

Longitudinal Brain Structural Changes Among Alzheimer’s Disease and Related Dementias from PUMCH Dementia Cohort

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Wenjun Wang, Xinying Huang Yuyue Qiu, Yunfan You, Bo Li, Meiqi Wu,Li Huo , Ling Qiu, Dan Lei, Yuhan Jiang,Tianyi Wang, Yuanheng Li, Wei Jin, Shanshan Chu, Liling Dong, Chenhui Mao, Feng Feng, Jing Gao

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	
Most imaging studies on Alzheimer’s disease (AD) and related dementias focus on cross-sectional analyses. The longitudinal dynamic changes of brain structure, and the moderating effects of age at onset, disease severity, and amyloid pathology, remain insufficiently characterized. This study aimed to characterize longitudinal brain structural changes in biomarker-defined AD across onset-age and cognitive-severity strata, and to compare structural evolution patterns between AD and related dementias.	A total of 280 patients with longitudinal data were included from PUMCH dementia cohort at Peking Union Medical College Hospital (ClinicalTrials.gov ID: NCT05023564). All participants had at least one AD-related biomarker (PET, cerebrospinal fluid, or plasma). Demographic and clinical information was collected, and each participant underwent at least two standardized brain MRI scans with concurrent cognitive assessments (MMSE, MoCA, ADL, CDR, CDR-SB, and domain-specific cognitive assessments). High-resolution 3D T1-weighted images were processed for regional volumetric segmentation. Intracranial volume–adjusted regional volumes were converted into age-matched Z scores based on Chinese normative data. Linear mixed-effects models were applied to assess longitudinal regional volume changes across onset-age groups, baseline cognitive strata, dementia types, and amyloid-β (Aβ) status.	A total of 280 patients were included, of whom 210 were biologically A+ [160 AD (A+T+), 35 ADmix (A+T+, +X), 11 ADlike (A+T–), and 4 AD-probable (A+T0)], and 70 were A-T- [31 ADmimic (clinical AD-possible) , 20 vascular dementia, 15 frontotemporal dementia, and 4 other neurodegenerative diseases]. In addition, 28 healthy control participants were included. Regarding age at onset, early-onset AD (EOAD, <60 years, 60 [37.5%]) showed significantly faster and more widespread structural decline in frontal, parietal, and temporal association regions, particularly in the temporal neocortex, compared with mixed-onset (MOAD, 60-70 years) and late-onset AD (LOAD, >70 years). In contrast, later-onset AD exhibited more regionally constrained and attenuated longitudinal structural changes. When stratified by baseline disease severity, similar heterogeneity in the rate and spatial distribution of brain structural change was observed across CDR groups (0.5, 1.0, and ≥2). Patients with CDR ≥2 showed significantly greater decline in the superior temporal gyrus compared with the other groups. Compared with ADmimic, AD showed significantly faster and more widespread structural decline, particularly in ventrolateral fronto-temporal regions. At the cohort level, A+ patients demonstrated significantly faster and more extensive structural decline than A- patients, especially in ventromedial fronto-temporal regions.	Age at onset and baseline cognitive status critically shape the rate and spatial pattern of longitudinal brain structural change in AD, whereas amyloid pathology exerts a dominant influence. Longitudinal brain structural changes in ADmimic differ substantially from those observed in AD. These findings highlight pronounced structural heterogeneity in AD and support biomarker-informed stratification for disease monitoring and clinical trial design.	No reference.
				CONTACT E-mail: 1051556993@qq.com  ALZHEIMER'S ASSOCIATION 