

Distinct molecular trajectories precede amyloid- β and tau pathology in Alzheimer's disease

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submitted work). K.B. has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, Beckman-Coulter, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Quanterix, Roche Diagnostics, Sanofi and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper.

Abstract

Alzheimer's disease (AD) progresses over a prolonged preclinical phase marked by early amyloid- β pathology (A β), followed by tau spread and neurodegeneration. However, limited understanding of longitudinal, stage-specific molecular processes constrains therapeutic timing and patient stratification. Here, we reconstructed molecular trajectories across the AD continuum by integrating longitudinal cerebrospinal fluid (CSF) proteomics with A β and tau biomarkers from two independent cohorts. We identified distinct trajectories emerging prior to A β and tau conversion. Preclinical A β -dominated transitions were characterized by immune- and lipid-associated programs, whereas tau-dominated transitions at the mild cognitive impairment stage were linked to synaptic, proteostatic, and autophagy-related signatures. These stage-specific trajectories predicted biomarker conversion, including from the preclinical, pre-A β stage. Longitudinal voxelwise analyses further revealed spatially distinct cortical A β and tau patterns corresponding to inflammatory and proteostatic-synaptic signatures. Together, these findings define temporally ordered molecular pathways underlying AD progression and inform stage-specific therapeutic strategies.

Main text

Alzheimer's disease (AD) develops over decades, with pathological processes emerging before the onset of clinical symptoms¹. Therapeutic strategies increasingly target early and preclinical stages², yet treatment development remains constrained by an incomplete understanding of the longitudinal molecular dynamics that drive progression during these phases. Cross-sectional biomarker studies provide valuable snapshots of pathology³ but are limited in their ability to resolve temporal ordering and transition dynamics of key biological processes, including inflammatory responses^{4,5}, synaptic dysfunction⁶, and disturbances in proteasomal function^{7,8}. These processes are thought to evolve sequentially over time, potentially defining stage-specific windows of vulnerability⁹⁻¹³ and therapeutic opportunity. Longitudinal molecular profiling across the early AD continuum is therefore essential to delineate the natural progression of amyloid- β (A β) and tau-associated biology and to inform mechanism-guided intervention strategies.

To characterize the molecular progression across the AD continuum, we anchored disease time to six clinically and biomarker-defined stages spanning (1) preclinical A β -negative (A-) cognitively unimpaired (CU) individuals who did not convert to A β -positivity (A+), (2) preclinical CU A- individuals who converted to A+, (3) CU A+ individuals, (4) A+ individuals with mild cognitive impairment (MCI), (5) A+ tau-positive (T+) individuals with MCI, and (6) A+T+ individuals with dementia. This framework was applied to cerebrospinal fluid (CSF) SomaScan proteomic data spanning 6094 proteins from two independent cohorts, comprising 526 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 316 participants from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort. Longitudinal CSF proteomics were available for 114 TRIAD participants over a follow-up of 2-4 years, enabling within-person modelling of proteomic change (Demographics in **Extended Data Tables 1-3**). Disease stages

were associated with the expected progression of established clinical, imaging, and fluid biomarkers, including cognitive decline, hippocampal atrophy, increasing A β and tau pathology measured by PET and CSF biomarkers (**Fig. 1a**, **Extended Data Fig. 1-2**). This anchoring strategy enabled integration of cross-sectional and longitudinal proteomic data within a unified concatenated disease-time (CDT) framework (**Fig. 1b**, **Extended Data Fig. 3a**), allowing reconstruction of molecular transition trajectories across early and late AD stages.

To identify temporal patterns of proteomic change, we performed unbiased clustering of protein trajectories across the CDT. This analysis identified four clusters with distinct temporal profiles (**Fig. 1c**, **Extended Data Fig. 3b-c**). While we detected inflammatory proteins like CD74, IL1B, and CLEC2D preceded A β -conversion, the largest proteomic changes were concentrated during the transition of A+T $^-$ into A+T $^+$, whereas a pronounced reversal of change was observed during later stages with established dementia in A+T $^+$ (**Extended Data Fig. 3d-e**). Functional enrichment analysis revealed that cluster 1, exhibiting steady decline, was associated with RNA processing and transcriptional regulation while the clusters that start to increase in CU A $^+$ were associated with synaptic and stress-response pathways (cluster 2) or inflammation-related processes (cluster 3). Cluster 4 followed a bi-phasic trajectory without significant pathway enrichment, consistent with heterogeneous, mixed-direction biology limiting pathway-level coherence (**Extended Data Fig. 3f-i**).

To disentangle A β and tau preceding molecular dynamics, we first identified proteins exhibiting significant longitudinal change across the full AD trajectory. For these proteins, we quantified stage-specific differences by comparing rates of change during the pre-A β stage (-5 to 0 years), the tau-conversion stage (0 to 10 years), and the period of clinical impairment (0 to 15 years). This framework enabled isolation of proteins showing preferential increases during A β -associated or tau-associated progression while remaining stable during the respective other stage, thereby capturing specific molecular changes that precede conversion to A β or tau positivity (**Fig. 1d**, **Extended Data Fig. 3j-k**). We observed a clear separation of molecular trajectories into A β -dominated and tau-dominated transition signatures (**Fig. 1e**). Proteins mostly increasing during the tau-conversion stage were associated with synaptic, proteasomal, redox and autophagic pathways, consistent with molecular programs causing tau spread and cognitive decline (**Fig. 1f-g**). Strikingly, proteins increasing during the A β conversion stage were enriched for immune- and lipid-associated processes and rose prior to the transition to A β positivity, revealing early inflammatory engagement during the preclinical phase of AD (**Fig. 1h**).

Finally, we examined whether the stage-specific transition signatures captured biological processes that are already operative before biomarker-defined conversion. The elevated A β -transition signature was associated with a higher risk of conversion from A $^-$ to A $^+$ (**Fig. 1i**), indicating that immune- and lipid-associated molecular programs precede A β conversion. Similarly, the increased tau-transition signature predicted progression from A+T $^-$ to A+T $^+$ (**Fig. 1j**), demonstrating that synaptic, proteasomal, and autophagic pathways anticipate tau conversion rather than only emerge as a downstream consequence. Next, we assessed voxelwise associations of the A β and tau transition signatures with longitudinal A β and tau PET changes in ADNI and TRIAD. The A β -associated signature

showed spatially distributed longitudinal associations with A β PET uptake, involving different cortical regions, consistent with widespread A β accumulation during preclinical disease stages (**Fig. 1k**). The tau-associated signature exhibited longitudinal associations with tau PET uptake in mesiotemporal, temporal pole and limbic regions implicated in early tau propagation (**Fig. 1l**). These findings demonstrate that distinct biological pathways are engaged prior to A β and tau conversion and that their molecular signatures predict biomarker conversion.

Here, we combined longitudinal CSF proteomics with repeated clinical, imaging, and biomarker assessments across two independent cohorts to reconstruct molecular trajectories spanning the AD continuum. We identified a pronounced A β -associated tissue response that exhausted in later disease stages with established dementia. Immune- and lipid metabolism-associated pathways were engaged during the preclinical A β stage and even preceded A β conversion, in line with genetic and preclinical evidence implicating microglial lipid handling and innate immune signaling as central risk mechanisms in AD^{14–17}. Synaptic, proteostatic, autophagic, and redox-related pathways rose during the A+T– stage and anticipated tau positivity and clinical impairment, supporting that proteasomal and autophagic dysfunction facilitate tau aggregation, propagation, and neuronal vulnerability^{7,18,19}. These pathways can synergize with inflammatory signaling to promote synaptic failure, oxidative stress and neuronal loss^{20,21}, providing a mechanistic framework linking proteostasis failure to neurodegeneration. By demonstrating that stage-specific molecular pathways are engaged before overt A β or tau positivity and predict subsequent disease transitions, this longitudinal framework supports a stage-informed approach to therapeutic targeting and patient stratification in AD.

Declarations

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Competing interests

M.S.W. received honoraria from Lilly for educational lectures outside the scope of this work. J.T. has served as a consultant for Neurotorium education, Alzheon Inc and Imagination AI, all outside of the scope of the present work. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Celectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a

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Figures

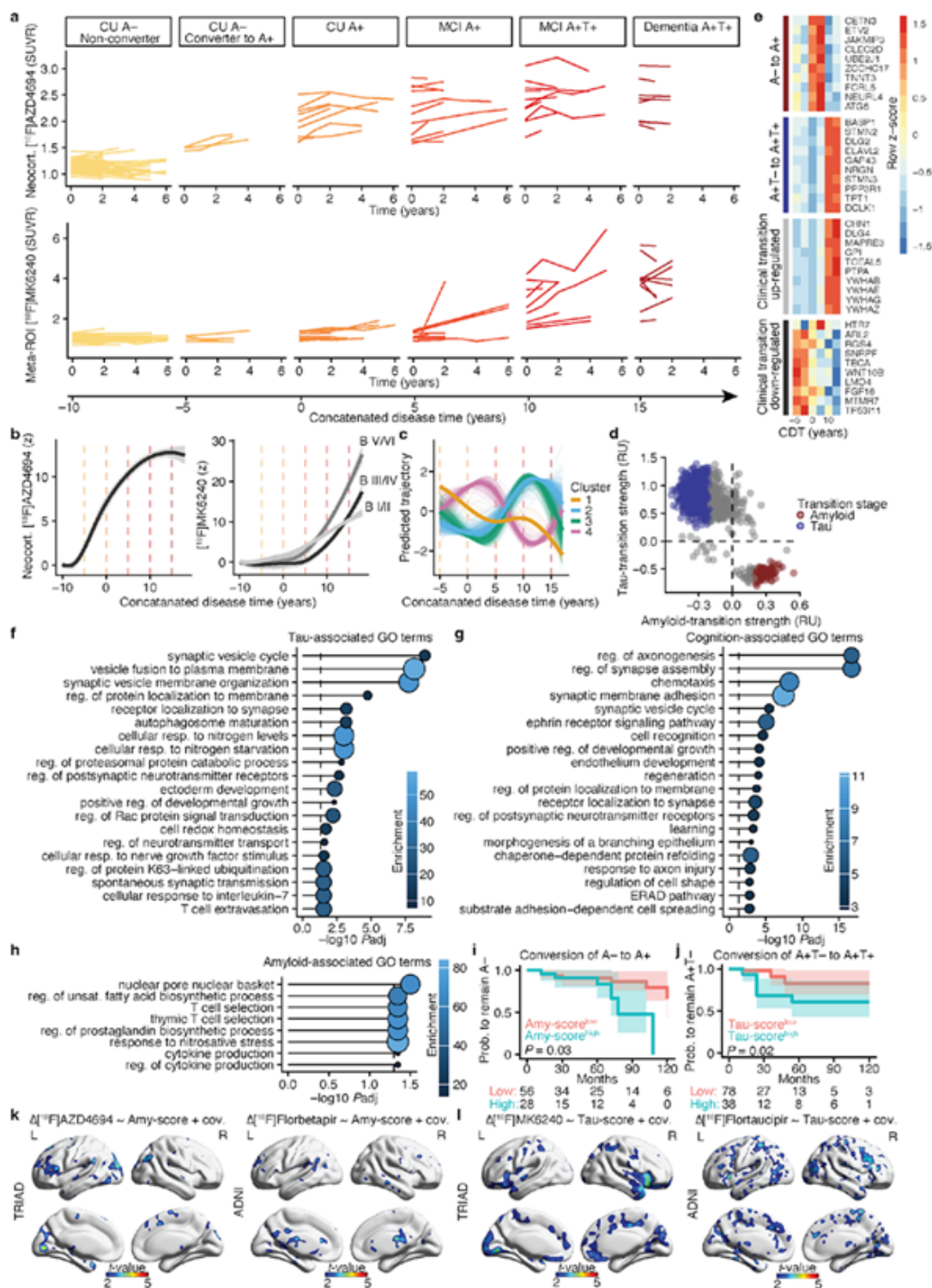


Figure 1

Distinct amyloid-β and tau dominated molecular transition programs shape Alzheimer's disease progression. (a) Longitudinal neocortical amyloid-β accumulation measured by [¹⁸F]AZD4694 positron emission tomography (PET), and temporal meta-ROI tau-accumulation measured by [¹⁸F]MK6240 PET in six clinically and biomarker-defined stages spanning the Alzheimer's disease (AD) continuum in TRIAD: cognitively unimpaired (CU) Aβ -negative (A-) non-converters (n = 69), CU A- converters to Aβ-positivity

(A+; $n = 4$), CU A+ ($n = 11$), A+ with mild cognitive impairment (MCI; $n = 12$), A+ tau-positive (T+) with MCI ($n = 10$), and A+T+ dementia ($n = 10$). Concatenated disease time (CDT) was generated by integrating the longitudinal with cross-sectional measurements from TRIAD ($n = 316$) and ADNI ($n = 526$) across the six stages. (b) Neocortical [^{18}F]AZD4694 PET and [^{18}F]MK6240 PET in Braak stages I/II, III/IV and V/VI of TRIAD participants across the CDT. (c) Temporal protein clusters of 1367 (of 6094) CSF proteins measured by SomaScan in TRIAD and ADNI that showed a significant overall change across the CDT. (d) Identification of proteins that were associated with A β -transition (CDT -5 years to 0 years), and tau transition (CDT 0 years to 10 years). Proteins that were exclusively associated with A β or tau (Δ predicted value > 0.2) but not with the other pathology (Δ predicted value < -0.2) are labeled. (e) Heatmap of top 10 proteins with the strongest positive change during the A β transition (CDT -5 to 0 years), tau transition (CDT 0 to 10 years), and clinical transition (CDT 0 to 15 years), top 10 proteins with the strongest negative change in the clinical transition phase. (f-h) Gene ontology analysis of the top 50 proteins selectively associated with tau conversion (f), top 50 proteins associated with clinical progression (g), top 50 proteins selectively associated with A β conversion (h). (i-j) Kaplan-Meier survival analyses depicting time to conversion stratified by A β -transition (i) or tau-transition (j) signature scores (top tertile vs. rest). A β -transition signatures were tested in A- for conversion to A+, and tau-transition signatures in A+T- for conversion to A+T+. P -values were calculated using log-rank tests. k-l) Voxelwise analyses of A β transition signature with longitudinal A β -PET (k; TRIAD, $n = 117$; ADNI, $n = 198$) change and the tau transition signature with longitudinal tau-PET change (l; TRIAD, $n = 117$; ADNI, $n = 43$).

Supplementary Files

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