IC-P-112 THE PATTERN OF CEREBRAL HYPOMETABOLISM AND ITS ASSOCIATION WITH CLINICAL RATINGS IN COGNITIVELY NORMAL OLDER ADULTS WITH AND WITHOUT SIGNIFICANT FIBRILLAR AMYLOID BURDEN: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

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Background: It has been suggested that fibrillar amyloid- b (A b) begins to accumulate prior to regional cerebral metabolic rate for glucose (CMRgl) and clinical declines. In this study, a voxel-based partial least squares (PLS) algorithm was used to 1) characterize the CMRgl pattern that best distinguished cognitively normal "fibrillar Aβ positive and negative" older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI), 2) compare the resulting FDG PET PLS subject scores in the Aβ positive and negative subjects, and 3) compare the extent to which these scores were associated with lower clinical ratings in each of the two subject groups. **Methods:** A b positivity was characterized in 225 cognitively normal subjects, 76 $\pm$ 6 years of age, using a mean cortical-to-cerebellar florbetapir SUVR threshold previously found to be associated with moderate or frequent neuritic plaques (Fleisher et al., 2011). A PLS routine in SPM environment was used to characterize the CMRgl pattern that best distinguished the resulting 71 Aβ positive and 154 Aβ negative subjects, characterize and compare their resulting FDG PET PLS subject scores, characterize and compare the extent to which the PLS scores were associated with clinical decline using the MMSE or ADAS-Cog, and determine the extent to which findings were solely attributable to fibrillar Aβ burden or APOE e 4 gene dose in each subject group. **Results:** The CMRgl pattern that best distinguished the Aβ positive from Aβ negative subjects included significantly lower measurements in posterior cingulate, parietal, and temporal regions. The resulting FDG PET PLS scores were significantly different in the Aβ positive and negative groups (p=8e-12). They were significantly associated with poorer MMSE and ADAS-Cog scores in the Aβ positive group(r=-0.50, p=9.1e-6; r=0.52,p=3.0e-6) but only significant for ADAS-cog in the Aβ negative group(r=0.16,p=0.05). The PLS score associations with MMSE or ADAS-Cog were stronger in the Aβ positive than in Aβ negative subjects(p=4.3e-4,p=2.2e-3). These results remained after correction for fibrillar A b or APOE- e 4 gene dose. **Conclusions:** Fibrillar A b burden in cognitively normal older adults is associated with a characteristic pattern of cerebral metabolism, and the metabolic pattern in those with fibrillar Aβ positive had stronger associations with poorer clinical ratings.

IC-P-113 CEREBROSPINAL FLUID BETA-AMYLOID 42, TAU, PTAU181 AND RESTING STATE FUNCTIONAL CONNECTIVITY

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Background: Cerebrospinal fluid (CSF) biomarkers detect early pathologic changes of Alzheimer's disease (AD). AD is associated with reduced default mode network (DMN) integrity as measured by resting state functional connectivity magnetic resonance imaging (rs-fcMRI). We assessed the relationship between rs-fcMRI measures of DMN integrity and CSF biomarker abnormalities in cognitively normal individuals. **Methods:** A total of 207 cognitively normal individuals, as assessed by the clinical dementia rating scale (CDR), underwent CSF assays of amyloid- Aβ 42 (Aβ 42), tau,and phosphorylated tau 181 (ptau 181) as well as rs-fcMRI (Table 1). The DMN was assessed by region-of-interest based and voxel-wise whole-brain analyses. **Results:** Decreased CSF Aβ 42, increased CSF tau or CSF ptau 181 was independently associated with reduced DMN integrity, with the most prominent decreases in functional connectivity observed between the posterior cingulate and medial temporal regions. Observed reductions in functional connectivity were not attributable to age or structural atrophy in the posterior cingulate and medial temporal areas. A similar pattern of functional connectivity decrease was observed in both region-of-interest based and voxel-wise analyses for decreased CSF Aβ 42 or increased CSF ptau 181 (Figure 1). **Conclusions:** Both Aβ and tau pathology affect DMN integrity prior to clinical onset of AD.

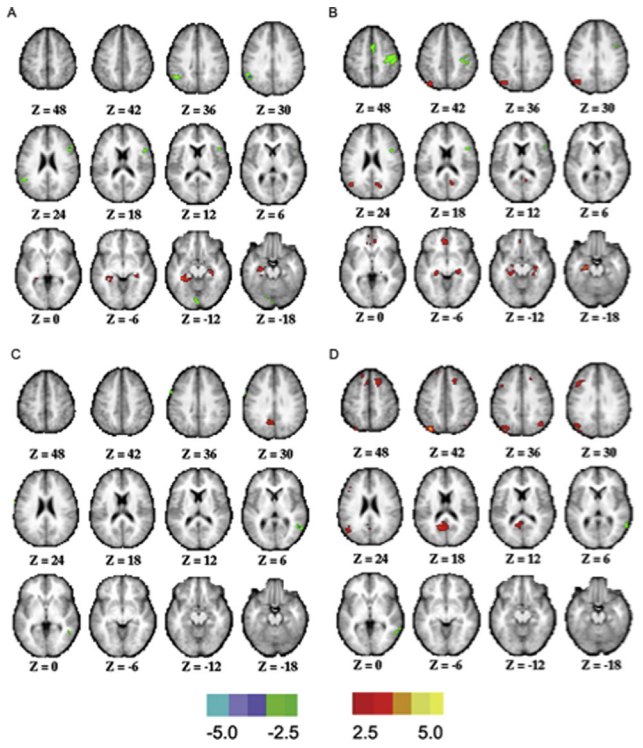

Figure 1. Voxel-wise analyses assessing functional connectivity of the posterior cingulate cortex (PCC) and medial temporal lobe (MTL) in cognitively normal individuals with abnormal levels of cerebrospinal fluid (CSF) Aβ_{42} or ptau$_{181}$ **A**: PCC functional connectivity compared between CSF Aβ_{42}-negative vs. CSF Aβ_{42}-positive; **B**: PCC functional connectivity compared between CSF ptau$_{181}$-negative vs. CSF ptau$_{181}$-positive; **C**: MTL functional connectivity compared between CSF Aβ_{42}-negative vs. CSF Aβ_{42}-positive; **D**: MTL functional connectivity compared between CSF ptau$_{181}$-negative vs. CSF ptau$_{181}$-positive. Functional connectivity maps were compared using random effects analyses. Maps display random effects decreases in correlations (hot color) and anti-correlations (cold color) in each comparison. Maps were thresholded at a voxel-level $|Z| > 2.5$ and cluster size > 35 voxels, uncorrected for multiple comparisons.