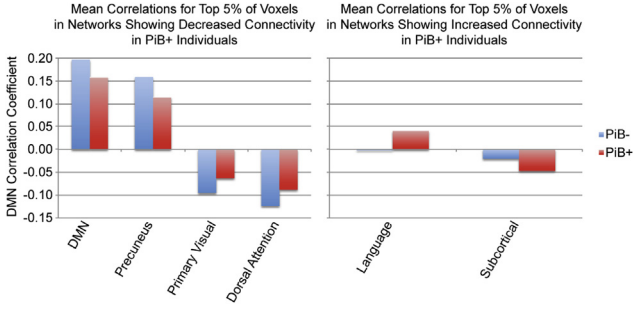
(CDS) approach that quantifies the deviance of clusters from a uniformly distributed pattern. **Methods:** We included 267 individuals from the 284 subject Harvard Aging Brain Study cohort with baseline PiB-PET and resting-state fMRI. Individuals with a PiB-PET value greater than 1.19, based on a Gaussian mixture model, were classified as PiB+. A two-sample t-test (PiB+ versus PiB-) with mean motion, SNR, age, and gender as covariates was used to evaluate the effect of amyloid on DMN connectivity as measured with TBR[1]. With CS, we used a traditional cluster-based significance threshold ($p<0.05$ corrected). Next, we developed the CDS approach to quantify the deviance of clusters from that of a uniformly distributed pattern across resting-state networks using the top (PiB->PiB+) or bottom (PiB+>PiB-) 5% of voxel-wise connectivity differences. The number of supra-threshold voxels in each of 11 principle resting state networks were compared to a simulated uniform distribution across networks using chi-square statistics ($p<0.05$). **Results:** Using CS, one cluster on the border of the primary visual and dorsal attention networks was less connected in PiB+. Using CDS, the spatial distribution of connectivity differences between PiB- and PiB+ individuals was significantly different than chance. Decreased connectivity in PiB+ individuals was most prominent in the default-mode, primary visual, dorsal attention, and precuneus; while increased connectivity in PiB+ individuals was most prominent in language and subcortical networks. **Conclusions:** In comparison to CS, our novel CDS approach appears to be more sensitive to detect potentially smaller amyloid-connectivity effects. The results support the notion that analyses of the spatial patterns provide additional insight into the effects of amyloid not revealed by the traditional cluster-based approaches. The main limitation of the CDS approach is the appropriateness of the simulated null distribution, and we are continuing to refine and validate the simulated distribution.



IC-P-126 DIVERGENT PATTERN OF CHANGES IN ASTROCYTOSIS AND FIBRILLAR AMYLOID PLAQUES AS MEASURED BY PET IN AUTOSOMAL-DOMINANT AND SPORADIC ALZHEIMER'S DISEASE

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Background: Early astrocytosis was reported from cross-sectional multitracer PET imaging in autosomal-dominant Alzheimer's disease (ADAD) and sporadic AD (sAD)[1,2]. Here we sought to validate the cross-sectional findings by a longitudinal follow-up investigation in a larger cohort, and investigate regional and temporal distributions of brain astrocytosis, amyloid deposition, glucose metabolism and brain perfusion. **Methods:** A cohort of ADAD (*APPswe/APParc/PS1*) and sAD participants underwent longitudinal multitracer PET imaging of astrocytosis with ^{11}C-Deuterium-L-Deprenyl (^{11}C-DED), fibrillar-Aβ (^{11}C-PIB) and glucose metabolism (^{18}F-FDG); and neuropsychological testing. 52 baseline participants (26 followed-up at ~3-years) included ADAD-carriers (n=11), non-carriers (n=16), sporadic MCI (sMCI) (n=17) and sAD (n=8). A modified-reference (cerebellum grey-matter) Patlak model was applied to ^{11}C-DED; early-frames (1-4 min) of ^{11}C-DED measured brain perfusion. ^{11}C-PIB and ^{18}F-FDG were expressed in SUVR(/pons). Voxel-wise z-score PET maps were obtained for individual ADAD-carriers relative to non-carriers (normal range: $|z|<1.645$). Linear mixed-effects models (LMMs) were applied to longitudinal PET data versus estimated years to symptom onset (EYO). **Results:** ^{11}C-DED binding in ADAD-carriers was highest from EYO $\approx$ –25 years. ^{11}C-PIB retention started in the striatum from EYO $\approx$ –25 years and in cortical regions from –20 years. ^{11}C-DED binding thus preceded Aβ deposition in several regions. ^{11}C-DED and ^{11}C-PIB subsequently followed divergent declining/increasing time-courses, respectively. Presymptomatic ADAD-carriers showed incipient hypometabolism but not hypoperfusion. In symptomatic ADAD-carriers, hypometabolism exceeded hypoperfusion. ^{18}F-FDG uptake showed decline rates in ADAD-carriers, and in PIB+ MCI until 5-years after diagnosis. Brain perfusion declined at slower rates than metabolism. Compared to sMCI/sAD, individual symptomatic ADAD-carriers demonstrated higher ^{11}C-PIB, lower ^{11}C-DED and lower ^{18}F-FDG. The longitudinal progression in PET-imaging biomarkers was associated to measures of cognitive decline. **Conclusions:** The longitudinal investigation of familial ADAD and sAD participants with a 3-year follow-up time demonstrated that astrocytosis precedes Aβ deposition. Prominent early and then declining astrocytosis, increasing fibrillar-Aβ deposition and decreasing metabolism and perfusion characterized both ADAD and sAD evolution, showing earlier onsets in ADAD but comparable rates of change in PET-imaging biomarkers in ADAD versus sAD. The observed early astrocytosis could be a response to pathophysiological changes including soluble oligomeric-Aβ, and might entail novel therapeutic applications. [1]Nordberg(2014),Neurodegener.-Dis.13:160-162; [2]Carter *et al.*(2012),J.Nucl.Med.53(1):37-46

IC-P-127 CSF PARAMETERS OF NEURODESTRUCTION AND ATROPHY OF THE BASAL FOREBRAIN CHOLINERGIC SYSTEM IN MILD COGNITIVE IMPAIRMENT

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Background: The basal forebrain cholinergic system (BFCS) is the major source of acetylcholine for the cerebral cortex in humans and shows typical patterns of atrophy in Alzheimer's disease

(AD) and mild cognitive impairment (MCI). Lowered levels of ß-amyloid 1-42 and elevated levels of tau and phopho-tau in cerebro-spinal fluid are related to plaque and tangle formation - the neuropathological hallmarks of AD. Little is known about possible interactions of BFCS atrophy and CSF levels of amyloid or tau. **Methods:** We analyzed high definition 3D structural magnetic resonance imaging data from the European DTI study in dementia (EDSD) of 64 participants with the clinical diagnosis of MCI. All individuals underwent lumbar puncture for CSF analysis. We automatically extracted BFCS volumes from 3D MPRAGE data using a post mortem based mask and determined correlations between volume of the BFCS and CSF levels of amyloid ß 1-42, tau and phospho-tau. **Results:** CSF levels of total tau were significantly correlated with BFCS volume of Ch4p, Ch4am_al and Ch3 subregions (Mesulam nomenclature), CSF total phospho-tau levels were significantly correlated only with the Ch3 region. Amyloid ß 1-42 levels did not show significant correlation with any of the BFCS subregions. **Conclusions:** Correlations of CSF tau/phospho-tau and BFCS atrophy agreed with neuropathological findings that neurofibrillary tangles in this area build up early in the course of AD. Furthermore, CSF levels of tau seem to better reflect the degree of atrophy of the BFCS in MCI than CSF amyloid levels.

IC-P-128 ALTERATIONS IN MYELIN CONTENT ARE RELATED TO COGNITIVE PERFORMANCE IN NONDEMENTED OLDER ADULTS: FINDINGS FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION STUDY

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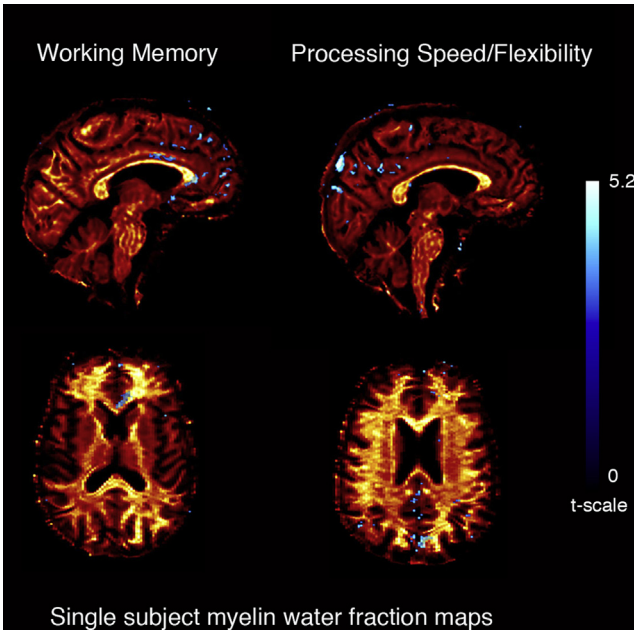
Background: Novel imaging biomarkers that directly target myelin provide unique information about the brain health. While converging studies underscore the relationship between white matter microstructure and cognitive function, particularly in the domain of processing speed, there is still a paucity of information about the relationship between other neurocognitive measures and myelin health. Defining the alterations of myelo-architecture associated with cognitive performance may provide additional information about the mechanisms underlying cognitive changes in healthy and pathological aging. **Methods:** 57 participants from the Wisconsin Registry for Alzheimer's Prevention study (62.84±6.62 years; range 45-74) underwent an extensive neuropsychological battery that was used to generate 4 factor scores: (1) Speed and flexibility, (2) Working memory, (3) Verbal learning and memory, and (4) Immediate memory. The cohort is enriched for Alzheimer's disease (AD) risk factors including parental family history and APOE4 genotype. Three-pool mcDESPOT processing of participants's MRI images was used to calculate T_1, T_2, and myelin water fraction maps (MWF). Parameter maps were transformed to a population template space using the Advanced Normalization Tools software package. In SPM12, each cognitive factor was regressed on T_1, T_2, and MWF maps ($p<0.001$, uncorrected), respectively, after adjustment for age, gender, and time interval between MRI scan and neuropsychological evaluation (1.9±4.1months). **Results:** In addition to known MWF associations with processing speed and flexibility, we found a positive relationship between working memory and MWF in the genu of the corpus callosum, anterior and middle cingulate gyrus, as well as other regions in the prefrontal cortex that have been shown to play a role in working memory (Figure 1). In contrast, speed and flexibility performance associations localized primarily to posterior cingulate gyrus and precuneus. No significant relationship was found between MWF and immediate memory nor verbal learning and memory. **Conclusions:** This study provides the first evidence that not only processing speed and flexibility but also working memory is associated with myelin content in nondemented late-middle-aged adults. Additional study is needed to determine the extent to which these findings are characteristic of healthy aging or due to early neurodegenerative changes in this cohort enriched for Alzheimer's disease risk factors.



IC-P-129 A JACOBIAN-BASED METHOD TO ASSESS CHANGES IN CORTICAL THICKNESS: APPLICATION TO ADNI DATA AND COMPARISON WITH LONGITUDINAL FREESURFER

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Background: Brain cortical thickness shows ability to discriminate between Normal Controls (NC), Mild Cognitive Impairment (MCI) and AD subjects. Longitudinal analysis allows assessing