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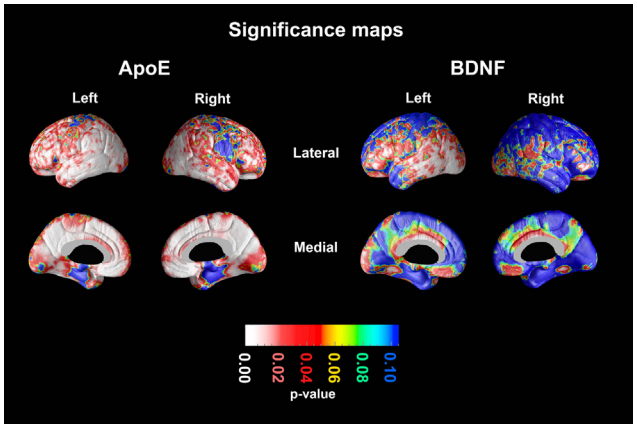
Background: Biomarkers are the only feasible approach to diagnose Alzheimer's disease (AD) in its presymptomatic stages, when a disease-modifying agent will have the greatest impact. Blood-based markers, that are inexpensive and easily obtainable, could become useful for presymptomatic diagnosis. Pittsburgh 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:

Frontal temporal dementia, Lewy Body Dementia, and non-amnestic MCI (n = 38). Average age was 68.4. High PiB index was associated with periventricular (PV) but not deep, WML volume. In a final logistic regression, high PiB index was associated with a diagnosis of MI (p =0.002), decreased gray matter volume (p = 0.06) and greater PV WMH volume (p = 0.04). PiB index was not associated with age or dementia severity. **Conclusions:** In a cognitively impaired cohort without significant history of cerebrovascular disease, greater amyloid binding was positively associated with AD/aMCI diagnosis and PV WMH burden. Regional WMH volumes may be helpful as a radiographic biomarker for identification of those at increased risk of having cortical AD pathology.

P1-287 GREY MATTER GRAPH PROPERTIES ARE RELATED TO DISEASE SEVERITY IN ALZHEIMER'S DISEASE

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Background: Coordinated patterns of cortical morphology in structural magnetic resonance imaging (MRI) scans have been described as structural graphs and such graphs are altered in Alzheimer's disease (AD). However, these grey matter graphs are restricted to group level analysis and can therefore not be used to study the relationship of altered graph properties and cognitive deficits in individual patients. Here we show for the first time that graph properties are related to disease severity using a recently developed method to describe single-subject grey matter networks. **Methods:** Figure 1 illustrates the pipeline of the new, fully automated method. Briefly, the nodes in the graphs represent grey matter areas that are connected when they are statistically similar. Graphs were constructed using grey matter segmentations that were obtained with SPM8 from T1 weighted structural MRI scans acquired at 3T from 38 AD patients (19 female, average age 72 ± 4 years) and 38 controls (19 females, average age 72 ± 4 years). For each node in each graph we the degree, path length, clustering coefficient, betweenness centrality and the small world coefficient. Group comparisons of standard graph properties were performed after correcting for grey matter volumetric measurements and were correlated to scores of global cognitive function as measured by the mini-mental state examination (MMSE). **Results:** AD networks were characterized by a more random topology as indicated by a decreased small world coefficient (p = 5.56 x10 -5). Global path length was strongly related with MMSE scores r = .49, p = 0.002), an association that was absent with volumetric measurements (p > 0.05). Altered path length of the parahippocampus, hippocampus, fusiform gyrus and precuneus showed the strongest relationship with cognitive decline. **Conclusions:** Single-subject grey matter graphs have a more random topology in AD. Importantly, graph alterations are related to disease severity at both whole brain level and in specific cortical areas. The present results support the clinical relevance of single-subject structural brain graphs and contribute to a better understanding of the relationship between structural changes and cognitive dysfunction in AD.

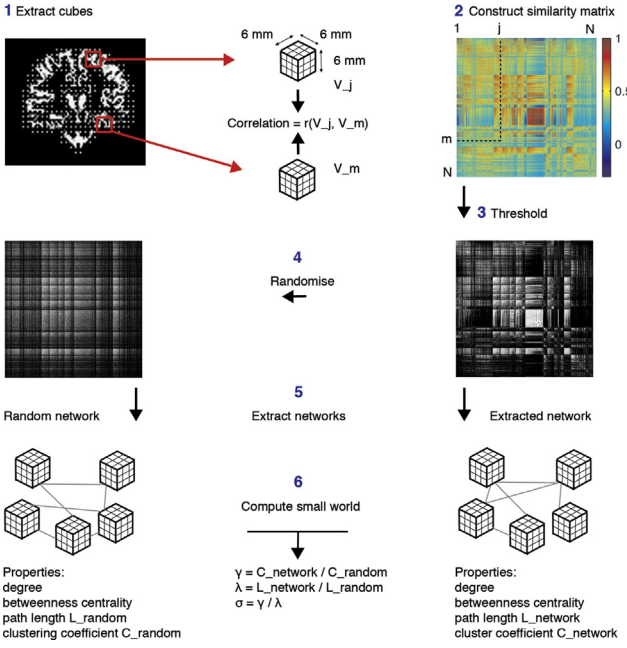

Figure 1. Schematic overview of method to extract single-subject grey matter graphs. After preprocessing, the gray matter segmentation is dvidied into 3×3×3 voxel cubes (1). The similarity between all *N* cubes within a scan was computed with the correlation coefficient and stored in a matrix with 1 to *N* rows and columns (2). In (3) this matrix is binarized when the similarity was significant with a $p_{FDR} < 0.05$. Twenty random matrices that kept intact the spatial degree distribution were generated for each similarity matrix (4). Finally we constructed the networks (5) and computed the degree, path length, clustering coefficient and small world property for all graphs (6). Figure adopted with permission from Tijms et al., 2012.

P1-288 DECLINE OF FIBER TRACT INTEGRITY OVER THE ADULT AGE RANGE: A DIFFUSION SPECTRUM IMAGING STUDY

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Background: Aging is associated with morphological brain changes. Diffusion spectrum imaging (DSI) is a powerful in vivo technique to determine structural connectivity in the living human brain. Here, we assessed the use of a novel DSI acquisition to determine associations between aging and subcortical fiber tract integrity. **Methods:** We studied 35 cognitively healthy subjects (17 women) spanning the adult age range between 23 and 77 years using high resolution anatomical MRI and a novel DSI acquisition at 3 Tesla. We determined effects of age on global fractional anisotropy (gFA) in selected fiber tracts as well as in a whole brain voxel-based analysis. For comparison, we studied effects of age on regional grey and white matter volumes. **Results:** We found significant decline of anterior corpus callosum fiber tract integrity with age, as well as significant gFA decline in widespread areas of subcortical white matter in absence of significant