IC-01-01

ARE LOW LEVELS OF PIB-PET SIGNAL CLINICALLY SIGNIFICANT?

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Background: In a previous study[1] we suggested that the current SUVR thresholds of $\sim$1.4-1.5 are too high to capture early amyloid accumulation. We showed evidence that by the time a person reaches these thresholds, amyloid is already widespread throughout the cortex and suggested an SUVR value of 1.21 as an optimal cutoff to detect early PIB-PET signal using whole-brain [^{11}C]PIB retention. The goal of this study was to characterize individuals with intermediate levels of amyloid on a variety of demographic, cognitive and brain markers (Table 1). **Methods:** This study included 242 subjects (183 normal older adults and 59 adults with mild cognitive impairment). Group comparisons between PIB- (SUVRs < 1.21), PIBi (SUVRs $\geq$ 1.21 and <1.4) and PIB+ (SUVRs $\geq$ 1.4) were first restricted to cognitively normal individuals and then repeated in the total sample. **Results:** In normal older adults, group differences were found for age, ApoE4 status and rate of amyloid accumulation. PIBi and PIB- individuals were younger than PIB+ individuals, and PIBi and PIB+ individuals had a higher frequency of ApoE4 carrier status and a higher rate of amyloid accumulation than PIB- individuals. When the analyses were performed in the total sample, the same results

were found. Additionally, PIB+ individuals showed lower cortical thickness in AD-regions[2] as well as lower global cognition (MMSE score) than PIBi and PIB-. **Conclusions:** While PIBi individuals showed similar rate of amyloid accumulation and ApoE4 status to PIB+, they were comparable to PIB- on the other markers. These results suggest that low levels of PIB-PET signal are clinically relevant and that subjects with SUVR values between 1.21 and 1.4 are early accumulators. [1] Villeneuve et al., AAIC 2014; [2] Wirth et al., JAMA Neurol. 2013

Table 1
Variables of interest

Demographic Markers	Cognitive Markers	Brain Markers

• Age
• Gender
• Education
• ApoE e4 status
	• Mini-Mental Status Examination (MMSE)
	• [1] Memory complaint
	• [1] Factor Scores (baseline and change data)
	  o Episodic Memory
	  o Executive Function
		• Hippocampal Volume
		• FDG AD-regions
		• Cortical Thickness AD-regions
		• Amyloid accumulation[2]

[1]Data only available in 127 cognitively normal older adults.
[2] Data only available in 55 cognitively normal older adults, rate of change in amyloid over 2 time points (3.4 years, 1.4 SD).

IC-01-02

LOCAL AMYLOID-B TOXICITY ON LARGE INTRINSIC BRAIN NETWORKS IN COGNITIVELY HEALTHY ELDERLY

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Background: Considerable in vitro and animal data suggests that Aβ, even in the absence of tau tangles, has adverse effects on neuronal dysfunction, supporting the hypothesis that neuronal dysfunction is due in part to direct Aβ toxicity that is not completely mediated by tau. Although previous studies demonstrated the effects of global Aβ burden on the default mode network in cognitively normal elderly individuals, effects of local network Aβ burden on the other large-scale intrinsic connectivity networks (ICNs) are not yet clear in asymptomatic individuals. In this study, we aimed to investigate the effects of both global and local Aβ deposition on various cortical ICNs in older adults with normal cognition. **Methods:** Fifty-three elderly subjects with normal cognition were included. We characterized the association of Aβ burden with intrinsic connectivity changes in a wide range of functional networks, including working memory, attention, motor and perceptual timing, and visual detection networks, as well as resting-state default
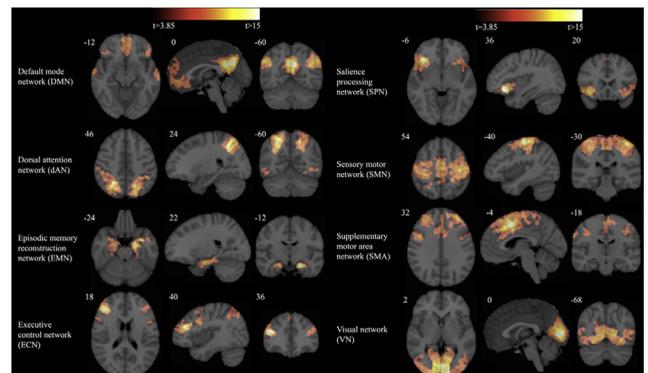

Figure 1. Spatial maps of the ICNs of interest identified by seed-to-voxel based analysis of Aβ– and ApoE ε4 non-carrier subjects.
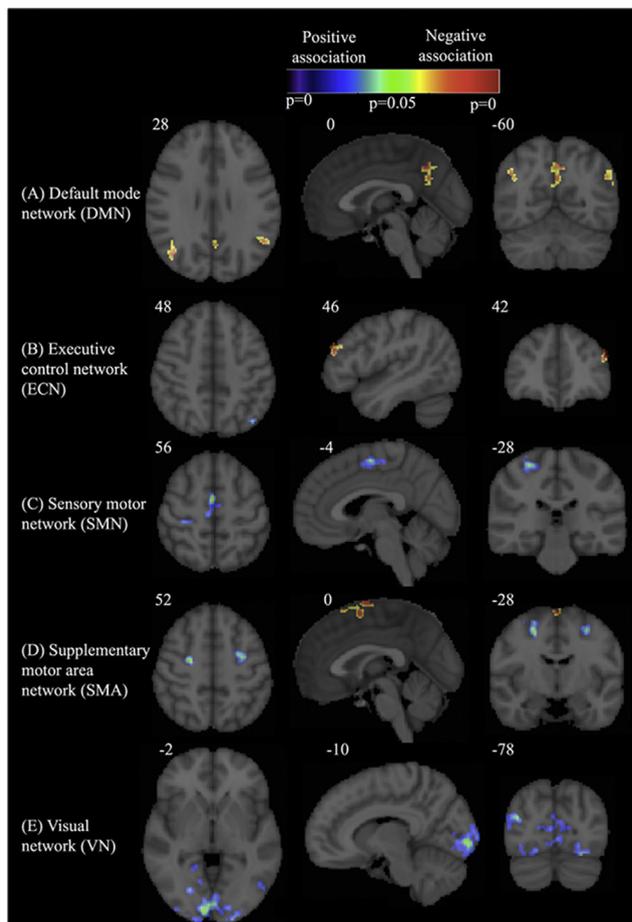
Figure 2. **Voxel**-based maps of latent variables inferred by partial least squares regression analyses of functional connectivity and global Aβ burden associations.

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

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 pre-clinical AD.

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-