Combining Multimodal Connectivity Improves Modelling of Pathology Spread in Alzheimer's Disease

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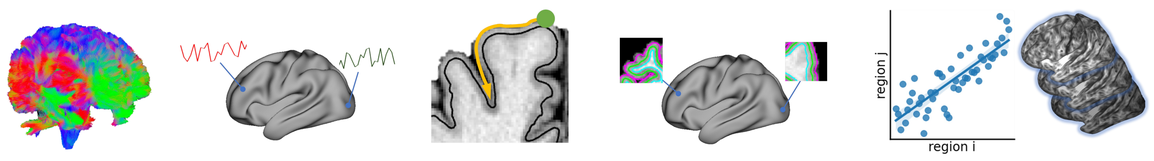
Introduction

- Neurofibrillary tangles of tau protein are a key biomarker of Alzheimer's disease. Tau burden is closely linked to grey matter atrophy and cognitive decline.
- Computational models have been used to probe the mechanisms underlying the propagation of tau and atrophy through the brain. They typically model the spread of disease agents between connected brain regions.
- Methods for estimating brain connectivity each have methodological biases, which lead to false positive and false negative connections.
- **Our hypothesis:** combining information from different measures of connectivity can help identify a network that best supports models of neurodegeneration and thus better reflects overall brain connectivity.

Data

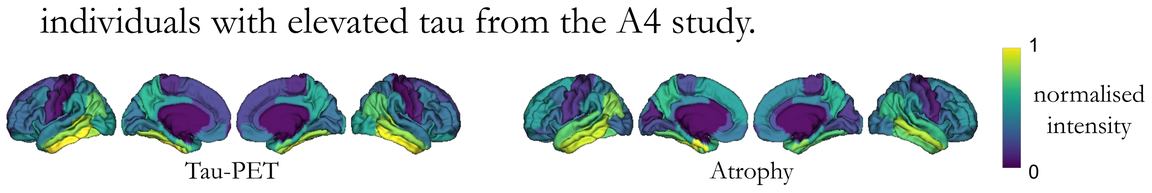
Connectivity Multi-modal connectomes were averaged across 50 participants from the MICA-MICS dataset (Royer et al., 2022, *Sci. Data*). A further morphological covariance network was generated from the T1-weighted images.



tractography | functional connectivity | inverse geodesic distance | microstructural profile covariance | morphological covariance

Pathology We used data from the ADNI. Inclusion criteria: amyloid-beta positive status and a diagnosis of dementia or mild cognitive impairment.

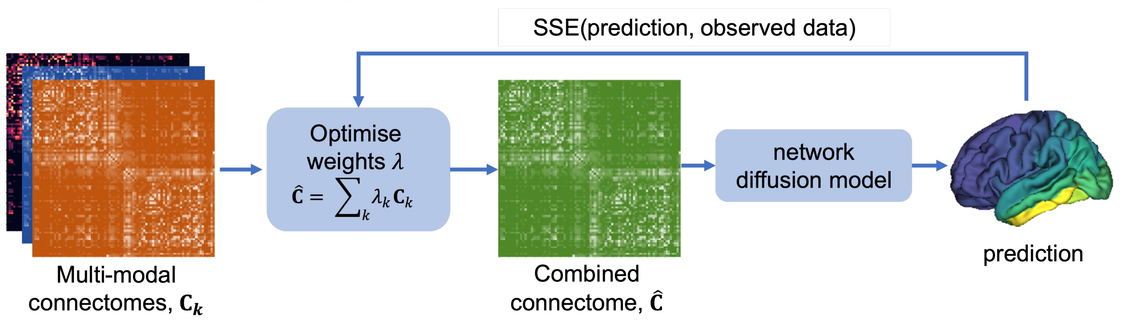
- Tau PET: regional flortaucipir SUVRs from 134 individuals.
- Atrophy: T1-weighted MRI data from 450 individuals. Subject-specific regional atrophy scores were estimated as z-scores of regional cortical volumes with respect to age-matched healthy controls.
- External validation set: Tau-PET data from 79 amyloid-positive individuals with elevated tau from the A4 study.



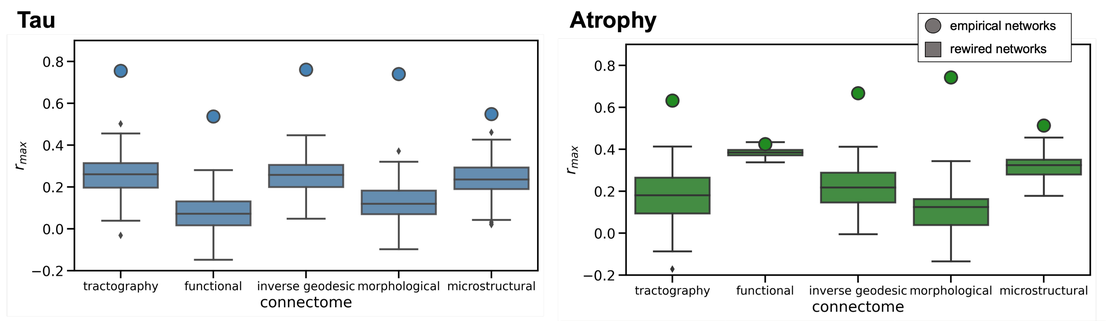
Tau-PET | Atrophy

Methods

- We used the network diffusion model (Raj et al., 2012, *Neuron*) to model the diffusive spread of pathology through the connectome.
- The Pearson's R value between the predicted and observed data at the optimal timepoint, r_{max}, was used to measure the goodness of model fit.
- The model is initialised with pathology starting in a bilateral seed region.
- We compared the ability of each connectome to capture the pathology patterns as a substrate in the network diffusion model, with different thresholds and seed regions from the Desikan-Killiany atlas.
- We tested whether using a multi-modal connectome would improve the model fit. We used a Gaussian-process minimiser to minimise the error between the model prediction and the measured data, by optimising the connectome weights λ_k in the combined connectome $\hat{\mathbf{C}}$:



Results – individual connectomes



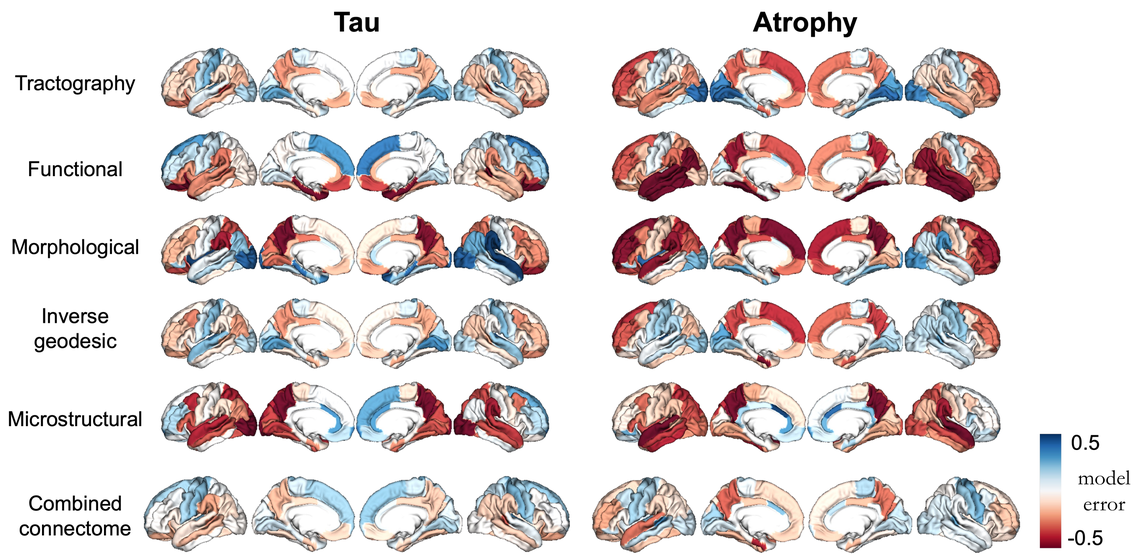
Connectome	Optimal Seed	Optimal Threshold	r_{max}
Tractography	Inferior temporal	0.5	**0.76**
Functional	Inferior temporal	0.05	0.54
Inverse geodesic	Inferior temporal	0.1	**0.76**
Morphological	Entorhinal	0.05	0.74
Microstructural	Inferior temporal	0.2	0.55

Connectome	Optimal Seed	Optimal Threshold	r_{max}
Tractography	Inferior temporal	0.2	0.63
Functional	Entorhinal	0.5	0.42
Inverse geodesic	Middle temporal	0.1	0.67
Morphological	Fusiform	0.05	**0.74**
Microstructural	Entorhinal	0.4	0.51

- Connectomes from tractography and inverse geodesic distance are best able to explain patterns of tau deposition
- Morphological covariance network provides the best model of atrophy
- Overall, the connectomes provided an improved substrate for the network diffusion model compared to a null distribution of rewired connectomes

Combined connectome improves modelling of pathology deposition

- Combined connectome optimised for tau spread: Functional, inverse geodesic, and morphological (r_{max} = 0.85, inferior temporal seed, weights: 0.70, 0.14, 0.16).
- Combined connectome optimised for atrophy: Functional and morphological (r_{max}= 0.78, middle temporal seed, weights: 0.42, 0.58).
- Model error is reduced when using the combined connectome, compared to individual connectomes:



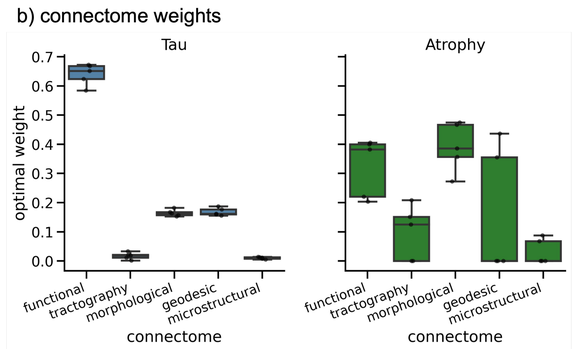
Five fold cross-validation analysis:

a) model agreement with measured data

Tau	r_{max} – train	r_{max} – test
best single modality (inv. geodesic)	0.76 ± 0.01	0.74 ± 0.05
best connectome combination	**0.85 ± 0.006**	**0.83 ± 0.03**

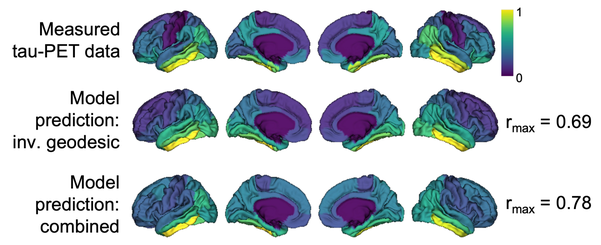
Atrophy	r_{max} – train	r_{max} – test
best single modality (morphological)	0.74 ± 0.003	0.68 ± 0.03
best connectome combination	**0.77 ± 0.01**	**0.71 ± 0.04**

b) connectome weights



Combined connectome generalises to unseen data

The combined connectome optimised for the ADNI data was better able to model tau spread in an independent test set than the best performing individual connectome.



Conclusions

- Combining multi-modal connectivity information improves our ability to explain pathology patterns with the network diffusion model
- This may suggest that combining sources of connectivity can mitigate the false positive and false negative connections from each individual modality and provide an overall connectome that is weighted more towards true positives/negatives.

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