

Stage-aware Adaptive Reaction–Diffusion Framework for Modeling Alzheimer’s Disease Progression with tau and Amyloid- β PET Scans

Hongyi Qin^{1*}, Yuheng Fan^{2*}, Uazman Alam¹, Kim Branson³, Yalin Zheng²,
and Wahbi K. El-bouri^{1†}

¹ Department of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, UK

² Department of Eye and Vision Sciences, University of Liverpool, Liverpool, UK

³ GSK.ai, GlaxoSmithKline, London, UK

W.El-Bouri@liverpool.ac.uk

*These authors contributed equally. †Corresponding author.

Abstract. Longitudinal PET enables regional quantification of amyloid- β ($A\beta$) and tau burden in Alzheimer’s disease, yet long-horizon forecasting is challenging due to sparse, irregular follow-up and strong heterogeneity in disease stage and pace of progression. Mechanistic progression models are interpretable but often rigid, while generic neural ODE regressors handle irregular sampling at the cost of mechanistic transparency and stability. We propose a lightweight, stage-aware mechanistic neural ODE that couples a connectome-constrained diffusion–reaction backbone with structured local residual dynamics. The model includes state-dependent diffusion modulation on a fixed structural connectome, an explicit negative-feedback channel, and a logistic-shaped residual gain, routed by a simple gating module over latent disease time and global burden with subject-specific affine time alignment. On ADNI tau-PET and amyloid-PET cohorts, we improve ROI-level forecasting on held-out subjects setting and reveal stage- and biomarker-dependent patterns in effective coupling and component contributions.

Keywords: Alzheimer’s disease · $A\beta$ and tau pathology · PET imaging · progression modeling · neural ODE

1 Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder in which amyloid- β ($A\beta$) and tau play central but distinct roles [16]. PET imaging enables in vivo, regional quantification of both proteinopathies, motivating cohort-level progression modelling for forecasting and timely intervention [15, 13].

Mechanistic modeling of brain networks offers an interpretable foundation for proteinopathy progression. Classic network diffusion models describe connectome-constrained propagation [19, 7] while reaction–diffusion extensions incorporate a logistic reaction term to capture local accumulation.[25, 20, 14] However, widely

used variants [2, 23, 8] often assume globally parameterised diffusion and a single reaction term that conflates multiple local processes (e.g., production, aggregation, clearance, and atrophy-related effects), limiting regional mechanistic dissection and flexibility under heterogeneous trajectories. Meanwhile, longitudinal PET is extremely sparse and irregular, motivating continuous-time approaches such as neural ODE-style models for irregular time-series regression [4, 22, 11]. Purely data-driven models, however, may trade interpretability for flexibility. Recent hybrid approaches [9, 27, 28, 26] therefore combine mechanistic priors with neural components, e.g., [9] introduces graph networks to capture diffusivity variability and [26] models subtypes to absorb regional heterogeneity, yet balancing predictive performance, model complexity, and physiological interpretability remains challenging. Finally, subjects enter studies at different disease stages and progress at different rates, so chronological time is a poor proxy for disease time; latent disease time and time-warping are increasingly used to align individuals onto a shared disease timeline [12, 29].

In this work, we propose **STARD**, a STage-aware Adaptive Reaction–Diffusion framework for proteinopathy progression. Built on a connectome-constrained reaction–diffusion neural ODE, STARD adds (i) *state-dependent diffusion modulation* on a fixed connectome and (ii) a *structured local residual* capturing within-region effects beyond global logistic kinetics (e.g., negative feedback and clearance-like influences). To handle inter-subject heterogeneity in stage and pace, we introduce affine temporal alignment to place individuals on a shared *latent disease-time* axis. A lightweight gate is introduced to balance mechanistic and residual dynamics as a function of latent time and global burden.

Our contributions summarize as: (1) We introduce a lightweight and interpretable neural ODE couples latent disease-time alignment with a connectome-constrained reaction–diffusion prior; (2) We provide structured flexibility while preserving interpretability via state-dependent diffusion modulation on a fixed connectome and a structured local residual term, yielding a relatively transparent mechanistic decomposition. (3) We demonstrate strong ROI-level forecasting on held-out ADNI subjects for both tau- and A β -PET, with post-hoc analyses revealing coherent disease stages separation, stage-dependent component contribution shifts, and biomarker-specific diffusion strength (d_{mod}), where A β shows lower and more heterogeneous coupling than tau, consistent with [1].

2 Methodology

2.1 Problem Formulation

Let $r \in \{1, \dots, R\}$ index brain regions of interest (ROIs). For each subject i , we observe an irregular longitudinal sequence with V_i visits $\{(t_{ij}, \mathbf{c}_{ij})\}_{j=1}^{V_i}$, where $t_{ij} \in \mathbb{R}$ denotes chronological time (e.g., years since baseline) and $\mathbf{c}_{ij} \in [0, 1]^R$ is the ROI-wise normalized protein burden vector. Here, $\mathbf{c}_{ij}$ is derived from PET standardized uptake value ratio (SUVR) measurements and can represent either A β PET or Tau PET, enabling a unified formulation across proteinopathies.

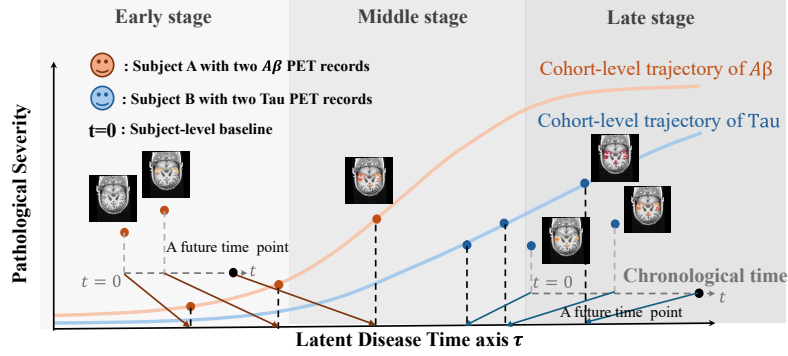


Fig. 1: Overview of the proposed framework. Subjects can map to the corresponding position on the disease progression axis for personalized prediction.

Our objectives are two-fold: (i) to learn a cohort-level continuous-time disease trajectory that captures progression dynamics and supports long-horizon forecasting for unseen subjects, shown in Fig. 1, and (ii) to provide a structured and interpretable decomposition of the learned dynamics into mechanistic components, enabling stage-wise attribution and hypothesis generation.

2.2 Subject-Specific Time Alignment

Chronological time is not comparable across subjects: the baseline visit ($t = 0$ by definition) does not represent a shared disease onset, and individuals progress at different rates due to substantial heterogeneity in AD. We therefore use a subject-specific affine time-warp to map chronological time t to a latent disease-time coordinate τ [12]:

$$\tau_i = g_i(t) = t_i^0 + \alpha_i t, \quad (1)$$

where t_i^0 is a stage offset (larger $\Rightarrow$ later stage) and $\alpha_i > 0$ is a pace factor ($\alpha_i < 1$: slower; $\alpha_i > 1$: faster). Unless stated otherwise, we model protein burden as a function of latent time, i.e., $\mathbf{c}_i(\tau)$, and use $\mathbf{c}$ to denote $\mathbf{c}(\tau)$ for brevity in later sections.

The parameters (t_i^0, α_i) are estimated jointly with the model parameters, enabling simultaneous temporal alignment and continuous-time trajectory fitting.

2.3 Stage-aware Adaptive Framework

We model disease progression dynamics as a stage-gated combination of a mechanistic backbone and a structured local residual as:

$$\frac{d\mathbf{c}}{d\tau} = \beta_{\text{phys}}(\tau, \mathbf{c}) \mathbf{f}_{\text{phys}}(\tau, \mathbf{c}) + \beta_{\text{loc}}(\tau, \mathbf{c}) \mathbf{f}_{\text{local}}(\tau, \mathbf{c}), \quad \beta_{\text{phys}} + \beta_{\text{local}} = 1. \quad (2)$$

where $\mathbf{f}_{\text{phys}}(\tau, \mathbf{c})$ is the mechanistic backbone, $\mathbf{f}_{\text{local}}(\tau, \mathbf{c})$ the structured local residual, and $\beta(\tau, \mathbf{c})$ the gate weight controlling their relative contributions.

Stage-aware gating. We produce $(\beta_{\text{phys}}, \beta_{\text{local}})$ via a lightweight gating network:

$$[\beta_{\text{phys}}(\tau, \mathbf{c}), \beta_{\text{loc}}(\tau, \mathbf{c})] = \text{softmax}\left(\text{MLP}_{\text{gate}}([\tau, \text{mean}(\mathbf{c})])\right), \quad (3)$$

where $\text{mean}(\mathbf{c})$ is the global average burden across ROIs, providing a stage proxy.

Mechanistic Backbone with Diffusion Modulation We use the diffusion-reaction model as our mechanistic foundation, and it is governed by the Fisher-Kolmogorov equation [7]:

$$\mathbf{f}_{\text{phys}}(\tau, \mathbf{c}) = -k \mathbf{L}_{\text{phys}}(\tau, \mathbf{c}) \mathbf{c} + r \mathbf{c} \odot (1 - \mathbf{c}), \quad (4)$$

where $k > 0$ is the diffusion strength, r is a global logistic reaction coefficient, and $\odot$ denotes element-wise multiplication. $\mathbf{L}_{\text{phys}}$ is derived from graph Laplacian, $\mathbf{L}_{\text{sc}} = \mathbf{D}_{\text{deg}} - \mathbf{A}$ (with $\mathbf{D}_{\text{deg}}$ the degree matrix), and $\mathbf{A} \in \mathbb{R}^{R \times R}$ is the structural connectome adjacency matrix.

State-dependent diffusion modulation (dmod). To relax the assumption of globally constant and time-invariant diffusivity, we learn an ROI-wise effective transmissibility vector $\mathbf{d}(\tau, \mathbf{c}) \in \mathbb{R}_+^R$:

$$\mathbf{d}(\tau, \mathbf{c}) = \text{softplus}(\text{MLP}_d([\tau, \mathbf{c}])) + \varepsilon \quad (5)$$

and define the modulated diffusion operator

$$\mathbf{L}_{\text{phys}}(\tau, \mathbf{c}) = \mathbf{S}(\tau, \mathbf{c}) \mathbf{L}_{\text{sc}} \mathbf{S}(\tau, \mathbf{c}), \quad \mathbf{S} = \text{diag}(\mathbf{d}). \quad (6)$$

This formulation keeps the structural topology fixed and models disease-dependent changes through effective coupling.

Structured Local Residual Term We parameterize residual ROI-wise dynamics as a structured sum of a negative component and a logistic-shaped term:

$$\mathbf{f}_{\text{local}}(\tau, \mathbf{c}_r) = -\gamma_r(\tau, c_r) c_r + \rho_r(\tau, c_r) c_r(1 - c_r), \quad r = 1, \dots, R. \quad (7)$$

The coefficients are produced by ROI-wise MLP heads:

$$\gamma_r(\tau, c_r) = \text{softplus}(\text{MLP}_\gamma([\tau, c_r])), \quad \rho_r(\tau, c_r) = \rho_{\text{max}} \tanh(\text{MLP}_\rho([\tau, c_r])), \quad (8)$$

where $\rho_{\text{max}} > 0$ bounds the magnitude of the local gain. The first term provides an explicit negative-feedback channel while $c_r(1 - c_r)$ enables stage-dependent local amplification or suppression beyond the global reaction in Eq. (4), together they can represent net clearance-like influences and other local compensatory effects in a model-structured manner. The parameters of these two MLPs are shared across ROIs.

2.4 Learning Objective

Let $\hat{\mathbf{c}}_i(\tau)$ denote the ODE solution of Eq. (2) for subject i evaluated at latent disease time τ . We jointly learn cohort-shared parameters θ (including k, r , and

all weights in MLP_{gate} , MLP_d , MLP_γ , and MLP_ρ) together with subject-specific temporal alignment parameters $\phi_i = \{t_i^0, \alpha_i\}$ by minimizing

$$\min_{\theta, \{\phi_i\}_{i=1}^N} \frac{1}{N} \sum_{i=1}^N \sum_{j=1}^{V_i} \|\hat{\mathbf{c}}_i(\tau_{ij}) - \mathbf{c}_{ij}\|_2^2 + \lambda_{\text{warp}} \sum_{i=1}^N (\alpha_i - 1)^2 + \lambda_d \mathcal{L}_d, \quad (9)$$

where the first term is the reconstruction loss over all observed visits, the second term is a mild regularizer that prevents optimisation from relying on overly aggressive scaling of time, and $\mathcal{L}_d = \frac{1}{|\Omega|} \sum_{n \in \Omega} (d_n - d_{n-1})^2$ optionally enforces temporal smoothness of the diffusion modulation along the numerical integration grid, where Ω is the set of discrete ODE integration steps.

3 Experiments

3.1 Dataset

Cohorts and ROI definition. We used longitudinal tau-PET and A β -PET data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) [17]. Cortical regions were parcellated using the Desikan–Killiany atlas (DK68) [5], and we additionally included the bilateral hippocampus and amygdala due to their relevance to AD, yielding $R = 72$ ROIs in total. The structural connectome used to define network transport was a group-average adjacency matrix computed from 50 healthy individuals in the Microstructure-Informed Connectomics (MICA-MICs) dataset [21]. Following prior practice [2], we constructed two composites to determine scan-level PET positivity: a medial temporal composite (entorhinal cortex and amygdala) and a lateral temporal composite (middle temporal and inferior temporal). For each composite (and separately for tau and A β), we fitted a two-component GMM to the composite SUVR values and classified a scan as positive if the posterior probability of belonging to the high-burden component exceeded 0.5. And the SUVR measurements are normalized to $[0, 1]$.

Inclusion criteria and cohort statistics. We retained subjects with at least two PET visits. Subject-level positivity was assigned using the baseline scan, and we excluded subjects whose scans were consistently negative across all visits. The tau-PET cohort contains 251 subjects with 708 visits (tau− / tau+: 47% / 53%). The A β -PET cohort contains 439 subjects with 1339 visits (A β − / A β +: 56% / 44%). To enable cross-protein analyses, we further identified 100 subjects with both tau-PET and A β -PET records as a held-out set.

3.2 Experimental Results

We conducted independent experiments for Tau and A β . Table 1 reports held-out forecasting performance using ROI sum squared error (SSE) and cross-ROI Pearson correlation (R). We compared against a recently proposed improved diffusion–reaction model (DRM) [2], a tau-focused deep model (IGND-MoE) [9], adapted to amyloid as well, and strong continuous-time baselines (GRU-ODE, ODE-RNN) [4, 22], conditioning on one or two historical visits ($n = 1/2$).

Table 1: Quantitative comparison on tau and $A\beta$ forecasting under different conditioning visits n

Model	n	ROI SSE $\downarrow$		Corr R $\uparrow$	
		tau	$A\beta$	tau	$A\beta$
GRU-ODE[4]	1	0.6394	1.8796	0.4995	0.5367
	2	0.6471	1.5192	0.4879	0.5283
ODE-RNN[22]	1	0.8323	1.8172	0.5588	0.6457
	2	1.7786	1.9666	0.4747	0.6486
DRM[2]	1	1.0460	2.3694	0.4275	0.5926
	2	0.6842	1.1016	0.4787	0.6474
IGND-MoE[9]	1	0.6035	1.2347	0.6086	0.6545
	2	0.5256	1.1872	0.6117	0.6611
Ours	1	0.3765	1.3943	0.6079	0.6754
	2	0.3422	1.0690	0.6135	0.6771
w/o dmod	2	0.3865	1.5465	0.5898	0.6246
w equal gate ($w = 0.5$)	2	0.3763	1.1986	0.5997	0.6695
w/o gate ($w = 1$)	2	0.5660	1.3835	0.5884	0.6407

STARD achieves strong and stable accuracy with $n = 1$ and further improves with $n = 2$, consistently outperforming all baselines. Fig. 2 shows that generic neural ODEs can fit plausible mean trajectories under sparse conditioning but incur large ROI-wise errors, reflecting weaker preservation of inter-regional structure and occasional non-physiological saturation. It also shows spurious late-time saturation. DRM, while interpretable, is less expressive and tends to over-predict progression in slow or heterogeneous cases due to missing local clearance-like effects. IGND-MoE can also exhibit spurious late-time saturation or non-monotonic decreases. ROI-wise residual maps indicate more uniform error reductions with STARD, suggesting improved robustness and generalisation.

Joint $A\beta$ -tau analysis. To better illustrate the stage-aware behavior of our model, we conduct a joint analysis on the hold-out test set who have both amyloid- and tau-PET. We stratify subjects into three commonly used A/T biomarker groups: A-T-, A+T-, and A+T+, which are widely interpreted as early, intermediate, and later positions along the Alzheimer’s disease continuum under the A/T(N) research framework [15, 10].

Time shift and scale on a latent disease-time axis. Our model aligns each subject to a common *latent disease-time* axis using an affine transform with time shift $t_0^{(i)}$ and time scale $\alpha^{(i)}$. Fig. 3 (a-b) shows $(t_0^{(i)}, \alpha^{(i)})$ inferred separately from Tau and $A\beta$: biomarker-positive subjects are consistently mapped to later latent times (larger $t_0^{(i)}$), supporting $t_0^{(i)}$ as a coherent staging coordinate. In the paired-PET subset, amyloid staging tends to precede Tau on the latent axis (mostly located in the upper corner), consistent with canonical biomarker cascade models [15]. In contrast, $\alpha^{(i)}$ shows weak separation across A/T groups, consistent with the notion that progression speed is highly heterogeneous even within biomarker-defined stages [12].

Diffusion modulation (d_{mod}). Across AT stages, d_{mod} decreases monotonically for both biomarkers (Fig. 3(c)). The box plots are constructed from subject-level summaries: for each subject, d_{mod} is averaged over all available observation

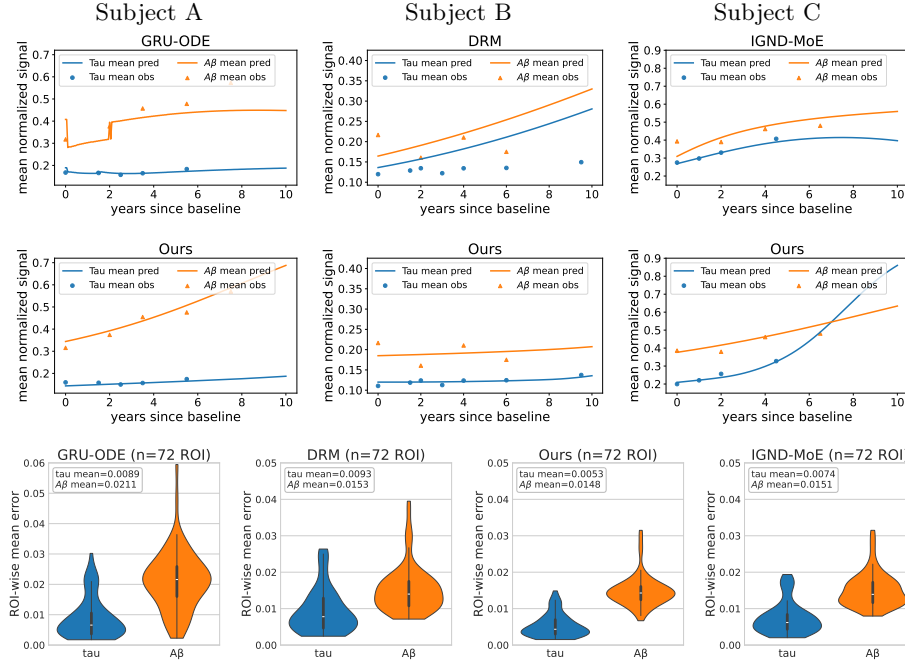


Fig. 2: Top two rows show the average trajectories of both $A\beta$ and tau progression. We compare baseline methods (Row 1) against our model (Row 2), each column corresponds to a representative subject, chosen to show method-specific failure cases. Bottom row shows ROI residual distributions on the whole test set.

visits, and the resulting subject means are pooled within each AT subgroup. The reduction is larger and the dispersion is broader for $A\beta$ than for tau, consistent with evidence that structural connectivity contributes disproportionately less to $A\beta$ topographical variance than to tau, implying weaker and more heterogeneous connectome-constrained propagation for $A\beta$ [1]. Moreover, the stage-dependent attenuation of d_{mod} is compatible with reports of stage-specific shifts from transport-dominated to more locally driven dynamics [2, 9].

Stage-dependent component contributions. Fig.3 (d) summarizes subject-mean component contributions across AT stages. With increasing pathological burden, the global reaction term $r c(1-c)$ increases monotonically, indicating rising net growth pressure. In parallel, the local negative-feedback channel $-\gamma(c, t) c$ becomes more negative, suggesting stronger engagement of negative-feedback processes, consistent with the progressive involvement of innate immune responses (e.g., microglial activation) in AD [24, 3]. By contrast, the logistic-shaped residual $\rho(c, t) c(1-c)$ shows the opposite trend and increases with stage; for Tau it can shift towards positive values, implying a growth-dominant local modulation beyond the global kinetics, compatible with self-amplifying Tau propagation and clearance-related pathway disruptions reported in Tauopathy [6, 18]. For $A\beta$,

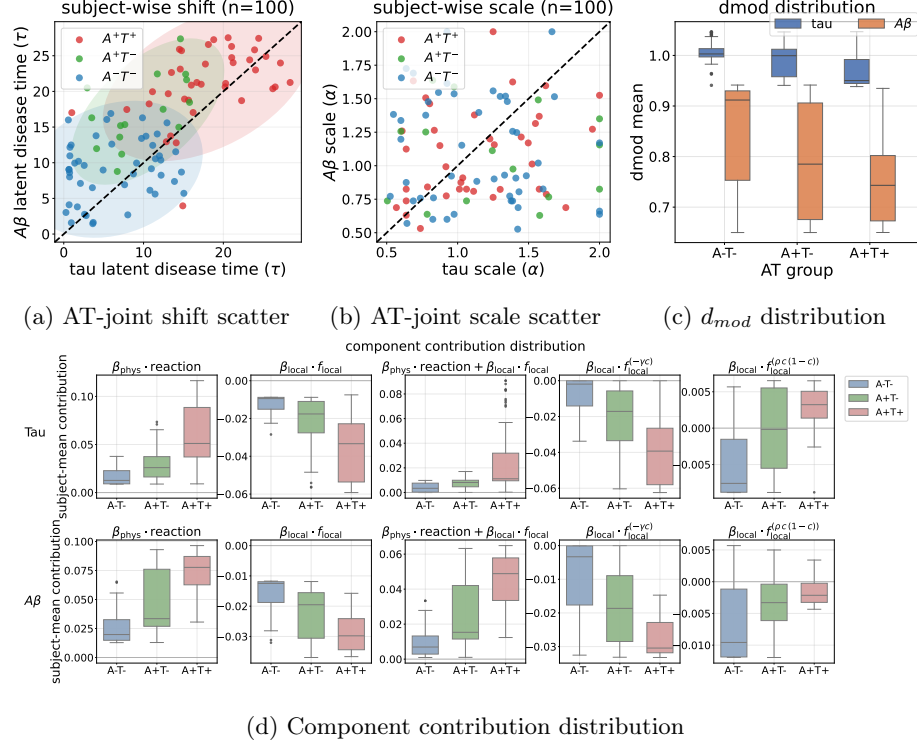


Fig. 3: (a) Shift distributions, (b) scale distribution, (c) diffusion modulation and (d) component contributions summary. Box plots are computed and averaged from the prediction values at all subjects' available observation time points. Thus, the model mechanism can be read out at real clinical sampling points.

an analogous sign shift is not prominent, but the residual still exhibits a clear stage-dependent trend opposite to the global reaction and negative-feedback terms. Overall, increasing global growth pressure is accompanied by stronger local negative feedback and biomarker-specific residual regulation, jointly yielding greater accumulation effects with disease progression.

4 Conclusion

We introduced a lightweight, stage-aware mechanistic neural ODE for regional proteinopathy progression from sparse, irregular longitudinal PET. The model integrates a diffusion-reaction backbone with state-dependent diffusion modulation and a structured local residual reaction comprising an explicit negative-feedback channel and a logistic-shaped residual gain. Subject-specific affine alignment provides a latent disease-time coordinate, while a simple gating mechanism enables stage-dependent adaptation without a dense neural network dark box.

Evaluated on ADNI tau-PET and amyloid-PET, our approach achieves strong ROI-level forecasting accuracy on held-out subjects and yields an interpretable decomposition of learned dynamics. Post-hoc analyses further show coherent stage-dependent shifts in component contributions and biomarker-specific effective coupling, with systematically lower and more heterogeneous connectome coupling for $A\beta$ than for tau. Future work will focus on external validation, detailed sensitivity analysis and explicit cross-protein coupling.

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Disclosure of Interests

The authors have no competing interests to declare that are relevant to the content of this article.

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