

Spatial Amyloid-informed Multimodal Brain Age
As An Early Marker Of Alzheimer’s-related
Vulnerability And Risk Stratification

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KEY TAKEAWAY: Amyloid-informed multimodal brain age gap integrates regional Aβ-PET and structural MRI features, capturing AD-related cognitive, biomarker, and network vulnerability beyond global amyloid burden alone.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Brain age gap (BAG), defined as the difference between predicted and chronological age, is a promising marker of neurobiological aging but MRI-only models may insufficiently reflect Alzheimer’s disease (AD) pathology. Whether incorporating regional amyloid-β (Aβ) PET information can improve the sensitivity of brain-age modeling to early AD-related vulnerability remains unclear.	We analyzed 990 participants from the Chinese Preclinical Alzheimer’s Disease Study (CPAS) recruited from community settings and memory clinics (NC n=185, SCD n=206, MCI n=402, dementia n=197). Brain age was estimated using machine learning models trained exclusively in Aβ-negative NC participants. Regional Aβ-PET SUVRs and AAL-based gray matter volumes were fused to build an amyloid-informed multimodal brain-age model. BAG associations were examined with cognitive status, discrimination of objective cognitive impairment, global cognition, plasma biomarkers, and hippocampus–DMN connectivity.	Support vector regression with PET+MRI features showed robust performance (MAE 2.07 years in males and 2.51 in females; R² 0.88/0.86; ε-bias <0.05). BAG increased progressively across cognitive stages, and this trend persisted in both Aβ-positive and Aβ-negative strata. Each 1-year higher BAG was associated with higher odds of MCI (OR=1.08) and dementia (OR=1.37), with stronger effects in Aβ-positive participants (OR=1.16 for MCI; OR=1.46 for dementia). Adding BAG to a demographic+APOE model improved discrimination of objective cognitive impairment (AUC 0.748 overall; 0.820 Aβ-positive) with ΔAUC 0.038 overall and 0.098 in Aβ-positive participants, alongside consistent NRI/IDI gains. BAG explained more variance in ACE-III than global Aβ SUVR (overall R² 0.495 vs 0.410), and residual BAG remained associated with cognitive outcomes after accounting for SUVR and demographics. Higher BAG correlated with higher p-tau217, p-tau181, NfL, and GFAP and lower Aβ42/40, and was associated with reduced hippocampus–DMN connectivity.	An amyloid-informed multimodal BAG integrates regional Aβ pathology and neurodegeneration and captures cognitive, biomarker, and network vulnerability beyond global amyloid burden alone, supporting its potential utility for individualized risk stratification along the AD spectrum.	Cui L, Zhang Z, Tu Y, Wang M, Guan Y, Li Y, et al. Association of precuneus Aβ burden with default mode network function. Alzheimer’s & Dementia 2025. Cui L, Zhang Z, Huang C-C, Yuan C-Y, Tu Y-Y, Wang M, et al. Beyond binary classification: comparing three region-based multi-phase aβ staging systems. Alzheimer’s Dement: J Alzheimer’s Assoc 2025 Cui L, Huang L, Pan F-F, Wang Y, Huang Q, Guan Y-H, et al. Chinese Preclinical Alzheimer’s Disease Study (C-PAS): Design and Challenge from PET Acceptance. The Journal of Prevention of Alzheimer’s Disease 2023
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