

Sex differences in seeding and propagation of amyloid, tau and neurodegeneration in Alzheimer's disease using a Bayesian network model

Vladimir S. Fonov¹, Seyyed Ali Hosseini², Lydia Trudel², Gleb Bezgin², Joseph Theriault², Arthur C. Macedo², Brandon J. Hall², Delphine Oliva-Lopez², Tevy Chan², Nesrine Rahmouni², Jenna Stevenson², Stijn Servaes², Serge Gauthier², Pedro Rosa-Neto^{1,2,3}, D. Louis Collins¹
¹McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada ²Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Douglas Hospital, McGill University, Montreal, Canada ³Peter O'Donnell Jr Brain Institute, UT Southwestern Medical Centre, Dallas, TX, USA

Background

Alzheimer's disease progression is reflected by propagation of amyloid- β and tau pathology and the resulting neurodegeneration. Using a Bayesian network framework informed by physical diffusion models [Schäfer 2021a,b; Fornari 2019] we model **sex-specific seeding and propagation** of amyloid- β , tau and neurodegeneration.

Materials

Normative volumes. Regional volume trajectories of **95 anatomical ROIs** estimated from MRI of **5691** cognitively normal subjects (ADNI, HCP, ICBM, NIHPD, NKI, UK Biobank). T1w scans were segmented into 70 regions with AssemblyNet [Coupé 2019]; cerebellar WM was subdivided into HCP-1065 WM tracts [Yeh 2022] via non-linear ANTs registration.

Disease cohort (TRIAD). 356 subjects (62% F) — 214 CU A- (67% F), 41 CU A+ (76% F), 64 MCI (53% F), 37 AD (38% F) — across 514 visits; age at baseline 69 ± 8.7 y. Per-ROI deviations from the normative trajectory give age-/sex-adjusted **W-scores** (neurodegeneration). Per-ROI SUVR for ¹⁸F-MK6240 (tau) and ¹⁸F-NAV4694 (amyloid- β)

Normative model – W-scores

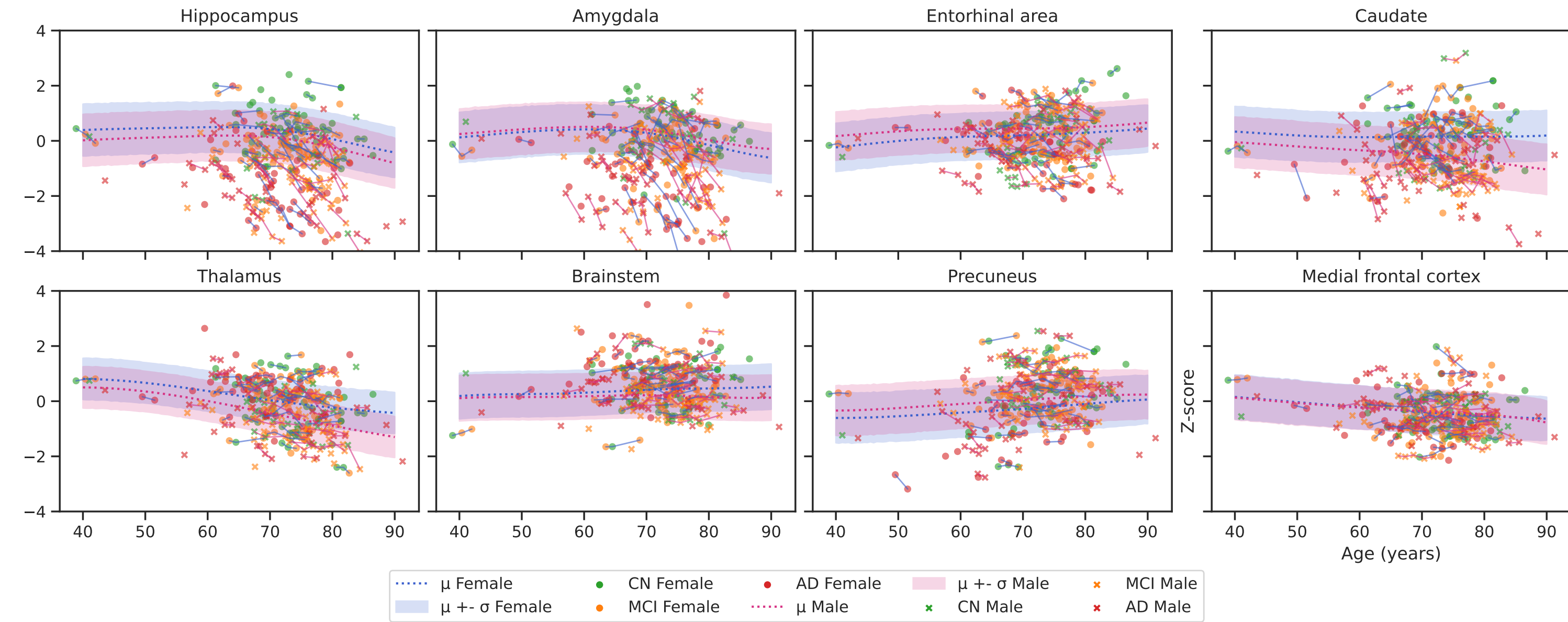


Figure 1. Normative volume trajectories for several ROIs by sex (Model 1) and illustration of the W-score (z-score) calculation.

Methods

Hypothesis. Amyloid- β and tau spread via distinct brain networks, with amyloid- β modulating tau propagation and neurodegeneration, and sex differences in the initial seeding and/or propagation of these pathologies. **Modelling approach.** Coupled Fisher–Kolmogorov spread on two networks (ROI proximity for amyloid- β ; HCP1065 DWI tracts for tau); logistic local growth with amyloid- β **modulating** tau; atrophy linear in tau+amyloid- β ; cognition a regularised-horseshoe function of accumulated atrophy. **Sex-specific** dynamics with a latent per-subject disease onset. Fit with **NumPyro**. The full Bayesian model has two parts – a normative trajectory model (Model 1) and a physics-informed generative propagation model (Model 2):

Model 1 — Normative Trajectory Model (W-scores)

Goal: fit smooth age/sex normative trajectories of 95 regional volumes (% of ICV) in CN subjects, then score any observation by how far it departs from its age/sex expectation. For observation i ($y_i \in \mathbb{R}^{95}$, sex $s_i \in \{-\frac{1}{2}, +\frac{1}{2}\}$):

$$\begin{aligned} \mu_i^{\text{fix}} &= B(\text{age}_i) \beta_{\text{bl}} + s_i B_{\text{sex}}(\text{age}_i) \beta_{\text{sex}}, \\ \mu_i &= \mu_i^{\text{fix}} + \beta_{[\cdot, \text{subj}]}^{\text{id}} + \beta_{[\cdot, \text{prot}]}^{\text{prot}}, \\ y_i &\sim \mathcal{N}(\mu_i, \Sigma_i), \quad \Sigma_i^{1/2} = r(\text{age}_i) L_{\text{res}}, \\ \Sigma_{\text{base}} &= \Lambda_{\text{res}} \Lambda_{\text{res}}^T + \text{diag}(\psi^2). \end{aligned}$$

Trajectories use cubic penalized B-splines (first-order random-walk smoothness); subject/protocol effects are factorized low-rank and **zero-mean** (rank 3) for identifiability; the residual covariance is a 3-factor model with an age-dependent log-scale $r(\text{age})$. **Score:** marginalizing random effects, $z_{if} = (y_{if} - \mu_{if}^{\text{fix}}) / \sigma_{if}^{\text{pred}}$ (negative = atrophy) — the neurodegeneration input to Model 2.

Symbol	Definition	Prior
$\beta_{\text{bl}}, \beta_{\text{sex}}$	cubic B-spline coeffs (age, sex trajectories)	penalized spline, RW1, $\sigma_{\text{diff}} \sim \mathcal{N}^+(0.1)$
$\beta_{\text{log res}}$	coeffs for log residual scale $r(\text{age})$	penalized spline (RW1)
$\lambda_{\text{id}}, \theta_{\text{id}}$	subject loadings/scores (rank 3, zero-mean)	$\mathcal{N}(0, 1) / \mathcal{N}(0, 0.2)$
$\Lambda_{\text{prot}}, \Theta_{\text{prot}}$	protocol loadings/scores (rank 3, zero-mean)	$\mathcal{N}(0, 1) / \mathcal{N}(0, 0.2)$
Λ_{res}	residual factor loadings (rank 3)	$\mathcal{N}(0, 1)$
ψ	residual uniquenesses (per region)	$\mathcal{N}^+(0.5)$
$B, B_{\text{sex}}, B_{\text{resid}}$	cubic B-spline design bases in age	fixed (data)

Model 2 — Physics-Informed Protein Propagation

Goal: jointly model the longitudinal spread of amyloid- β A, tau T (both PET SUVR) and neurodegeneration N (W-scores from Model 1) across 95 regions, sharing kinetics across a latent disease timeline. Three submodels: (a) a network ODE for protein dynamics, (b) a latent disease-stage / regional-seed process generating each subject's initial state, and (c) a multimodal observation model.

(a) **Network ODE** (sex-specific rates; $A_i, T_i \in [0, 1], N_i \geq 0$):

$$\begin{aligned} \dot{A}_i &= -k_A [L_{\text{mesh}} A]_i + a_A A_i (1 - A_i), \\ \dot{T}_i &= -k_T [L_{\text{conn}} T]_i + a_T (1 + \gamma A_i) T_i (1 - T_i), \\ \dot{N}_i &= \nu_T T_i + \nu_A A_i. \end{aligned}$$

L_{mesh} (anatomical adjacency) spreads amyloid- β geometrically; L_{conn} (tractography) spreads tau along the connectome; both are eigenvalue-normalized ($\lambda_{\text{max}} = 1$, rates in yr^{-1}). The $(1 + \gamma A_i)$ term means amyloid- β **modulates** tau growth. Integrated by a 50-step Euler scheme.

(b) **Disease stage & seeds.** Subject onset $t_{\text{onset}} \sim \text{Beta}(1, 1)$ is mapped to $(-1, 1)$; for follow-up $f u$ the horizon and a sharp gate are $t_{\text{stage}} = \text{softplus}_{100}(f u + t_{\text{onset}})$, $t_{\text{gate}} = \sigma_{100}(f u + t_{\text{onset}})$. The gate multiplies the **tau seed only**. Region $\times$ sex seeds: $\text{seed}_T = \text{sigmoid}(\ell^T) \exp(s_T)$, $\text{seed}_A = \text{sigmoid}(\ell^A) \exp(s_A)$, $\text{seed}_N = 0$.

(c) **Observation model.** $A_i^{\text{PET}} \sim \mathcal{N}(b_i^A + \sigma^A A_{ij}, \sigma_A)$, $T_i^{\text{PET}} \sim \mathcal{N}(b_i^T + \sigma^T T_{ij}, \sigma_T)$, positive off-target $b_j = \sigma_j^{\text{off}} \exp(z_j)$. $N_i^{\text{W}} \sim \mathcal{N}(-N_{ij} + \text{intercept}_{j, \text{subj}}, \sigma_N)$; cognition $\text{cog}_i \sim \mathcal{N}(\sum_j N_{ij} \beta_{j, \text{cog}}, \sigma_{\text{cog}})$ with a regularized horseshoe prior on β^{cog} .

Symbol	Definition	Prior
(a) Kinetics — per sex		
k_A, a_A, k_T, a_T	amyloid- β /tau diffusion & growth rates = $\exp(\cdot)$	$\log(\cdot) \sim \mathcal{N}(-2, 0.5)$
γ	amyloid- β →tau coupling	$\mathcal{N}(0, 1)$
ν_T, ν_A	tau / amyloid- β toxicity on neurodegeneration	$\mathcal{N}^+(1)$
$L_{\text{mesh}}, L_{\text{conn}}$	mesh / connectome graph Laplacians	fixed (data, $\lambda_{\text{max}} = 1$)
(b) Disease stage & seeds		
t_{onset}	subject disease onset, remapped to $(-1, 1)$	$\text{Beta}(1, 1)$
s_A, s_T	log seed scales (amyloid- β / tau)	$\mathcal{N}(\log 0.1, 0.5) / \mathcal{N}(\log 0.01, 0.1)$
ℓ^A, ℓ^T	region $\times$ sex seed logits	$\mathcal{N}(0, 1)$
(c) Observation model		
σ_A^A, σ_T^T	PET signal scales	$\mathcal{N}^+(0.5)$
b_i^A, b_j^T	off-target binding = $\sigma_j^{\text{off}} \exp(z_j)$	$z_j \sim \mathcal{N}(0, 1), \sigma_j^{\text{off}} \sim \mathcal{N}^+(0.5)$
σ_A, σ_T	PET observation noise (amyloid- β / tau)	$\mathcal{N}^+(0.5)$
$\text{intercept}_{j, s}$	per-subject neuro random intercept (rank-3, non-zero-mean)	loadings & scores $\mathcal{N}(0, 1)$
$\sigma_N, \sigma_{\text{cog}}$	neuro / cognition noise	FoldedStudentT(3, 0.5)
β^{cog}	neurodegeneration→cognition weights	regularized horseshoe ($\tau = 0.5$)

Connectivity networks

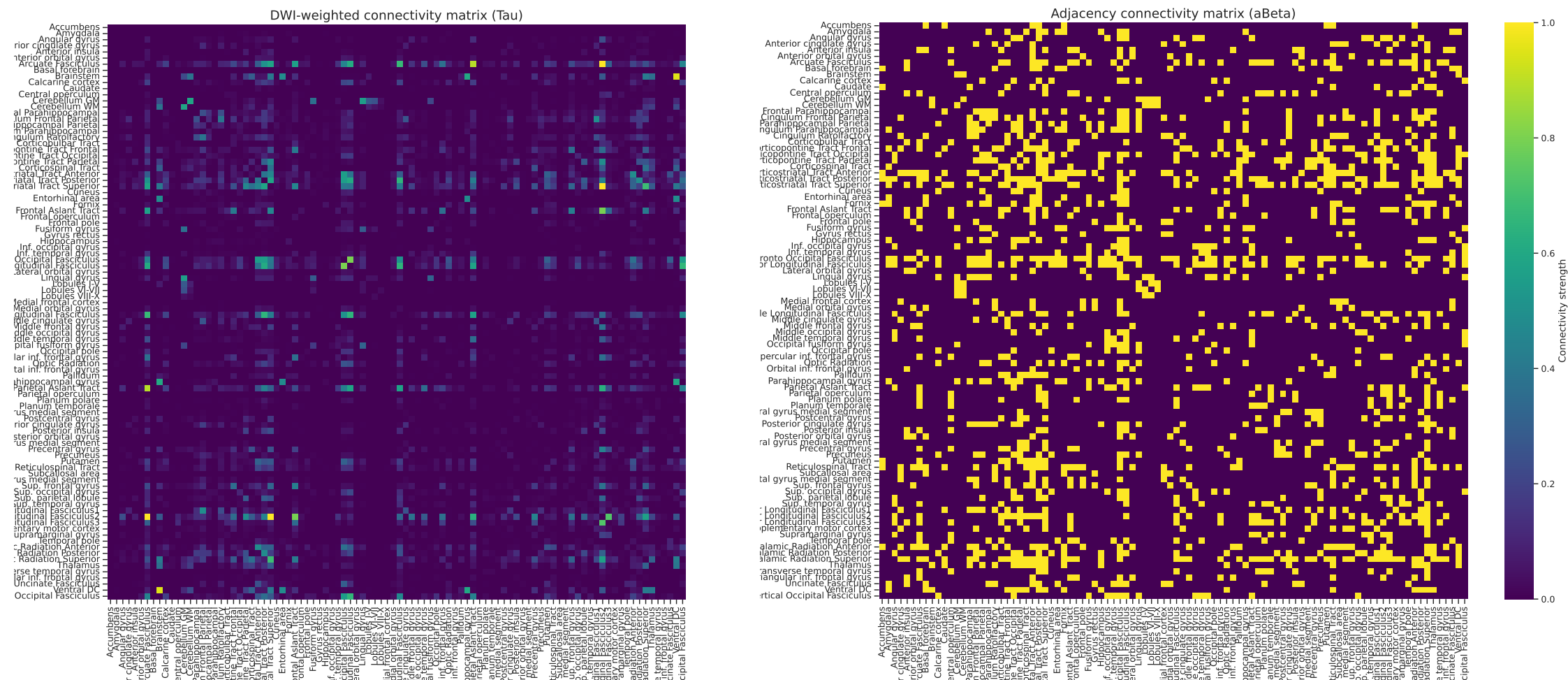


Figure 2. Connectivity matrices: left: tau, DWI tractography based and right: amyloid- β , anatomical proximity.

Acknowledgements

Funding: Famille Louise & André Charron; CIHR (MOP-111169). Data collection and sharing for the Alzheimer's Disease Neuroimaging Initiative (ADNI) is funded by the National Institute on Aging (National Institutes of Health Grant U19AG024904). UK Biobank Application 45551. Compute: Calcul Québec & the Digital Research Alliance of Canada.

Contact and download link

Vladimir S. FONOV, vladimir.fonov <at> mcgill.ca



Results

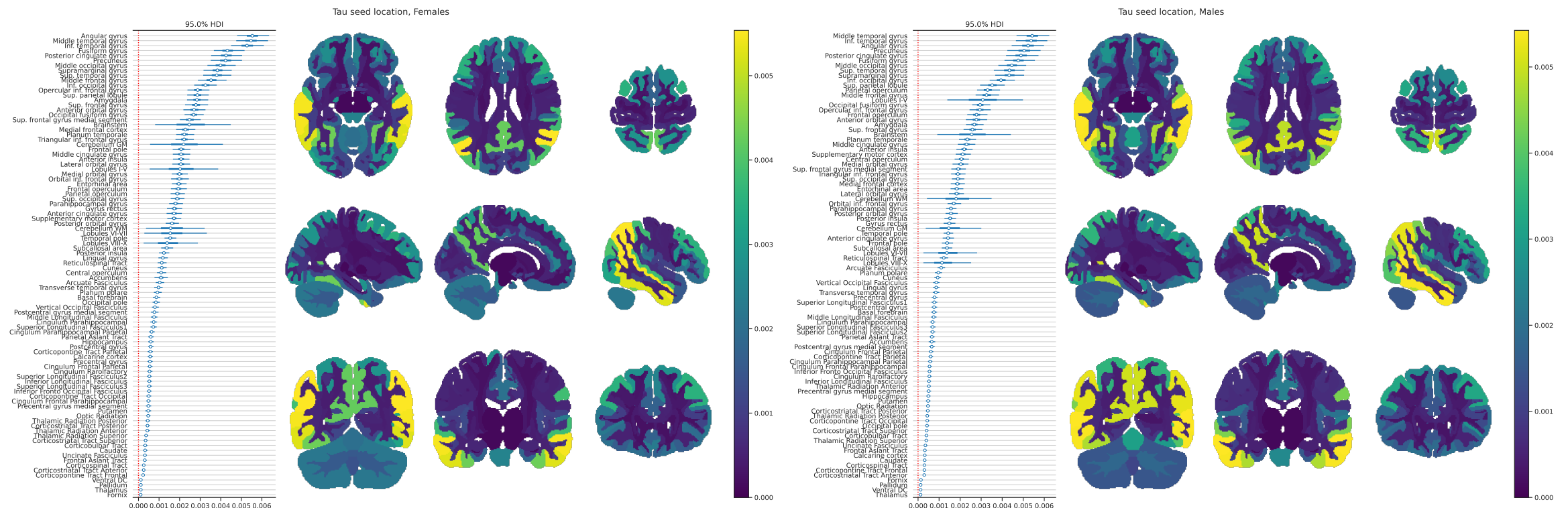


Figure 3. Recovered tau seed locations: **left:** Males, **right:** Females.

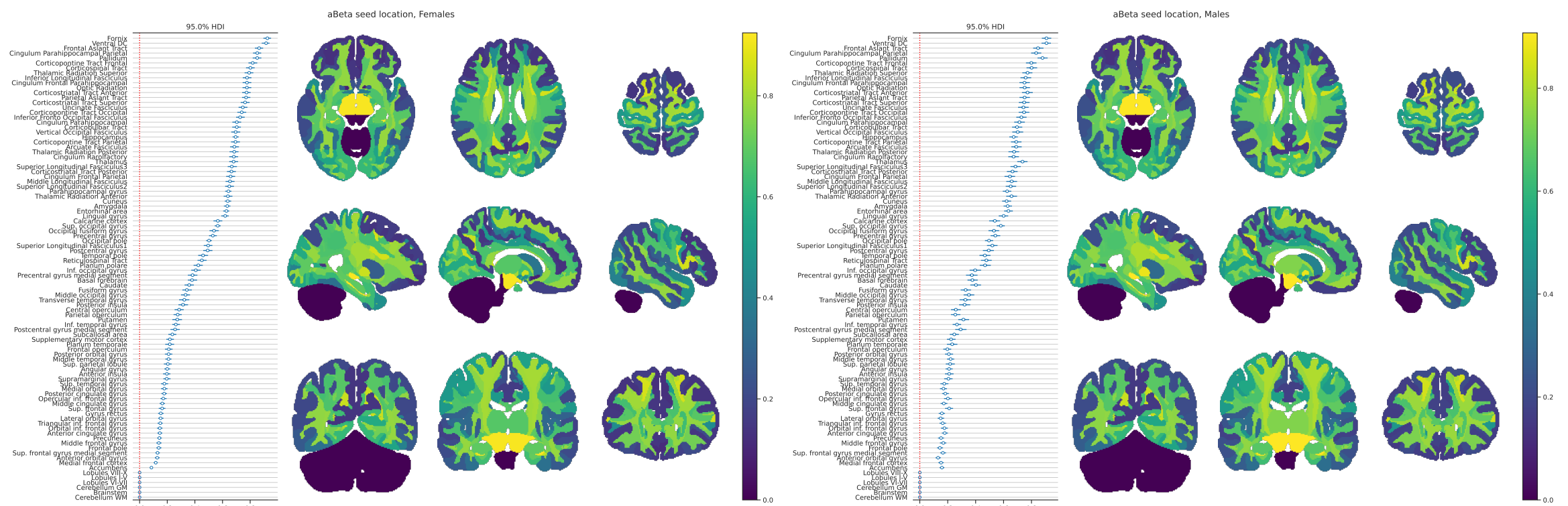


Figure 4. Recovered amyloid- β seed locations: **left:** Males, **right:** Females.

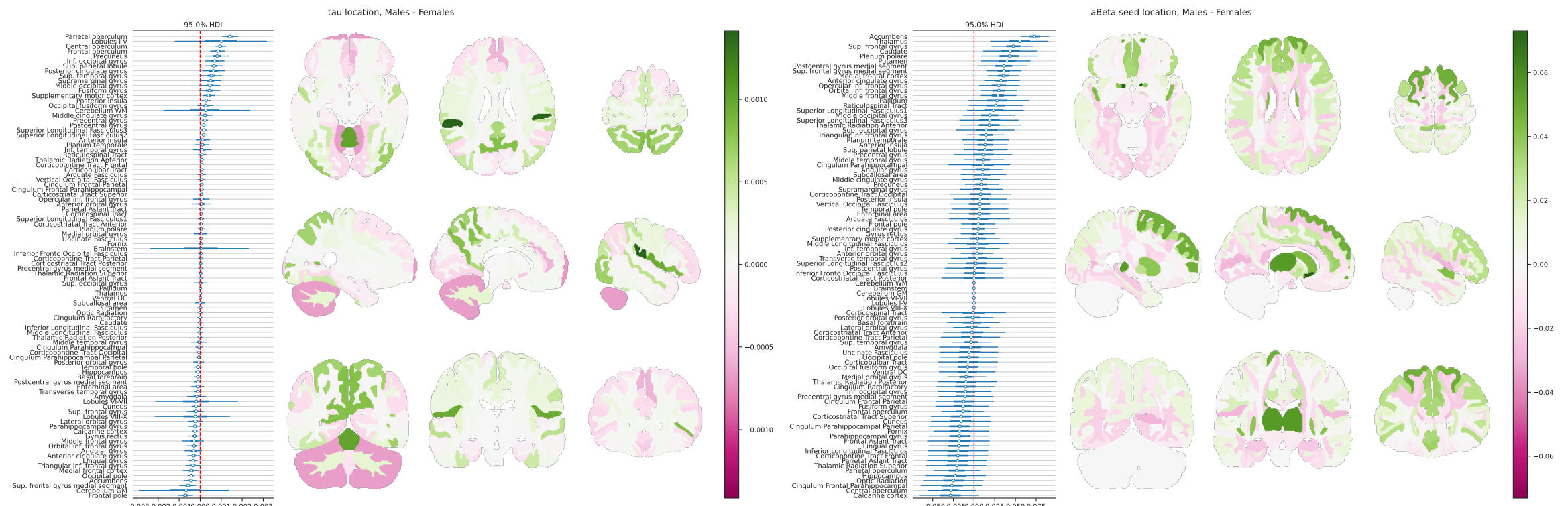


Figure 5. Male–Female difference, tau (**left**) amyloid- β (**right**).

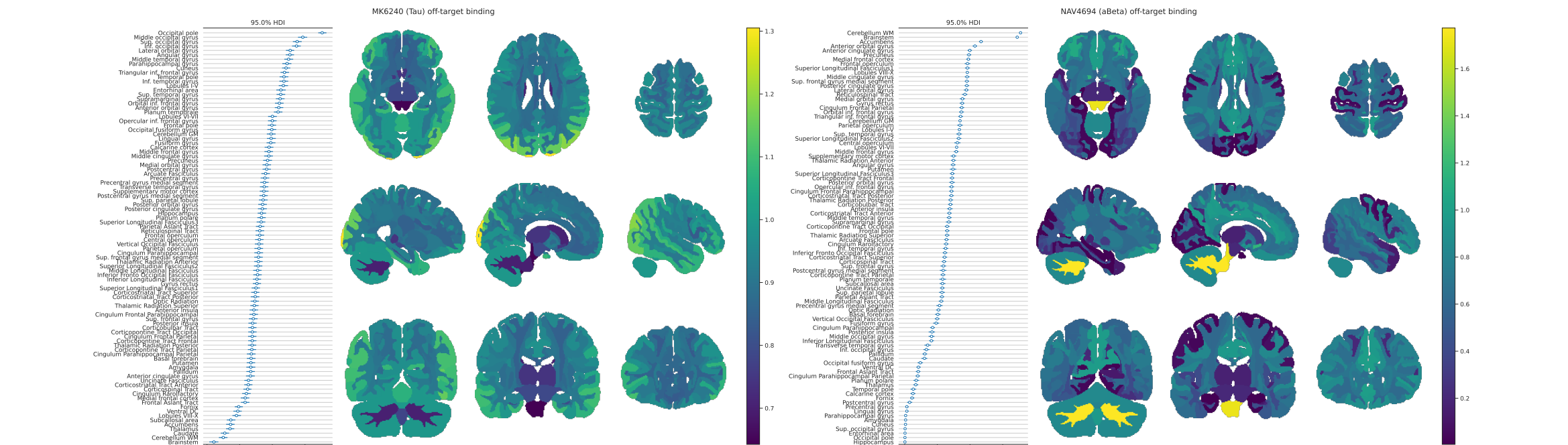


Figure 6. Estimated off-target binding for MK6240 (**left**) and NAV4694 (**right**).

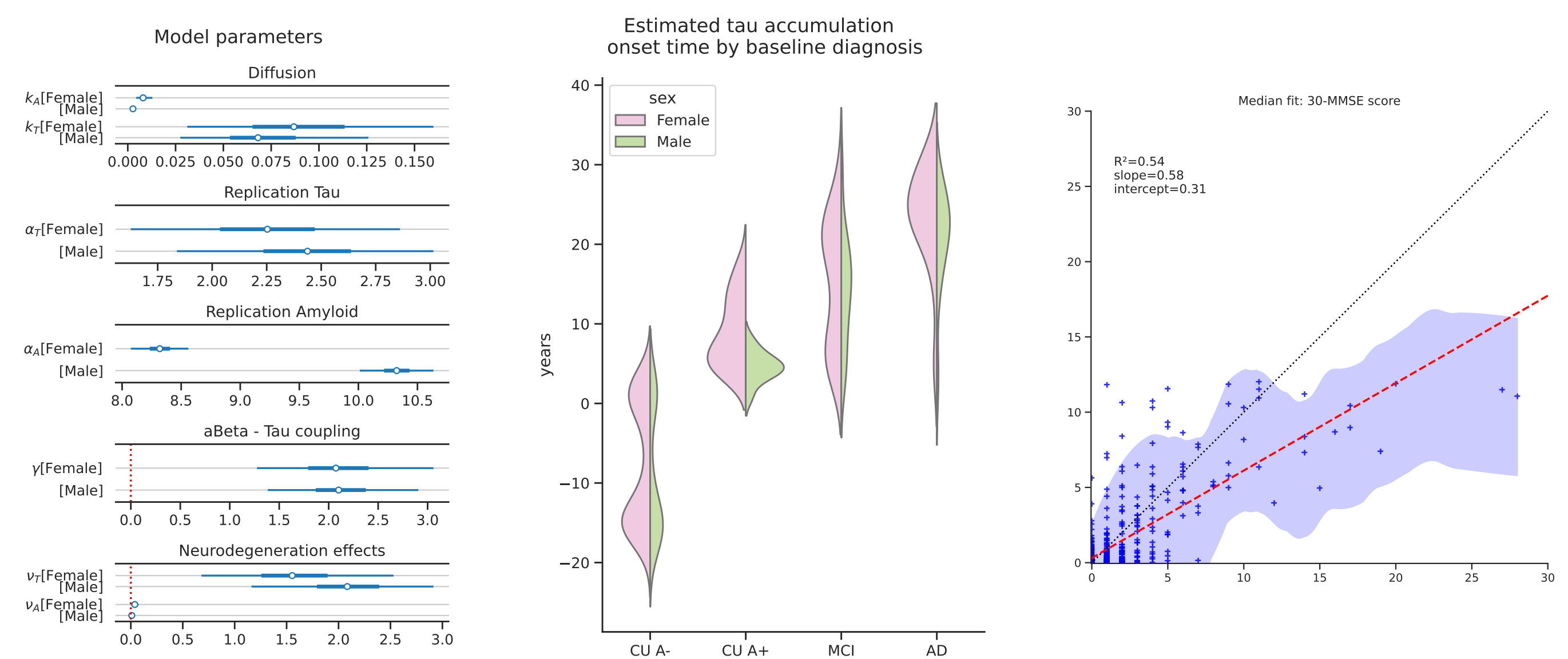


Figure 7. Estimated dynamic model parameters (**left**), estimated tau accumulation onset time by baseline diagnosis (**center**), median fit of cognitive impairment (**right**).

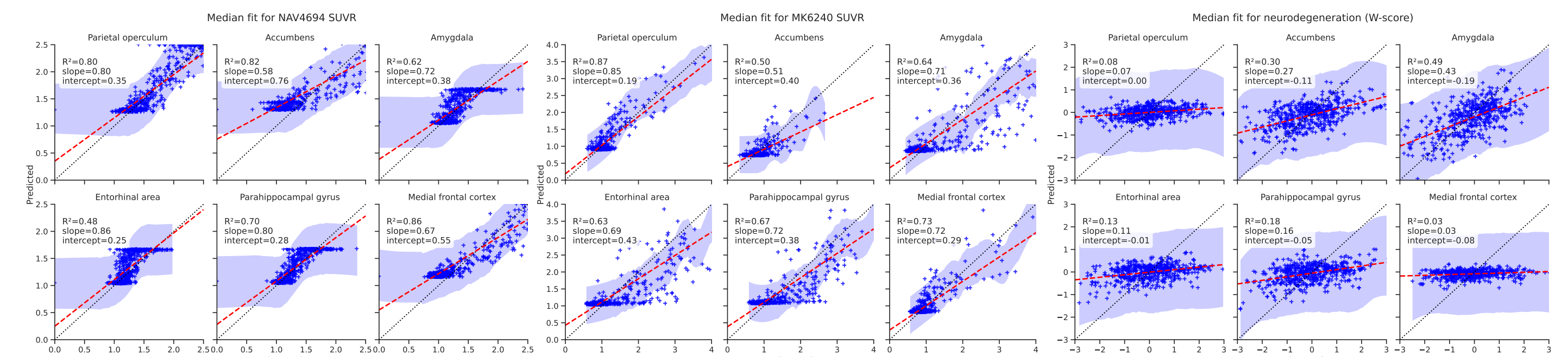


Figure 8. Median fits for NAV4694 (**left**), MK6240 (**center**), neurodegeneration (**right**).

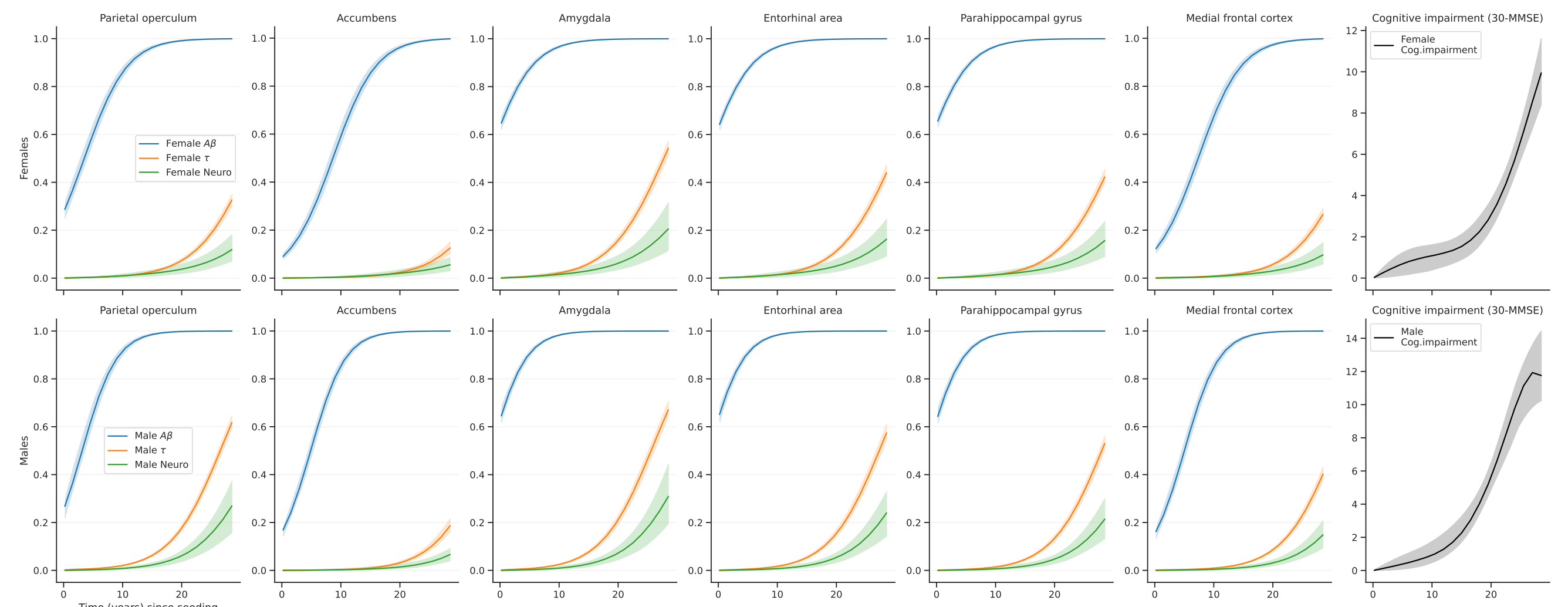


Figure 9. Simulated biomarker trajectories, demonstrating discovered differences in Alzheimer's Disease progression between males and females.

Conclusions

Our Bayesian network diffusion model captures Alzheimer's disease progression, **pinpoints tau and amyloid- β seeding regions** consistent with Braak and Thal staging, and highlights **sex differences** in the AT(N) cascade, demonstrating the utility of physics-informed Bayesian network modelling for characterising protein propagation.

References

Schäfer et al 2021a. “Predicting brain atrophy from tau pathology: a summary of clinical findings and their translation into personalized models”; Schäfer et al 2021b. “Bayesian Physics-Based Modeling of Tau Propagation in Alzheimer's Disease”; Coupé P, et al 2019. “Lifespan Changes of the Human Brain In Alzheimer's Disease”; Yeh 2022 “Population-based tract-to-region connectome of the human brain and its hierarchical topology”; Fornari 2019 “Prion-like spreading of Alzheimer's disease within the brain's connectome”; Braak 1991 “Neuropathological staging of Alzheimer-related changes”; Thal 2002 “Phases of A β -deposition in the human brain and its relevance for the development of AD”.