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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- | | | |
|-------------------------------------|-------------------------------------|--|
| ☐ | ☒ | The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection no software was used

Data analysis Analyses were conducted in MATLAB (version R2024a; MathWorks), SPSS (version 27.0; IBM) and R (version 4.4.1; <http://www.R-project.org>), with code available at <https://github.com/ZM50149/Tau-pathology>. The rsfMRI was preprocessed using AFNI (v25.1.03; <https://afni.nimh.nih.gov>). DTI were preprocessed in MRtrix3 (v3.0.4; <https://www.mrtrix.org>).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The code is available at <https://github.com/ZM50149/Tau-pathology>. Data is openly available at Supplementary Data.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	The participants had a mean age of 73.02 ± 7.94 years, and 47.22% were male (365/773) while 52.78% were female (408/773).
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable.
Population characteristics	The characteristics included years of education, APOE ϵ 4 carrier status, and neuropsychological assessments.
Recruitment	Not applicable.
Ethics oversight	All participants provided written informed consent. Ethical approval from the individual Institutional Review Board (IRB; https://adni.loni.usc.edu/help-faqs/adni-documentation/) was granted to the investigators at each ADNI participating site. All the ADNI data were collected per the principles of the Declaration of Helsinki.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No a priori sample size calculation was performed; the study yielded statistically significant effects.
Data exclusions	Participants were included if they met the following criteria: (i) MRI acquired on 3T scanners; (ii) complete T1-weighted MRI, DTI, rs-fMRI, A β PET, and tau PET; (iii) complete key covariates (age, sex, APOE ϵ 4 status); (iv) diagnostic classification as cognitively normal, MCI due to AD, or AD; and (v) imaging data passed quality control.
Replication	The Schaefer-200, Schaefer-400, and Desikan-Killiany atlases were used for reproducibility analyses.
Randomization	Not applicable.
Blinding	Not applicable.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	Not applicable.
Study protocol	Details can be found in the Alzheimer's Disease Neuroimaging Initiative (ADNI, https://adni.loni.usc.edu).
Data collection	We analyzed data from 192 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who had available A β -PET, tau-PET, T1-weighted imaging (T1WI), diffusion tensor imaging (DTI), and resting-state functional magnetic resonance (rsfMRI). Details can be found in the Alzheimer's Disease Neuroimaging Initiative (ADNI, https://adni.loni.usc.edu).
Outcomes	Tau topography

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.

Magnetic resonance imaging

Experimental design

Design type	resting state
Design specifications	Design specifications
Behavioral performance measures	Neuropsychological assessment included measures spanning global cognition, dementia severity, episodic memory, executive function, and daily functioning. Global cognition and dementia severity were indexed with the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating Scale–Sum of Boxes (CDR–SB), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-11/13/Q4) and the modified Preclinical Alzheimer's Cognitive Composite (mPACC). Episodic memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) and Logical Memory delayed recall (LDELTOTAL), executive function with Trail Making Test Part B time (TRABSCOR), and daily functioning with the Everyday Cognition scales completed by the participant and study partner (ECogPT and ECogSP) and the Functional Activities Questionnaire (FAQ).

Acquisition

Imaging type(s)	functional, structural, and diffusion.
Field strength	3T
Sequence & imaging parameters	High-resolution structural imaging was performed with a three-dimensional magnetization-prepared rapid gradient-echo (3D MPRAGE) sequence. DTI was acquired using a spin-echo echo-planar imaging (EPI) sequence, and rsfMRI was obtained with a gradient-echo EPI sequence under eyes-open resting conditions.
Area of acquisition	Whole brain.
Diffusion MRI	☒ Used ☐ Not used
Parameters	Diffusion tensor imaging (DTI) used a spin-echo echo-planar imaging (EPI) sequence (TR 7200ms; TE 56ms; matrix 232×232; 160 slices; voxel size 2.0mm isotropic).DTI was acquired using diffusion sensitization with b-values of 0 and 1000 s/mm ² across 60 diffusion-encoding directions.

Preprocessing

Preprocessing software	The rsfMRI was preprocessed using AFNI (v25.1.03; https://afni.nimh.nih.gov). DTI were preprocessed in MRtrix3 (v3.0.4;
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Preprocessing software	https://www.mrtrix.org .
Normalization	Images were rigidly aligned to each participant's T1-weighted anatomical image
Normalization template	subject space
Noise and artifact removal	Diffusion MRI was processed in MRtrix3 (v3.0.4). A brain mask was generated for skull stripping. Data were denoised using Marchenko–Pastur principal component analysis and corrected for Gibbs ringing with a local subvoxel-shift approach. Eddy-current distortions and head motion were corrected, and diffusion images were rigidly aligned to each participant's T1-weighted anatomical image. T1-derived tissue segmentation was used to classify cortical and subcortical grey matter, white matter, cerebrospinal fluid, and, when present, lesion/pathological tissue. The white–grey matter interface was extracted for downstream diffusion-based analyses. Functional images were co-registered to the individual T1-weighted image and normalized to standard space. The data were spatially smoothed to a full width at half maximum of 4 mm, and linear trends, the 6 head-motion parameters, their 6 temporal derivatives, and signals from white matter and cerebrospinal fluid were included as nuisance regressors and regressed out from the data. Finally, time series were band-pass filtered (0.01–0.10 Hz) to retain low-frequency fluctuations relevant to intrinsic functional connectivity.
Volume censoring	The first five volumes were discarded, followed by slice-timing correction and motion correction. Framewise displacement was calculated, and volumes exceeding the censoring threshold (>0.3 mm), together with their neighboring time points, were removed from analysis.

Statistical modeling & inference

Model type and settings	We fitted linear models with tau uptake as the dependent variable and the corresponding propagation signatures as predictors. Separate models were estimated using β derived from A β covariance, SC, and FC individually, as well as from combined predictors (SC+FC and A β +SC+FC).
Effect(s) tested	Standardized mean differences (SMDs) are reported to quantify effect size.
Specify type of analysis:	☒ Whole brain ☐ ROI-based ☐ Both
Statistic type for inference	Not applicable.
(See Eklund et al. 2016)	
Correction	P values were adjusted using the false discovery rate (FDR) method to control multiple testing.

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☐	☒ Multivariate modeling or predictive analysis
Functional and/or effective connectivity	SC was reconstructed from preprocessed DTI. Diffusion tensors were fitted using weighted least squares with iteratively reweighted refinement to derive fractional anisotropy (FA) maps. Fiber orientation distributions were then estimated and whole-brain probabilistic tractography was performed using second-order integration over fiber orientation distributions (iFOD2). Streamlines were seeded within the white-matter mask and terminated upon reaching low anisotropy (FA < 0.2), excessive curvature (turning angle > 45°), or exiting the brain mask. Two parcels were deemed structurally connected if at least one streamline linked them; the resulting undirected SC matrix was weighted by streamline counts. Group-mean SC were then derived by averaging individual matrices within each group. For rsfMRI, parcel-wise blood-oxygen-level-dependent (BOLD) time series were obtained by averaging voxel signals within each region. FC was estimated as Pearson correlations between regional time series, with coefficients Fisher z-transformed and self-correlations set to zero. Group-mean FC were then derived by averaging individual matrices within each group.
Multivariate modeling and predictive analysis	We fitted linear models with tau uptake as the dependent variable and the corresponding propagation signatures as predictors. Model performance and stability were summarized using R-square (R^2), root mean square error (RMSE), and mean absolute error (MAE), and were evaluated using repeated 10-fold cross-validation (10 repeats) to assess out-of-sample generalizability.