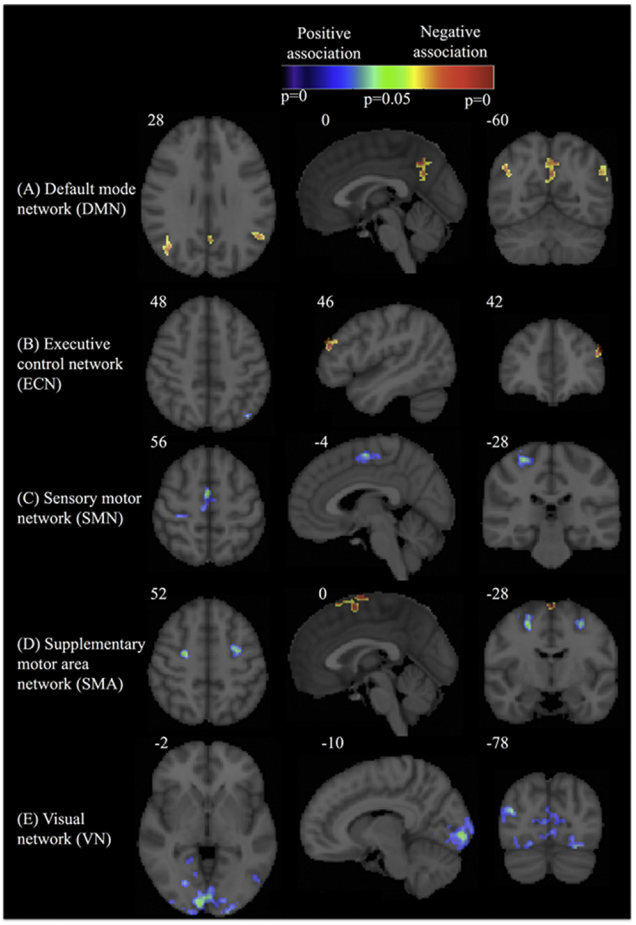

Figure 2. **Voxel**-based maps of latent variables inferred by partial least squares regression analyses of functional connectivity and global Aβ burden associations.

mode network. Aβ deposition was quantified both globally, and also within ICN-specific cortical regions. **Results:** We found that even in the absence of any cognitive or structural changes, global cortical Aβ burden was associated with functional connectivity in the DMN as well as cortical networks involved in executive control, motor and perceptual timing, and visual detection but not salience processing, attention, and working memory. We also found that there were significant effects of local network Aβ burden (i.e., ICN Aβ burden) on the network functional connectivity for all ICNs considered in this study; and the effects were associated more closely to local network Aβ burden than global Aβ burden. **Conclusions:** The relationship between local network Aβ burden and disrupted intrinsic connectivity in various brain networks, in the absence of cognitive deficit and brain atrophy (and presumably absence of cortical tau tangles and neurodegeneration based on previous pathology reports), suggests that neuronal dysfunction may be due to local toxicity of Aβ independent of the presence of tau. Furthermore, the results suggest that local toxicity of Aβ may represent an early change in preclinical AD.

Table
Coefficients of determination (R^2) of the endogenous latent variables inferred by partial least squares regression analyses to assess the amount of variance in functional connectivity explained by global Aβ burden and ICN Aβ burden.

ICN	
Global Aβ burden	
ICN Aβ burden	
Default mode network (DMN)	
	0.23
	0.29
Dorsal attention network (dAN)	
	NS
	0.39
Episodic memory network (EMN)	
	NS
	0.19
Executive control network (ECN)	
	0.34
	0.46
Salience processing network (SPN)	
	NS
	0.34
Sensory motor network (SMN)	
	0.27
	0.21
Supplementary motor area network (SMA)	
	0.33
	0.49
Visual network (VN)	
	0.15
	0.11

IC-01-03 DIFFERENT PATHWAYS TO ALZHEIMER'S DISEASE? ATROPHY, HYPOMETABOLISM, AND BETA-AMYLOID DEPOSITION IN DIAGNOSTIC GROUPS AT INCREASED RISK

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Background: Existing findings of Alzheimer's disease (AD)-typical atrophy without concurrent β-amyloid (Aβ) burden suggest that β-amyloidosis might not be the only entrance point to AD pathogenesis. The present study aimed to characterize AD-pathological mechanisms in at-risk diagnostic groups, namely, cognitively normal (CN) older APOE4 carriers and patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). Brain regions showing characteristic variation in the relative degree of Aβ deposition, glucose hypometabolism, and gray-matter atrophy were previously identified in AD patients (La Joie et al., 2012). Here, we used a similar approach to detect AD-typical patterns in biomarker expression within each diagnostic group. **Methods:** Structural MRI, 18F-

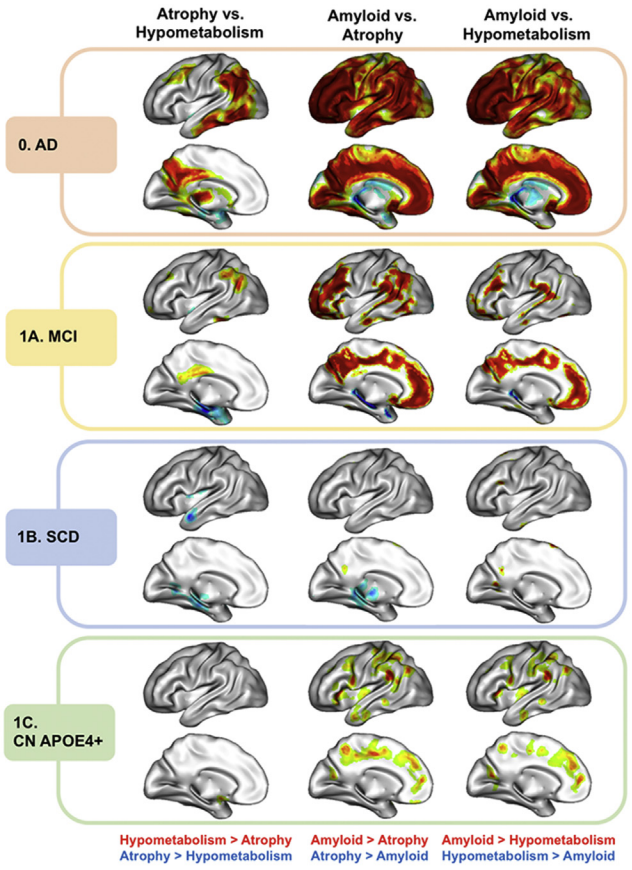

Figure 1. Voxel-wise intra-modality comparisons between regional degrees of atrophy, hypermetabolism and amyloid deposition in diagnostic groups with 1A. Mild Cognitive Impairment (MCI), 1B. Subjective Memory Decline (SCD), 1C. CN APOE4 carriers as well as 0. AD patients (for visual comparison). Contrast maps were displayed on the left hemisphere thresholded at t -values of $p < 0.001$ uncorrected, k = 20.

fluorodeoxyglucose PET and 18F-florbetapir PET data were collected from Aβ-negative/neurodegeneration-negative CN controls (n=41, 66±8 years), CN APOE4 carriers (n=17, 64±9 years), and patients with SCD (n=16, 69±7 years), MCI (n=30, 73±7 years) and AD (n=22, 69±9 years). For each imaging modality, standardized age-adjusted maps were computed using the controls as reference group. Relative degrees of biomarker expression were assessed in each diagnostic group via voxel-wise inter-modality comparisons of standardized maps. In addition, discriminatory power of AAL ROIs preferentially sensitive to Aβ deposition, hypometabolism, or atrophy (as derived in AD patients) was examine. **Results:** In the MCIs voxel-wise analyses detected AD-typical patterns in the relative degree of biomarker expressions (Figure 1a). In SCD only predominant medial-temporal atrophy was recovered (Figure 1b), while CN APOE4 carriers showed greater degree of Aβ deposition (Figure 1c). Confirming these findings, MCI patients were discriminated from controls by Aβ deposition-, hypometabolism-, and atrophy-predominant ROIs. Only the atrophy-predominant ROI distinguished SCD patients, and only the Aβ deposition-predominant ROI discriminated CN APOE4 carriers. **Conclusions:** MCI patients exhibit regional variation in the relative degree of Aβ deposition, hypometabolism, and atrophy typically seen in AD, although less extended and pronounced. SCD appears to reflect pathological mechanisms linked to atrophy in the absence of Aβ deposition. CN APOE4 carriers predominately harbor Aβ pathology without AD-typical patterns of atrophy or hypometabolism. Our findings suggest that Aβ and non-Aβ pathways could emerge first in different at-risk groups and converge in prodromal AD.

IC-01-04 DIAGNOSTIC IMPACT OF [^{18}F]FLUTEMETAMOL AMYLOID IMAGING IN YOUNG-ONSET DEMENTIA

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Background: In young onset dementia, approximately one out of three patients has an atypical clinical presentation, which substantially complicates correct nosological diagnosis. *In vivo* detection of amyloid pathology can be useful in the diagnostic process. The present study aimed to examine the diagnostic impact of the amyloid-PET imaging agent [^{18}F]flutemetamol in assessing patients with young onset dementia. **Methods:** The present study included 200 patients visiting our tertiary memory clinic and diagnosed with young onset dementia (age <70 years). Patients were enrolled when physician's diagnostic confidence was <90% after a full routine diagnostic work-up for dementia. All patients underwent a [^{18}F]flutemetamol PET scan which was visually assessed as amyloid positive or negative. Scans were performed 90-110 minutes after injection of 185 MBq [^{18}F]flutemetamol. Before and after disclosing PET results to the physician, clinical diagnosis and confidence in this diagnosis were determined. In addition, the impact on healthcare management plan, including medication and care, and request for additional investigations was assessed. **Results:** [^{18}F]Flutemetamol scans were positive in 107 out of 137 (78%) patients with a pre-PET AD diagnosis and in 20 out of 63 (32%) patients diagnosed with a non-AD dementia prior to PET. Overall, confidence in diagnosis increased in 87% of the patients, on average from 69±12% to 89±15% after disclosing PET results (p<0.001). In 68 (34%) patients, [^{18}F]flutemetamol PET results led to a change in patient healthcare management (i.e. medication changed in 61 patients and care plan altered in 22 patients). A positive PET scan resulted in change of management plans (either medication, care, or both) nine times more often than a negative PET scan (n=61 vs. n=7; p<0.001). For 43 (22%) patients, additional ancillary investigations were planned after PET results were disclosed, predominantly when PET results were negative (n=33; p<0.001). In patients with a pre-PET AD diagnosis and a positive PET scan, additional ancillary investigations were less often requested compared to patients with a negative PET scan (p<0.001). **Conclusions:** [^{18}F]Flutemetamol PET increased physician's overall confidence in clinical diagnosis. In