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NEUROIMAGING

Regional Amyloid Load Predicts Tau and Atrophy Dynamics

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Abstract

Background: A generative model of tau PET was applied to multiple cohorts across the Alzheimer's disease (AD) spectrum, revealing longitudinal changes in tau production and transport. A generalisation of the model accounts for amyloid, tau and neurodegeneration (ATN) interactions and accurately explains longitudinal ATN biomarker data, adding potential for region specific and individualized tracking of ATN biomarkers.

Method: A model of tau spreading and production as measured through PET was developed and applied to longitudinal data from amyloid negative (A-), amyloid positive tau negative (A+T-) and amyloid positive tau positive (A+T+) cohorts from the Alzheimer's disease neuroimaging iniative (ADNI; N = 159) and BioFINDER-2 (BF2; N = 135) datasets. The model was extended to include ATN biomarkers and their interactions, explaining regional tau and atrophy dynamics as a by-product of regional amyloid load. This model was applied to longitudinal amyloid PET, tau PET and atrophy data from A+T+ subjects in ADNI (N = 39).

Result: The tau PET model faithfully reproduces Braak staging (Figure 1a). In A+T- subjects (N = 39 ADNI; N = 18 BF2) inference reveals faster tau spreading through the brain network and slower tau production, compared to A+T+ subjects (N=57 ADNI; N = 54 BF2) who show a higher production rate with slower transport (Figure 1b). This implies greater movement of tau during early AD before an acceleration in production when participants have high levels of both amyloid and tau. This is supported by comparison with spatially shuffled null models (Figure 1c). The generalization to the dynamical ATN model shows that an amyloid-induced acceleration in tau production explains regional variations in tau load (as measured through PET), Braak staging and downstream neurodegeneration (Figure 2). The ATN model calibrated to longitudinal

data from ADNI can accurately describe regional longitudinal ATN biomarkers (Figure 3).

Conclusion: Tau production and transport dynamics vary across the AD spectrum, characterised by an early period of fast tau spreading through the brain network followed by accelerated production of tau aggregates. A dynamical ATN model explains variations in tau and neurodegeneration through regional amyloid load and allows for accurate simulation of personalised ATN biomarkers.

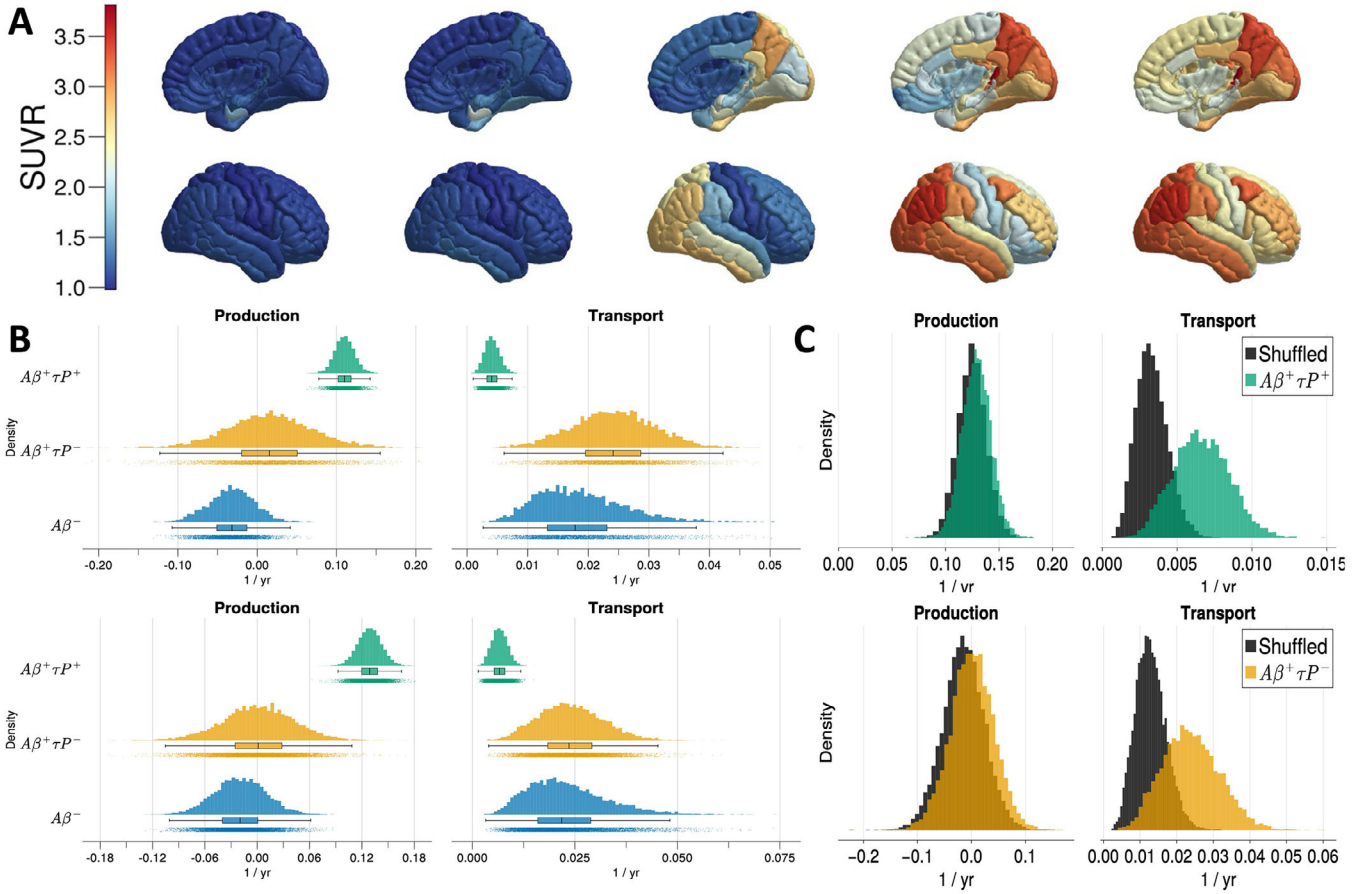

Figure 1. Mathematical model of tau production and transport. (A) Simulated trajectory from the physics-based tau PET model with an initial seed in the entorhinal cortex shows close correlation with Braak staging observed through tau PET. **(B)** Posterior distributions for groups in the ADNI dataset with N = 159 subjects (Top) and reproduced on BF2 Dataset with N = 135 subjects (Bottom). (Left) Production coefficient. As tau accumulates, there is an acceleration in disease progression, with A+T+ progressing the fastest, followed by A+T- and A- observed in both ADNI and BF2. (Right) Transport coefficient. A+T+ tends toward zero, whereas the A+T- is significantly higher indicating a higher level of transport through the structural connectome. **(C)** Null Distributions from spatially shuffled data for tau production and transport parameters. Inference on the hierarchical Bayesian model was rerun for 10 random spatial shuffles and their posterior distributions were concatenated. (Top) Production coefficient. As expected, there is little to no change in production as the temporal sequences of scans is maintained. (Bottom) Transport coefficient. There is significant change in the transport parameter for both A+T+ and A+T- groups, showing that the transport effect represents true dynamics and not statistical patterns in data.

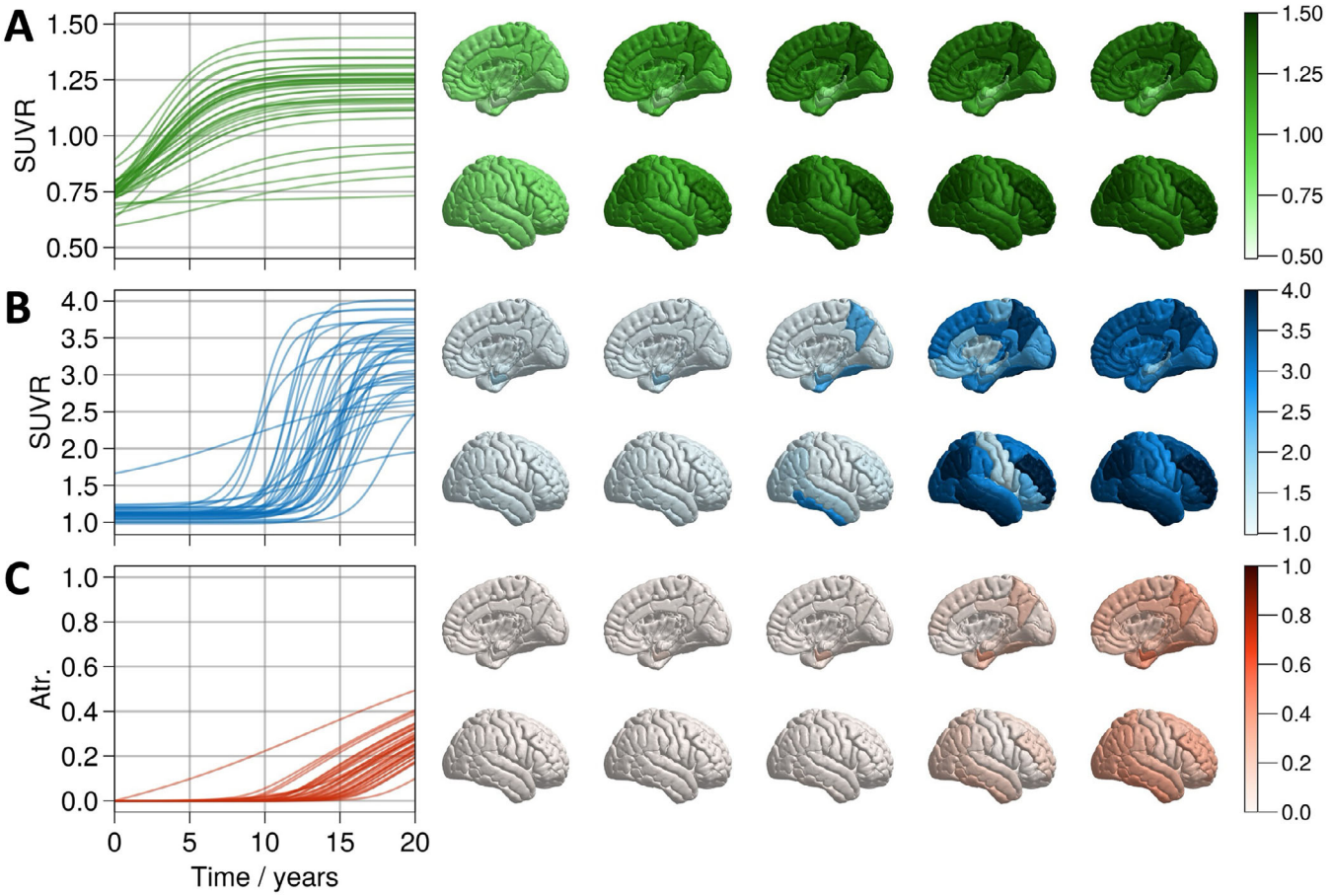

Figure 2. Simulation from the Dynamical Amyloid-Tau-Neurodegeneration Model. (A) Predicted amyloid trajectory using a uniform seed of 20% concentration relative to regional baseline and maximal SUVR. Amyloid baseline and maximal SUVR values were determined by modelling cross-sectional amyloid to order subjects on a disease timeline corresponding to amyloid load, then the ordered regional SUVR was modelled using sigmoid functions. **(B)** Predicted tau trajectory using a seed of 20% concentration in the entorhinal cortex relative to the baseline SUVR and estimated carrying capacity predicted maximal amyloid SUVR in the entorhinal cortex. Baseline tau values are determined using mixture modelling on cross-sectional tau SUVR. Maximal tau SUVR values are given as a linear scaling of regional amyloid SUVR describe the catalytic effect of amyloid on tau. **(C)** Predicted atrophy using a uniform baseline value of 0. Atrophy is given as a function of regional tau concentration.

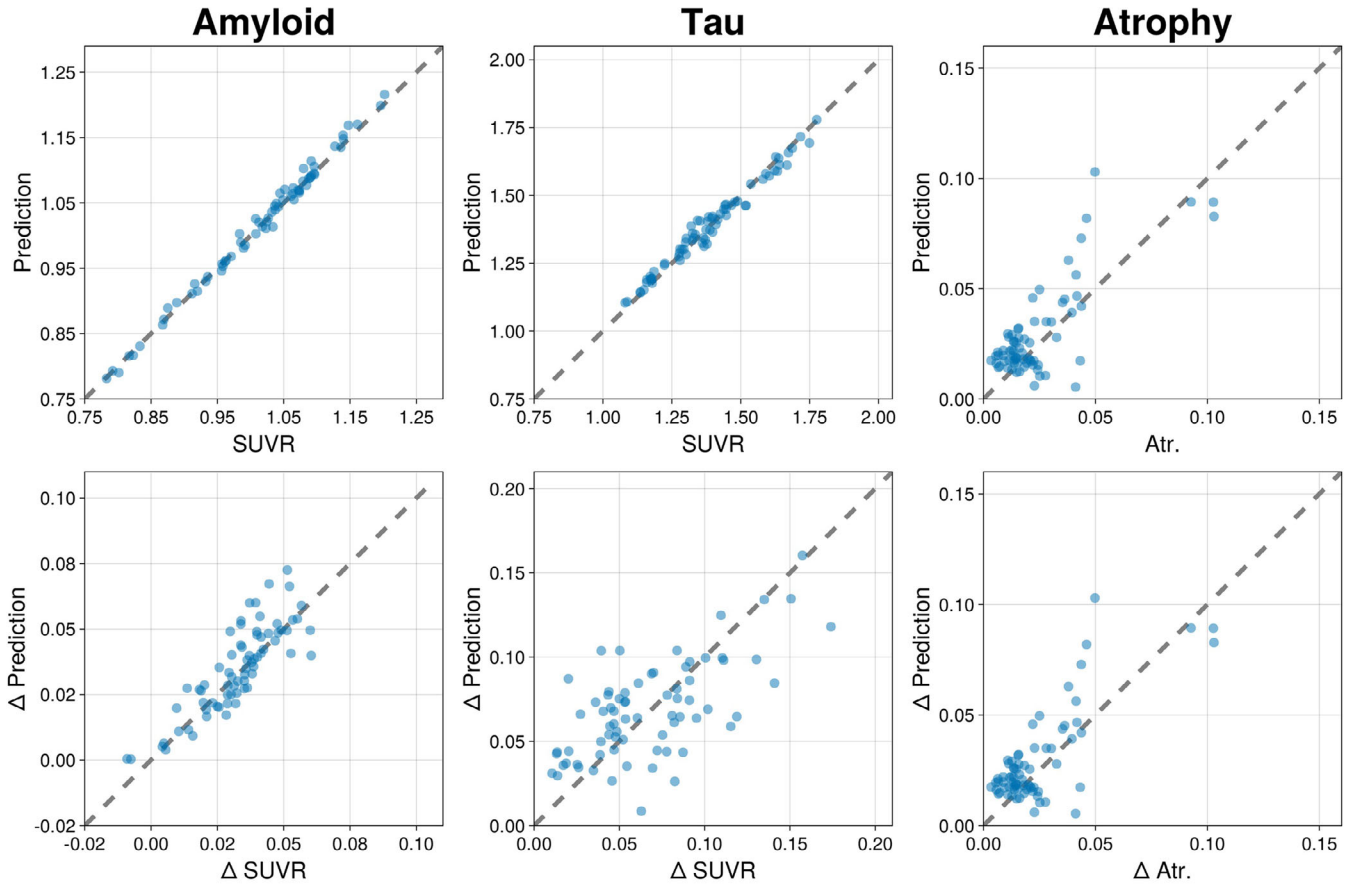

Figure 3. Dynamical ATN model fit on longitudinal amyloid, tau and atrophy data. The dynamical ATN model was fit using a hierarchical Bayesian model to N = 39 A+T+ subjects from ADNI who have at least 2 amyloid PET scans and at least 3 tau PET scans. Atrophy was fit to volume data obtained from tau PET analysis. (Top row) Predicted vs observed SUVR values for amyloid, tau and atrophy. (Bottom row) Predicted SUVR change vs observed SUVR change for amyloid, tau and atrophy. Each point represents a region in the Desikan-Killiany-Tourville atlas, averaged over subjects.