

Flexible Amyloid-tau Coupling Improves Tau Pathology Prediction In Alzheimer's Disease

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Poster 4409

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1 – Background

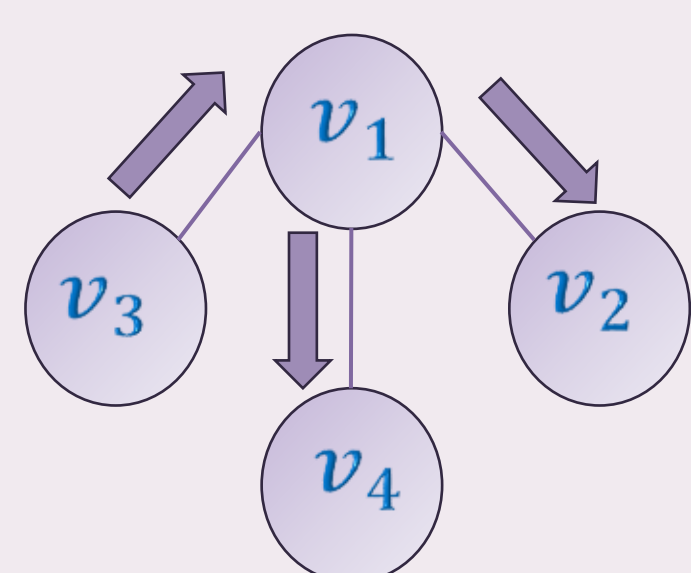
- Network spreading models simulate pathology propagation through brain connectomes to probe disease mechanisms in Alzheimer's disease.
- We previously demonstrated that enhancing tau production with regional amyloid burden using the weighted Fisher-Kolmogorov-Petrovsky-Piscounov (WFKPP) model can improve fit to tau-PET patterns[1]. However, the strength of amyloid-tau coupling may vary across individuals, motivating a flexible interaction term.
- We therefore use the **Interaction-Weighted FKPP (IWFKPP) model**, which extends the WFKPP with a bounded coupling parameter controlling the maximum influence of regional weights on local pathology production.

3 – Methods / Models

- We compare two frameworks (Figure 1) for modelling tau accumulation: WFKPP and IWFKPP.
- Each model was seeded at one bilateral epicentre at maximum pathology and zero elsewhere. Amyloid-weighted models use subject-specific amyloid SUVRs as regional production weights.
- Model performance was assessed between measured and predicted tau regional values at the optimal timepoint using sum-of-squared error (SSE) and Pearson correlation.
- Corrected Akaike Information Criterion (AICc) is used to account for model complexity and FDR-adjusted Wilcoxon p-values for statistical significance.

Weighted Fisher-Kolmogorov-Petrovsky-Piscounov (WFKPP) [2]

The spreading model with a logistic growth term and amyloid weighting to seed each region.

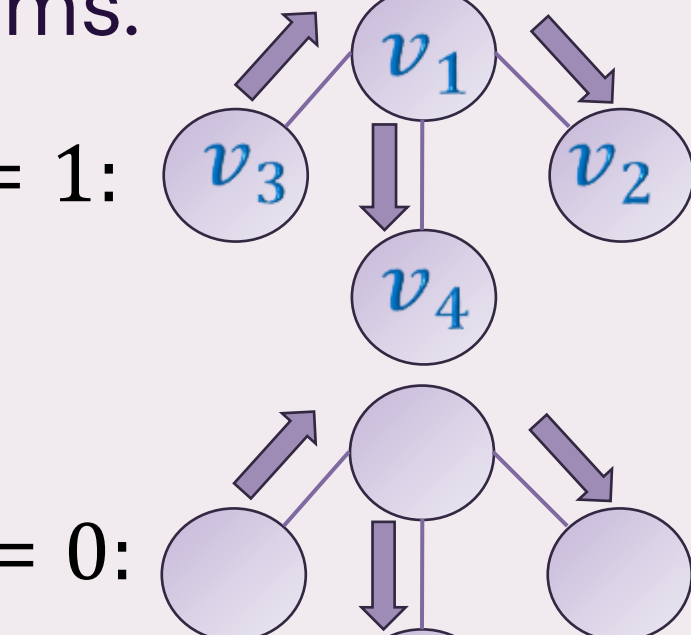


$$\frac{dx(t)}{dt} = \underbrace{-\alpha Hx(t)}_{\text{Spreading term / NDM [3]}} + \underbrace{v(1-\alpha)x(t)(1-x(t))}_{\text{Logistic growth term / FKPP [4]}}$$

Vector of regional production weights

Interaction-Weighted FKPP (IWFKPP)

Extends the WFKPP with a coupling term. Conceptually, this is a combination of the amyloid weighted and unweighted logistic growth terms.



$$\gamma = 1: \frac{dx(t)}{dt} = \underbrace{-\alpha Hx(t)}_{\text{Spreading term}} + \underbrace{(1-\alpha)x(t)(1-x(t))}_{\text{Logistic growth term}} \underbrace{[\gamma v + (1-\gamma)]}_{\text{Mixing coefficient}}$$

Vector of regional production weights

$\gamma = 0:$

Figure 1 – Network spreading models.

4 – Results

- Both individual-level (Figure 2) and group-level analysis (Figure 3) showed IWFKPP achieved significantly improved fit in each pathology group versus WFKPP.
- However, AICc weights show the additional parameter is only warranted in amyloid-positive individuals, where SSE is reduced by 17–25%.

Best-Fitting Model – Pairwise Wins

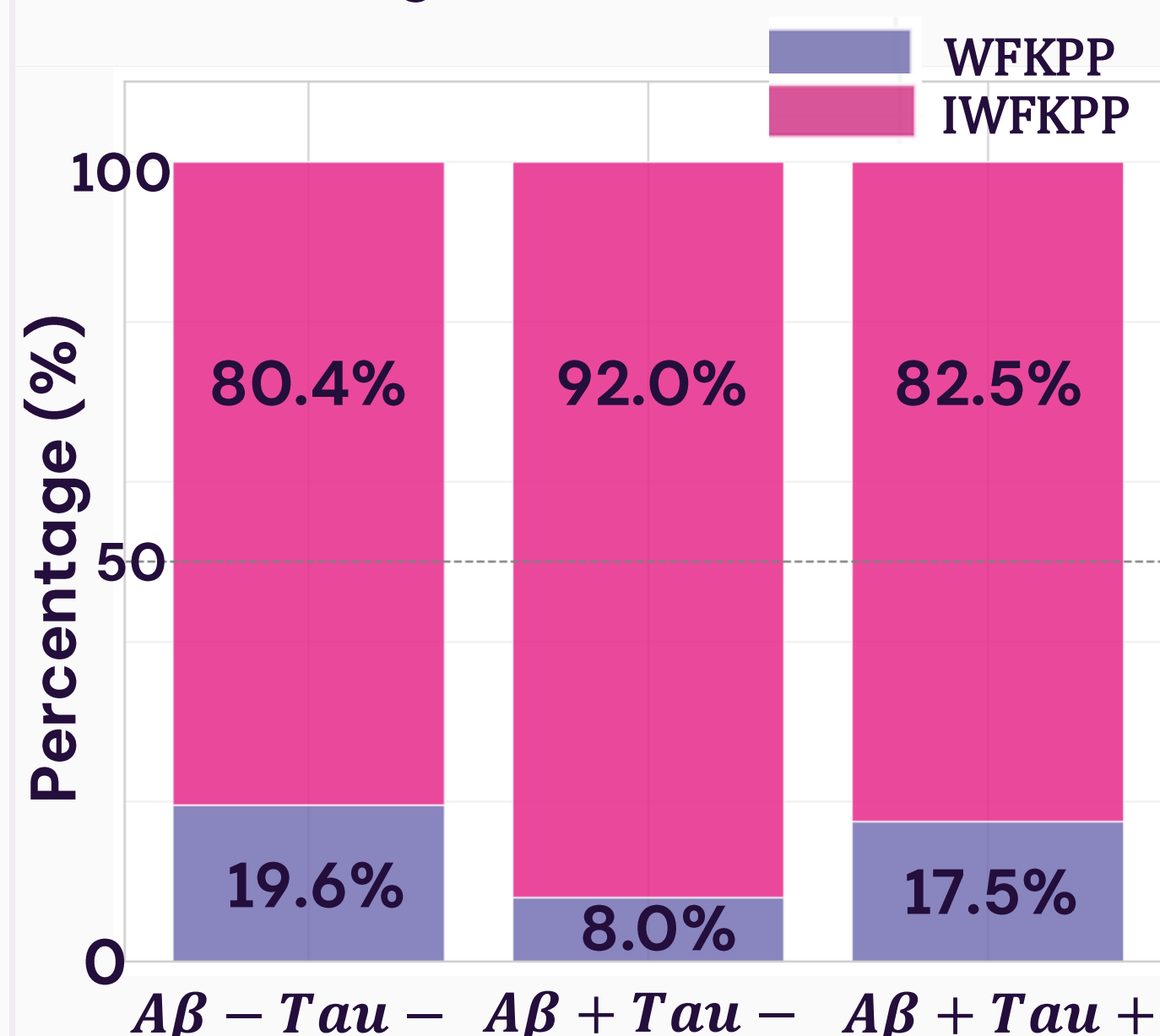


Figure 2 – Individual data: best-fitting model by group.

Best-Fitting Model – Per Cohort Sum of Squared Errors AICc Weights

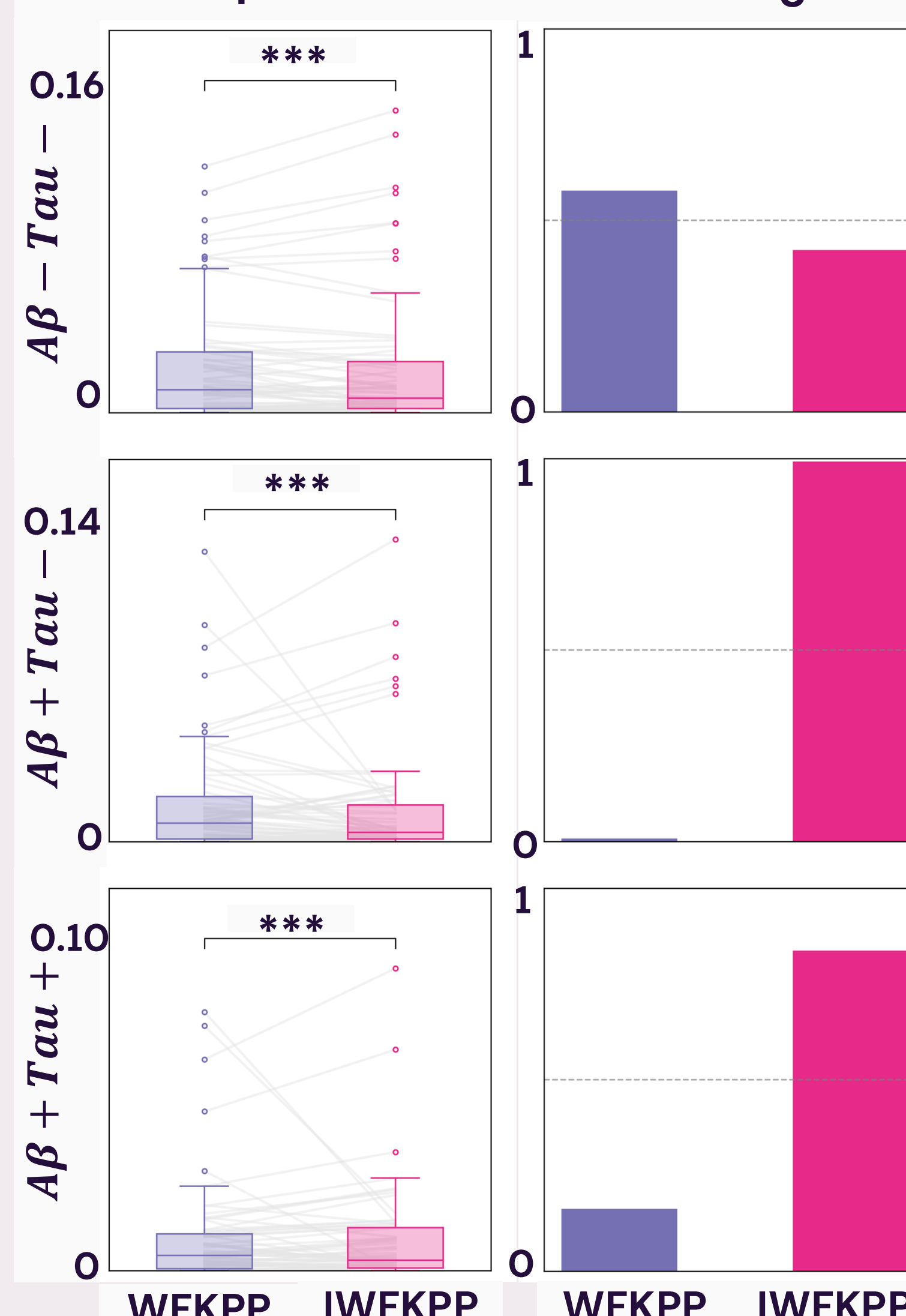


Figure 3 – Group averaged data: SSE & AICc comparison.

2 – Methods / Data

- We use ADNI data for all analyses (Table 1).
- Individual tau-PET (flortaucipir) regional SUVRs are model targets and individual amyloid-PET regional SUVRs provide subject-specific production weights for the WFKPP and IWFKPP models.
- Group-averaged structural connectome from 42 cognitively normal individuals is utilised as the substrate for pathology spread in all simulations.

Biomarker	N	Age (years)	Gender (male %)	Education (years)	Diagnosis (%)		
					CN	MCI	DEM
Aβ-Tau-	372	73.7 ± 9.1	50.0	16.5 ± 2.5	67.7	28.8	3.2
Aβ+Tau-	163	77.6 ± 8.5	50.3	16.5 ± 2.5	62.0	27.6	10.4
Aβ+Tau+	241	77.2 ± 8.2	46.1	16.1 ± 2.4	29.0	37.3	33.2

Table 1 – Participant demographics.

CN = Cognitively Normal; MCI = Mild Cognitive Impairment; DEM = Dementia

5 – Conclusion

The IWFKPP model's flexible coupling parameter improves personalised tau forecasting for amyloid-positive individuals, supporting a key role of amyloid-modulated tau production during early-to-intermediate pathology stages.

References

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Try out the Network Spreading Models toolbox at https://github.com/ucl-pond/network_spreading_models.

