both APOE and family history independently added to the prediction of amyloid load after adjusting for the other. In a multivariate model, APOE e4 genotype was associated with an 11% increase in amyloid load compared to e4 non-carriers (7%-16%, 95% CI; $p<0.001$) and parental family history of dementia was associated with a 5% increase in amyloid load compared to no parental history (1%-9%, 95% CI; $p=0.02$). **Conclusions:** 1) APOE status and family history were significantly associated with amyloid load but not with neurodegeneration. 2) While APOE genotype appears to be the larger driver of amyloid levels, family history of dementia, which reflects a composite risk factor encompassing known and unknown genetic and environmental risk of dementia, appears to be independently associated with higher levels of amyloid. 3) An individual subject's risk of brain amyloid given by their APOE status may be more precise than their family history. 4) Higher levels of amyloid load seen in asymptomatic APOE e4 carriers as well as cognitively normal individuals with a family history of dementia without neurodegeneration provides evidence that increasing amyloid levels may be the earliest indicator of AD.

P1-283 PERIPHERAL BLOOD PLASMA PROTEIN LEVELS ARE ASSOCIATED WITH PITTSBURGH COMPOUND B BINDING IN THE BRAIN

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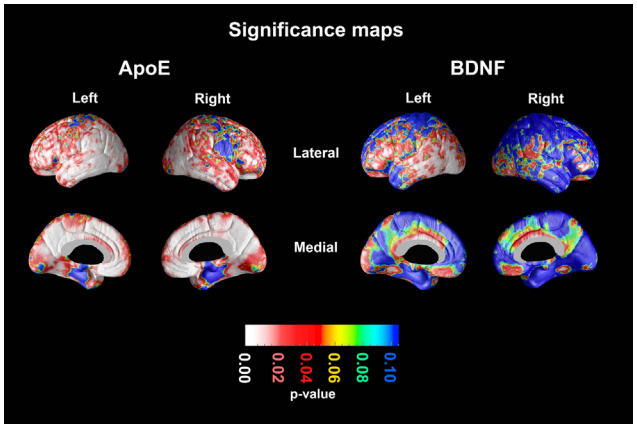
Background: Biomarkers are the only feasible approach to diagnose Alzheimer's disease (AD) in its presymptomatic stages, when a disease-modifying agent will have the greatest impact. Blood-based markers, that are inexpensive and easily obtainable, could become useful for presymptomatic diagnosis. Pittsburgh compound B is a positron emission tomography (PET) radiotracer that binds to fibrillar A b in the brains of symptomatic and presymptomatic AD subjects. Here we examined the association between several AD-relevant blood plasma proteins and PIB binding in the brain. **Methods:** Our dataset consisted of 18 AD, 56 mild cognitive impairment and 3 normal control Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects with available [11 C] PIB and peripheral blood protein data. MRI-coregistered PET data was smoothed with a 15 mm kernel and convected onto the 3D hemispheric models along the warping deformations computed in cortical pattern matching of the associated MRI scans. We applied linear regression to examine in 3D the associations between apolipoprotein E (ApoE), apolipoprotein J (ApoJ), brain-derived neurotrophic factor (BDNF), interleukin 6 receptor (IL6R), interleukin 13 (IL13) and tumor-necrosis factor a (TNF a) and PIB SUVR, while adjusting for age and sex. We used permutation statistics thresholded at $p<0.01$, for multiple comparisons correction. **Results:** Plasma ApoE showed significant negative association with PIB SUVR throughout the brain, except in the sensorimotor and entorhinal cortex (left p corrected =0.004, right p corrected =0.008). Plasma BDNF levels showed significant negative associations with left greater than right amyloid burden in the lateral temporal, inferior parietal, inferior frontal, anterior and posterior cingulate, and orbitofrontal regions (left p corrected =0.03). ApoJ, IL6R, IL13 and TNF a failed to show significant associations with PIB SUVR. **Conclusions:** Lower peripheral blood levels of proteins that are involved in A b degradation and clearance (ApoE) and neuroprotection against A b toxicity (BDNF) showed a significant widespread association with severity of brain amyloidosis. This further establishes the role of these two proteins in AD. The lack of association between IL6R, IL13 and TNF a may be explained by their stronger relevance to the neuroinflammatory aspects of AD, which are not directly measured by amyloid imaging.



P1-284 GENETIC RESILIENCE TO AMYLOID-RELATED NEURODEGENERATION IN OLDER ADULTHOOD

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Background: The pathophysiological cascade in sporadic Alzheimer's disease (AD) has been widely debated, with recent models suggesting that amyloid pathology early in the disease course may initiate or accelerate neurodegeneration. Yet a subset of individuals who present no clinical symptoms of AD during their lifetime show full blown AD pathology at autopsy. The present project sought to identify genetic variants that differentiate neurodegenerative and neuroprotective responses to amyloid pathology. **Methods:** We used data from ADNI-1 as a discovery dataset to identify gene-amyloid interactions in relation to brain atrophy. Amyloid was previously quantified using data acquired with 11 C-PIB. For replication, an independent dataset from ADNI- GO and ADNI-2 was used with amyloid data quantified using 18 F-AV-45. All volume data were quantified using FreeSurfer. Cognitive performance was evaluated using composite measures of executive function and memory. **Results:** In the discovery dataset, we used a statistical threshold of $p<5x10$ -5 and identified 13 genes which interacted with amyloid load to predict brain atrophy. In the cross-sectional replication dataset, two genetic-amyloid interactions remained significant when correcting for multiple comparisons taking linkage disequilibrium into account (IGFBP7 and SLC10A2). In a posthoc analysis, IGFBP7 also showed a significant interaction with amyloid in predicting cognitive performance, along with GRID2, ELTD1, and SEL1L. **Conclusions:** SNPs annotated to IGFBP7 were located in two distinct clusters. The first group clustered around a recent GWAS hit associated with cognitive function; in these SNPs, there was a strong negative relationship between amyloid deposition and cognitive function in homozygous major carriers. The second cluster was in closer proximity to LPHN3 and showed the allelic effect with a strong relationship between amyloid and cognition/volume in minor allele carriers. The significant GRID2 interaction provides further evidence that proper function of this gene, which plays an important role in the aborizations of Purkinje cells, may be a necessary component of a pro-inflammatory response to amyloid deposition. The ELTD1 SNPs cluster around a region of 40 SNPS that were recently implicated in risk for a catastrophic events in a GWAS study of longevity. This multidisciplinary approach has identified biologically plausible genetic associations related to positive and negative neural responses to amyloid deposition.

P1-285 WITHDRAWN

P1-286 REGIONAL WHITE MATTER LESIONS AND PITTSBURGH COMPOUND B RETENTION IN COGNITIVELY IMPAIRED ELDERLY

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Background: Increased white matter lesions (WML) are common in the elderly and associated with increased risk of cognitive impairment. Pathological studies indicate associations between WMLs and small vessel ischemic disease. Recent imaging studies suggest that some component of MRI-detected WM change may be due to axonal degeneration secondary to cortical neurodegenerative disease. **Methods:** 78 cognitively impaired subjects (MMSE 14-30) were recruited through the University of Michigan Cognitive Disorders Clinic for brain MRI and 11C-PiB imaging. Subjects with a Hachinski scale score >4 or meeting NINDS-AIREN vascular dementia criteria were excluded. MRI's from 6 subjects were not evaluated due to artifact. Parametric PiB distribution volume ratio (DVR) images were used to obtain DVR values for 7 cortical regions of interest in the following areas: lateral frontal, medial frontal, posterior parietal, posterior cingulate, anterior cingulate, lateral temporal, and occipital lobe. A PiB index was derived by averaging the mean DVR of these 7 ROI's. WML volumes were log transformed to address skewed distributions. Brain volumes were adjusted for intracranial volume. PiB index was examined as High and Low values. Logistic regressions determined associations between PiB binding and regional WML volume. A final logistic regression analysis examined High/Low PiB DVR index in relation to WML volume, adjusted for relevant variables. **Results:** Subject diagnoses were grouped into those with memory impairment (MI): amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (n=34), and those without significant memory impairment: