Amyloid PET predicts atrophy in older adults without dementia: Results from the AMYPAD Prognostic & Natural History study

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Abstract:

The impact of amyloid-β (Aβ) accumulation on regional brain atrophy in preclinical Alzheimer's disease (AD), and its interaction with risk factors like sex and APOE-ε4 carriership, remains unclear. In this study, we examined these associations in a population of older adults without dementia and evaluated the potential of Aβ-PET for risk stratification.

We included 1329 participants (56 % female) with an age of 68.2 ± 8.78 years from the prospective multi-center AMYPAD Prognostic and Natural History Study who underwent [18F]Flutemetamol or [18F]Florbetaben Aβ-PET and T1-weighted MRI, with longitudinal data for 684 participants (median follow-up = 3.4 years). Linear mixed models assessed the effect of baseline Aβ burden through the Centiloid approach on longitudinal changes in regional gray matter volume and thickness. Sensitivity analyses were performed in cognitively normal only (CDR = 0) individuals and while correcting for CSF p-tau181 and t-tau. A second model investigated the effects of sex or APOE-ε4 carriership.

Baseline global Aβ was predictive of widespread atrophy in several brain regions, most strongly in the fusiform (βVolume = -0.006, βThickness = -0.009), hippocampus (βVolume = -0.005), posterior cingulate (βVolume = -0.006), and precuneus (βVolume = -0.004, βThickness = -0.007), also when investigating only in cognitively normal individuals. Only fusiform atrophy (βp-tau = -0.011; βt-tau = -0.011) remained predicted by Aβ when correcting for p-tau181 or t-tau. Temporal atrophy was exacerbated in women, while frontal, lateral-temporal and hippocampal atrophy was exacerbated by carriership of at least one APOE-ε4 allele, with volumetric loss more sensitive to sex effects and thinning more sensitive to APOE-ε4 effects.

Our findings suggest that in older adults with mostly preserved cognition, baseline Aβ-PET predicts future brain atrophy, with fusiform atrophy showing independence from tau pathology and Aβ-dependent atrophy being exacerbated in region-dependent manners in females and APOE-ε4 carriers. Regional cortical volume and thickness may serve as sensitive markers for early Aβ-related neurodegeneration and aid in stratifying risk in AD prevention trials.

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