

Supplementary Materials

Hierarchical organization of tau topography across the Alzheimer's disease continuum integrates amyloid, connectome, and intrinsic molecular vulnerability

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Table of contents

Supplementary Methods	4
Supplementary Method 1. Patients Inclusion	4
Supplementary Method 2. Neuropsychological assessments	5
Supplementary Method 3. Imaging acquisition	6
Supplementary Method 4. Imaging preprocessing	7
Supplementary Method 5. Euclidean distance between ROIs	8
Supplementary Method 6. Donor sampling profile and parcel coverage	9
Supplementary Tables	10
Supplementary Table 1. Demographic and Clinical Characteristics of All Participants.....	10
Supplementary Table 2. Spatial regression of tau covariance on A β covariance, SC, and FC with and without Euclidean-distance adjustment.	13
Supplementary Table 3. Correlation analyses linking tau uptake to propagation signatures and seed-based coupling from tau hotspots and coldspots across the AD continuum.....	14
Supplementary Table 4. Variance inflation factors of A β covariance, structural connectivity, and functional connectivity across the AD continuum.	15
Supplementary Table 5. Predictive performance of models using A β covariance, structural connectivity, and functional connectivity	16
Supplementary Table 6. Associations between propagation signatures and regional tau uptake under the Destrieux atlas.	18
Supplementary Table 7. Predictive performance of models using A β covariance, structural connectivity, and functional connectivity under the Destrieux atlas. ...	19
Supplementary Table 8. Leave-one-donor-out analysis of gene-weight consistency.....	21
Supplementary Table 9. Variance explained by PLS1 in the full-donor and leave- one-donor-out analyses	22
Supplementary Table 10. Genes associated with the tau map across the AD continuum.	23
Supplementary Table 11. Pathway and process enrichment analyses for shared gene set across the AD continuum.....	26
Supplementary Table 12. Associations of tau spatial gradient, epicenter segregation, and perivascular diffusion with neuropsychological performance..	30
Supplementary Figures	33
Supplementary Figure 1. Stage-stratified cortical topography of A β and tau across the AD continuum.....	33
Supplementary Figure 2. Group-mean A β covariance, structural connectivity, and functional connectivity matrices across the AD continuum.	34
Supplementary Figure 3. Spin-test null distributions for associations between tau uptake and propagation signatures, and between tau uptake and residual tau.....	35

Supplementary Figure 4. Target tau uptake associated with seed-to-target A β covariance, SC, and FC from hot and cold spot.	36
Supplementary Figure 5. Predicting regional tau uptake from propagation signatures across the AD continuum.....	37
Supplementary Figure 6. Predicting regional tau uptake from propagation signatures across the AD continuum under the Destrieux atlas.....	38
Supplementary Figure 7. Stage-specific pathway enrichment and PPI networks of residual tau across the AD continuum.	39
Supplementary Figure 8. Sensitivity analysis of tau spatial gradient across alternative cortical parcellation schemes.	40
Supplementary Figure 9. Associations between epicenter segregation, glymphatic function, and tau spatial gradient across alternative epicenter definitions and DTI–ALPS indices.....	41
Supplementary Figure 10. Mediation and multi-mediation effects of tau spatial gradient linking epicenter segregation, perivascular diffusion, and cognition. ...	42

Supplementary Methods

Supplementary Method 1. Patients Inclusion

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), an ongoing longitudinal, multicenter observational study initiated in 2003 to validate biomarkers for mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Using multimodal neuroimaging from cognitively normal individuals and participants with AD-spectrum impairment, we examined how tau pathology is spatially organized across the AD continuum. Imaging included 3T T1-weighted MRI, diffusion tensor imaging, resting-state fMRI, and amyloid- β (A β) and tau PET, complemented by spatially resolved cortical transcriptomic profiles.

Specifically, we tested three hypotheses: **(1)** regional tau is constrained by A β covariation and by the structural and functional connectome, and network-mediated propagation accounts for a substantial fraction of regional tau burden in a stage-dependent manner; **(2)** beyond network-mediated propagation, a reproducible connectome-independent tau component persists, anchored by shared transcriptional gradients and linked to physiological variation, implicating convergent structural, synaptic and metabolic mechanisms; and **(3)** tau propagation geometry provides an integrative bridge from brain network architecture and glymphatic function to neurodegeneration and clinical expression.

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, or AD; and (v) imaging data passed quality control.

Supplementary Method 2. Neuropsychological assessments

Neuropsychological testing was used to quantify global cognition, dementia severity, domain-specific performance (memory and executive function/processing speed), and everyday functional capacity. The following measures were included: the Mini-Mental State Examination (MMSE), a brief global cognitive screening instrument; the Montreal Cognitive Assessment (MoCA), a screening tool sensitive to mild cognitive impairment; the Clinical Dementia Rating-Sum of Boxes (CDR-SB), a semi-structured interview providing a continuous index of clinical dementia severity across six cognitive and functional domains; and the Functional Activities Questionnaire (FAQ), an informant-rated measure of instrumental activities of daily living.

Episodic memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT), including immediate recall, learning across trials, forgetting, and percentage forgetting indices, and Logical Memory delayed recall (LDELTOTAL). Additional cognitive outcomes included the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-11, ADAS-13, and ADAS-Q4), as well as the modified Preclinical Alzheimer's Cognitive Composite (mPACC) for detecting subtle preclinical cognitive change. Executive function/processing speed was evaluated using the Digit Symbol Substitution Test (Digit Symbol) and Trail Making Test Part B (Trails B), with time to completion (TRABSCOR) used as the primary outcome. Everyday cognition was further captured by the Everyday Cognition scales, including participant report (ECogPT) and study partner report (ECogSP), with domain scores (memory, language, visuospatial, and executive subdomains) and a total score.

Supplementary Method 3. Imaging acquisition

3.1 PET acquisition. Amyloid PET was acquired using either ^{18}F -florbetapir (AV-45) or ^{18}F -florbetaben (FBB). For AV-45, ~ 10 mCi was administered intravenously followed by a 50-min uptake period and a 20-min scan; for FBB, ~ 8 mCi was administered with a 90-min uptake period and a 20-min scan. Tau PET used ^{18}F -flortaucipir (AV-1451), with ~ 10 mCi administered intravenously, a 75-min uptake period, and a 30-min acquisition.

3.2 MRI acquisition. All MRI scans were performed on 3.0 T systems. High-resolution T1-weighted anatomical images were acquired using a 3D MPRAGE sequence (TR 2300 ms; TI 900 ms; TE minimum full echo; matrix 208×240 ; 256 slices; isotropic voxel size 1.0 mm). Diffusion tensor imaging (DTI) used a spin-echo echo-planar imaging (EPI) sequence (TR 7200 ms; TE 56 ms; matrix 232×232 ; 160 slices; voxel size 2.0 mm isotropic). Resting-state fMRI was collected with a gradient-echo EPI protocol (TR 3000 ms; TE 30 ms; flip angle 90° ; matrix 220×220 ; 163 volumes; voxel size 2.5 mm isotropic). More imaging details can be found at <https://adni.loni.usc.edu/help-faqs/adni-documentation/>.

Supplementary Method 4. Imaging preprocessing

4.1 PET preprocessing for regional quantification. A β -PET and tau-PET images were processed using a standard workflow including motion correction, registration to native T1-weighted space, and spatial smoothing. Regional tracer uptake was then quantified within the study parcellation to ensure anatomical correspondence across PET and MRI modalities.

4.2 Diffusion MRI preprocessing. 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.

4.3 Resting-state fMRI preprocessing. Resting-state fMRI was preprocessed using AFNI (v25.1.03). 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. 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.

Supplementary Method 5. Euclidean distance between ROIs

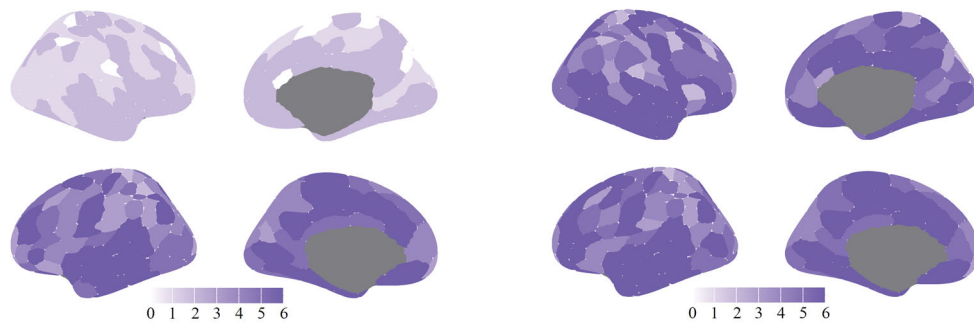
To evaluate whether the associations between A β covariance/SC/FC and tau covariance were attributable to spatial proximity, we quantified inter-regional Euclidean distance for all ROI pairs. For each of the 200 parcels, we computed a representative coordinate by taking the centre-of-mass. Pairwise Euclidean distance was then calculated between parcels i and j using their centroid coordinates:

$$Distance_{i,j} = \sqrt{(i_x - j_x)^2 + (i_y - j_y)^2 + (i_z - j_z)^2}$$

where x_i, y_i, z_i and x_j, y_j, z_j denote the coordinates of the centroids of ROIs i and j , respectively.

Supplementary Method 6. Donor sampling profile and parcel coverage

Regional gene-expression data were derived from the Allen Human Brain Atlas (AHBA), which includes microarray data from six adult donors. According to the AHBA donor profiles, only donors H0351.2001 and H0351.2002 were sampled bilaterally, covering left and right cerebral, cerebellar, and brainstem structures. Donor H0351.1009 was sampled in the left cerebral cortex, striatum, and white matter. Donors H0351.1012, H0351.1015, and H0351.1016 were sampled in the left cerebral, cerebellar, and brainstem structures. Following standard AHBA processing procedures, samples from the available hemisphere were mirrored to the contralateral hemisphere to mitigate right-hemisphere undersampling. The spatial distribution of per-parcel donor coverage after mapping AHBA samples to the Schaefer2018 200-parcel atlas is shown below; the left panels display the original donor coverage, and the right panels display the mirrored coverage used to mitigate right-hemisphere undersampling.



Supplementary Tables

Supplementary Table 1. Demographic and Clinical Characteristics of All Participants.

Characteristic	Overall (<i>n</i> = 192)	CN Aβ- (<i>n</i> = 74)	MCI Aβ- (<i>n</i> = 26)	CN Aβ- (<i>n</i> = 45)	MCI Aβ+ (<i>n</i> = 22)	AD (<i>n</i> = 25)	<i>P</i> value	SMD
Age, mean (SD), y	74.76 (7.74)	72.63 (6.64)	75.21 (9.24)	75.62 (6.75)	75.87 (8.50)	78.09 (8.90)	0.022	0.293
Sex, n (%)							0.086	0.266
Male	105 (54.69)	32 (43.24)	19 (73.08)	27 (60.00)	13 (59.09)	14 (56.00)		
Female	87 (45.31)	42 (56.76)	7 (26.92)	18 (40.00)	9 (40.91)	11 (44.00)		
Education, median (IQR), y	16.00 (15.00, 18.00)	16.00 (16.00, 18.00)	16.00 (13.25, 18.00)	18.00 (16.00, 19.00)	16.00 (12.00, 17.00)	16.00 (14.00, 18.00)	0.074	0.334
APOE ε4, n (%)							<0.001	0.835
No alleles	118 (61.46)	58 (78.38)	24 (92.31)	18 (40.00)	7 (31.82)	11 (44.00)		
One allele	61 (31.77)	15 (20.27)	2 (7.69)	23 (51.11)	12 (54.55)	9 (36.00)		
Two alleles	13 (6.77)	1 (1.35)	0 (0.00)	4 (8.89)	3 (13.64)	5 (20.00)		
MMSE, n (%)	29.00 (27.00, 30.00)	29.00 (29.00, 30.00)	29.00 (27.25, 30.00)	30.00 (29.00, 30.00)	27.00 (25.25, 28.00)	23.00 (22.00, 25.00)	<0.001	1.035
MOCA, median (IQR)	25.00 (22.00, 27.00)	27.00 (25.00, 28.00)	25.00 (22.00, 27.00)	27.00 (24.00, 29.00)	23.00 (20.00, 24.00)	18.00 (15.00, 21.00)	<0.001	1.184
CDR-SB, median (IQR)	0.00 (0.00, 1.12)	0.00 (0.00, 0.00)	1.00 (0.50, 1.88)	0.00 (0.00, 0.00)	1.50 (1.00, 2.38)	4.50 (4.00, 6.50)	<0.001	1.596
ADAS, median (IQR)								
ADAS11	6.33 (3.67, 11.33)	4.16 (3.08, 6.25)	7.50 (6.08, 12.25)	5.67 (3.33, 8.33)	11.00 (5.42, 15.08)	17.50 (14.67, 21.75)	<0.001	1.313
ADAS13	10.50 (6.00, 17.25)	6.67 (4.33, 9.33)	12.16 (10.75, 17.91)	8.67 (5.33, 13.67)	19.50 (11.08, 25.34)	28.66 (22.92, 32.50)	<0.001	1.489
ADASQ4	3.50 (1.75, 6.00)	2.00 (1.00, 3.00)	4.00 (3.25, 6.00)	2.00 (1.00, 4.00)	7.00 (4.25, 8.00)	9.00 (8.00, 10.00)	<0.001	1.494
RAVLT, mean (SD)								

Immediate	42.00 (30.00, 52.00)	49.00 (44.00, 56.00)	37.00 (31.25, 45.75)	42.00 (35.00, 54.00)	29.00 (23.25, 36.25)	24.50 (20.75, 28.00)	<0.001	1.327
Learning	5.00 (3.00, 7.00)	6.00 (5.00, 8.00)	4.00 (3.25, 6.00)	6.00 (4.00, 7.00)	3.00 (1.25, 5.00)	3.00 (0.00, 3.00)	<0.001	0.935
Forgetting	4.00 (2.00, 5.75)	3.00 (1.00, 5.00)	4.00 (2.00, 5.75)	3.00 (2.00, 5.00)	4.00 (4.00, 6.00)	5.00 (4.00, 6.00)	0.002	0.436
Perc forgetting	40.00 (16.67, 75.00)	23.08 (7.14, 41.67)	44.16 (18.99, 66.67)	30.00 (14.29, 46.15)	76.19 (44.64, 100.00)	100.00 (78.75, 100.00)	<0.001	1.191
LDELTOTAL, median (IQR)	12.00 (6.75, 15.00)	14.00 (12.00, 16.00)	7.00 (5.00, 12.50)	13.00 (11.00, 15.00)	4.50 (1.00, 7.75)	1.00 (0.00, 3.00)	<0.001	1.656
mPACC, median (IQR)								
Digit	-0.81 (-6.95, 1.81)	1.38 (-0.80, 2.29)	-4.45 (-6.66, -0.45)	-0.02 (-1.18, 2.34)	-9.05 (-11.52, -6.18)	-16.26 (-17.76, -12.44)	<0.001	1.618
Trails B	-0.54 (-5.79, 1.60)	1.31 (-0.12, 2.31)	-3.42 (-5.49, -0.47)	-0.08 (-1.52, 1.88)	-7.97 (-10.56, -4.46)	-13.25 (-16.61, -10.84)	<0.001	1.639
TRABSCOR, median (IQR)	72.50 (57.00, 106.00)	59.00 (51.00, 80.00)	78.00 (66.25, 97.50)	70.00 (62.00, 91.00)	124.50 (82.25, 144.75)	164.50 (95.50, 300.00)	<0.001	0.820
EcogPt, median (IQR)								
MD	1.75 (1.38, 2.38)	1.50 (1.25, 1.75)	2.12 (1.41, 2.77)	1.75 (1.50, 2.25)	2.75 (2.16, 3.12)	2.00 (1.88, 2.62)	<0.001	0.799
LD	1.33 (1.11, 1.78)	1.22 (1.11, 1.33)	1.44 (1.15, 2.03)	1.56 (1.22, 1.89)	1.67 (1.33, 2.47)	1.39 (1.14, 2.08)	<0.001	0.428
VSP	1.17 (1.00, 1.50)	1.00 (1.00, 1.17)	1.17 (1.00, 1.79)	1.17 (1.00, 1.50)	1.33 (1.17, 1.67)	1.25 (1.00, 1.79)	0.001	0.463
EF-P	1.00 (1.00, 1.40)	1.00 (1.00, 1.20)	1.20 (1.00, 1.79)	1.00 (1.00, 1.60)	1.50 (1.05, 1.80)	1.30 (1.00, 1.75)	<0.001	0.468
EF-O	1.17 (1.00, 1.67)	1.00 (1.00, 1.17)	1.33 (1.00, 2.17)	1.17 (1.00, 1.67)	1.67 (1.17, 2.17)	1.33 (1.00, 2.00)	<0.001	0.526
EF-DA	1.50 (1.25, 2.00)	1.25 (1.00, 1.75)	1.75 (1.31, 2.19)	1.50 (1.25, 2.00)	1.75 (1.25, 2.25)	1.50 (1.25, 2.19)	0.040	0.277
Total	1.39 (1.18, 1.82)	1.26 (1.13, 1.38)	1.58 (1.25, 2.11)	1.47 (1.24, 1.74)	1.85 (1.54, 2.12)	1.49 (1.34, 2.19)	<0.001	0.620
EcogSP, median (IQR)								
MD	1.50 (1.12, 2.38)	1.25 (1.00, 1.50)	2.12 (1.47, 2.38)	1.25 (1.12, 1.62)	2.75 (1.81, 3.44)	3.62 (3.12, 3.88)	<0.001	1.794
LD	1.22 (1.00, 1.67)	1.00 (1.00, 1.22)	1.50 (1.22, 1.97)	1.11 (1.00, 1.33)	1.67 (1.11, 2.42)	2.67 (1.78, 3.11)	<0.001	1.080
VSP	1.00 (1.00, 1.50)	1.00 (1.00, 1.13)	1.33 (1.00, 1.67)	1.00 (1.00, 1.17)	1.40 (1.00, 2.33)	2.67 (2.00, 3.17)	<0.001	1.218
EF-P	1.00 (1.00, 1.60)	1.00 (1.00, 1.00)	1.60 (1.00, 1.80)	1.00 (1.00, 1.20)	1.40 (1.00, 2.60)	2.30 (2.00, 3.40)	<0.001	1.033
EF-O	1.17 (1.00, 1.75)	1.00 (1.00, 1.00)	1.50 (1.17, 1.92)	1.00 (1.00, 1.33)	1.75 (1.00, 2.33)	3.17 (2.30, 3.50)	<0.001	1.314
EF-DA	1.25 (1.00, 2.00)	1.00 (1.00, 1.25)	2.00 (1.50, 2.00)	1.00 (1.00, 1.81)	1.75 (1.25, 3.00)	3.25 (2.50, 3.75)	<0.001	1.187
Total	1.28 (1.05, 1.87)	1.08 (1.00, 1.28)	1.68 (1.31, 1.98)	1.16 (1.05, 1.42)	1.77 (1.24, 2.54)	2.92 (2.39, 3.27)	<0.001	1.593
FAQ, median (IQR)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)	1.00 (0.00, 2.75)	0.00 (0.00, 0.00)	2.00 (0.00, 7.50)	17.00 (11.00, 22.00)	<0.001	1.421

Note. Continuous variables are summarized as mean $\pm$ SD for approximately normally distributed data and as median (IQR) for skewed distributions. Differences across groups were assessed using one-way ANOVA for normally distributed continuous variables and the Kruskal-Wallis test for non-normally distributed continuous variables. Categorical variables are presented as n (%) and compared using χ^2 tests. Standardized mean differences (SMDs) are reported to quantify effect size. *P* values are two-tailed; *P* < 0.05 was considered statistically significant.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; SMD, standardized mean difference; SD, standard deviation; IQR, interquartile range; ANOVA, analysis of variance; APOE ϵ 4, apolipoprotein E ϵ 4 allele; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS, Alzheimer's Disease Assessment Scale (ADAS-11/ADAS-13/ADAS-Q4); RAVLT, Rey Auditory Verbal Learning Test; LDELTOTAL, Logical Memory delayed recall total score; mPACC, modified Preclinical Alzheimer's Cognitive Composite; TRABSCOR, time to complete Trail Making Test Part B; ECogPT/ECogSP, Everyday Cognition scales completed by participant/study partner; MD, Memory Domain; LD, Language Domain; VSP, Visuospatial Abilities; EF-P, Executive Function–Planning; EF-O, Executive Function–Organization; EF-DA, Executive Function–Divided Attention; FAQ, Functional Activities Questionnaire.

Supplementary Table 2. Spatial regression of tau covariance on A β covariance, SC, and FC with and without Euclidean-distance adjustment.

Group	β_1 (95%CI)	β_2 (95%CI)
Aβ covariance		
CN A β -	0.595(0.595, 0.595); $P < 0.001$	0.570(0.570, 0.570); $P < 0.001$
MCI A β -	0.419(0.419, 0.420); $P < 0.001$	0.327(0.327, 0.327); $P < 0.001$
CN A β +	0.470(0.470, 0.470); $P < 0.001$	0.446(0.445, 0.446); $P < 0.001$
MCI A β +	0.510(0.510, 0.510); $P < 0.001$	0.480(0.480, 0.481); $P < 0.001$
AD	0.367(0.367, 0.367); $P < 0.001$	0.306(0.306, 0.306); $P < 0.001$
Structural connectivity		
CN A β -	7.669(7.658, 7.681); $P < 0.001$	4.188(4.176, 4.201); $P < 0.001$
MCI A β -	12.206(12.183, 12.228); $P < 0.001$	4.749(4.730, 4.767); $P < 0.001$
CN A β +	10.613(10.599, 10.626); $P < 0.001$	6.889(6.874, 6.904); $P < 0.001$
MCI A β +	15.213(15.194, 15.233); $P < 0.001$	10.377(10.354, 10.400); $P < 0.001$
AD	11.992(11.978, 12.006); $P < 0.001$	6.368(6.353, 6.382); $P < 0.001$
Functional connectivity		
CN A β -	0.200(0.199, 0.200); $P < 0.001$	0.089(0.088, 0.089); $P < 0.001$
MCI A β -	0.436(0.436, 0.437); $P < 0.001$	0.213(0.213, 0.214); $P < 0.001$
CN A β +	0.392(0.392, 0.393); $P < 0.001$	0.296(0.295, 0.296); $P < 0.001$
MCI A β +	0.361(0.360, 0.361); $P < 0.001$	0.171(0.170, 0.172); $P < 0.001$
AD	0.570(0.570, 0.571); $P < 0.001$	0.364(0.363, 0.364); $P < 0.001$

Note. β coefficients were estimated using matrix-based spatial regression with the tau covariance matrix as the dependent variable and A β covariance, structural connectivity, or functional connectivity as predictors. β_1 denotes the unadjusted model; β_2 denotes the model additionally adjusted for inter-regional Euclidean distance. Values are reported as β (95% CI); P value. All P values are two-sided.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval.

Supplementary Table 3. Correlation analyses linking tau uptake to propagation signatures and seed-based coupling from tau hotspots and coldspots across the AD continuum.

Group	r_1 (95%CI)	r_2 (95%CI)	r_3 (95%CI)
Aβ covariance			
CN A β -	0.682 (0.600, 0.750); $P < 0.001$	-0.057 (-0.195, 0.082); $P=0.421$	0.465 (0.348, 0.567); $P<0.001$
MCI A β -	0.654 (0.567, 0.727); $P < 0.001$	-0.289 (-0.412, -0.156); $P<0.001$	0.404 (0.281, 0.514); $P<0.001$
CN A β +	0.776 (0.715, 0.826); $P < 0.001$	-0.659 (-0.731, -0.573); $P<0.001$	0.512 (0.402, 0.608); $P<0.001$
MCI A β +	0.706 (0.629, 0.770); $P < 0.001$	-0.212 (-0.341, -0.075); $P=0.003$	0.263 (0.128, 0.388); $P<0.001$
AD	0.626 (0.533, 0.703); $P < 0.001$	-0.323 (-0.442, -0.193); $P<0.001$	0.425 (0.304, 0.532); $P<0.001$
Structural connectivity			
CN A β -	0.714 (0.639, 0.776); $P < 0.001$	-0.375 (-0.489, -0.249); $P < 0.001$	0.386 (0.261, 0.499); $P<0.001$
MCI A β -	0.689 (0.608, 0.756); $P < 0.001$	-0.390 (-0.502, -0.265); $P<0.001$	0.391 (0.267, 0.503); $P<0.001$
CN A β +	0.758 (0.692, 0.811); $P<0.001$	-0.430 (-0.537, -0.310); $P<0.001$	0.309 (0.178, 0.430); $P<0.001$
MCI A β +	0.763 (0.698, 0.815); $P < 0.001$	-0.389 (-0.501, -0.264); $P < 0.001$	0.347 (0.218, 0.463); $P<0.001$
AD	0.739 (0.668, 0.796); $P < 0.001$	-0.351 (-0.467, -0.222); $P<0.001$	0.442 (0.322, 0.547); $P<0.001$
Functional connectivity			
CN A β -	0.719 (0.645, 0.780); $P<0.001$	-0.602 (-0.684, -0.506); $P < 0.001$	0.394 (0.269, 0.505); $P < 0.001$
MCI A β -	0.711 (0.635, 0.773); $P<0.001$	-0.584 (-0.668, -0.484); $P<0.001$	0.265 (0.131, 0.390); $P<0.001$
CN A β +	0.761 (0.696, 0.814); $P < 0.001$	-0.717 (-0.778, -0.642); $P < 0.001$	0.471 (0.355, 0.573); $P<0.001$
MCI A β +	0.781 (0.721, 0.830); $P < 0.001$	-0.676 (-0.745, -0.592); $P<0.001$	0.351 (0.223, 0.467); $P<0.001$
AD	0.830 (0.781, 0.869); $P<0.001$	-0.522 (-0.616, -0.413); $P<0.001$	0.619 (0.525, 0.698); $P<0.001$

Note. Values are Pearson's correlation coefficients with 95%CI and two-tailed P values. Analyses were performed separately within each subgroup and for each modality. r_1 quantifies the association between seed-region tau uptake and the corresponding propagation signature. r_2 quantifies the association between target-region tau uptake and seed-to-target coupling values from tau hotspot seeds. r_3 quantifies the association between target-region tau uptake and seed-to-target coupling values from tau cold-spot seeds.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval.

Supplementary Table 4. Variance inflation factors of A β covariance, structural connectivity, and functional connectivity across the AD continuum.

Propagation signatures	CN A β -	MCI A β -	CN A β +	MCI A β +	AD
A β covariance	1.669 (1.391, 2.052)	1.443 (1.257, 1.669)	2.657 (1.995, 3.488)	2.024 (1.699, 2.431)	1.931 (1.628, 2.306)
SC	3.608 (2.867, 4.474)	3.335 (2.727, 4.112)	4.172 (3.302, 5.327)	2.960 (2.395, 3.676)	3.043 (2.430, 3.805)
FC	4.012 (3.173, 4.987)	3.085 (2.514, 3.781)	4.108 (3.241, 5.199)	3.015 (2.422, 3.797)	2.911 (2.360, 3.572)

Note. Values are VIFs with 95% CIs obtained from 2000 bootstrap resamples. VIFs were calculated for the three propagation-signature predictors entered simultaneously into the regression model used to derive subgroup-specific residual tau maps. Across all subgroups, VIF values were below 5, indicating no substantial multicollinearity.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; SC, structural connectivity; FC, functional connectivity; VIF, variance inflation factor; CI, confidence interval.

Supplementary Table 5. Predictive performance of models using A β covariance, structural connectivity, and functional connectivity

Predictors	Group	R2	RMSE	MAE
A β covariance	CN A β -	0.488 (0.219, 0.786)	0.048 (0.034, 0.063)	0.039 (0.028, 0.049)
	MCI A β -	0.453 (0.150, 0.712)	0.052 (0.040, 0.068)	0.043 (0.032, 0.055)
	CN A β +	0.615 (0.373, 0.799)	0.051 (0.037, 0.064)	0.042 (0.030, 0.052)
	MCI A β +	0.510 (0.247, 0.742)	0.086 (0.063, 0.105)	0.066 (0.047, 0.084)
	AD	0.412 (0.200, 0.671)	0.133 (0.102, 0.162)	0.108 (0.078, 0.134)
SC	CN A β -	0.537 (0.297, 0.823)	0.047 (0.037, 0.057)	0.038 (0.030, 0.045)
	MCI A β -	0.506 (0.228, 0.777)	0.050 (0.037, 0.065)	0.040 (0.030, 0.052)
	CN A β +	0.592 (0.314, 0.814)	0.053 (0.039, 0.069)	0.044 (0.031, 0.058)
	MCI A β +	0.601 (0.340, 0.817)	0.079 (0.059, 0.099)	0.063 (0.045, 0.081)
	AD	0.568 (0.251, 0.784)	0.114 (0.088, 0.156)	0.092 (0.070, 0.121)
FC	CN A β -	0.536 (0.357, 0.705)	0.046 (0.035, 0.055)	0.037 (0.029, 0.046)
	MCI A β -	0.528 (0.221, 0.782)	0.049 (0.036, 0.062)	0.040 (0.028, 0.051)
	CN A β +	0.599 (0.377, 0.780)	0.053 (0.041, 0.065)	0.044 (0.033, 0.056)
	MCI A β +	0.625 (0.381, 0.828)	0.076 (0.057, 0.099)	0.062 (0.046, 0.084)
	AD	0.699 (0.473, 0.829)	0.095 (0.071, 0.118)	0.078 (0.059, 0.100)
SC+FC	CN A β -	0.572 (0.383, 0.777)	0.045 (0.034, 0.053)	0.036 (0.028, 0.044)
	MCI A β -	0.559 (0.285, 0.794)	0.047 (0.035, 0.062)	0.038 (0.027, 0.050)
	CN A β +	0.635 (0.398, 0.820)	0.050 (0.039, 0.065)	0.042 (0.031, 0.055)
	MCI A β +	0.672 (0.475, 0.839)	0.071 (0.054, 0.089)	0.058 (0.043, 0.077)
	AD	0.713 (0.525, 0.851)	0.093 (0.068, 0.122)	0.076 (0.056, 0.097)
A β covariance + SC + FC	CN A β -	0.646 (0.436, 0.833)	0.040 (0.030, 0.051)	0.033 (0.024, 0.042)
	MCI A β -	0.648 (0.394, 0.847)	0.042 (0.030, 0.055)	0.034 (0.024, 0.045)
	CN A β +	0.692 (0.464, 0.842)	0.046 (0.034, 0.058)	0.038 (0.027, 0.047)
	MCI A β +	0.700 (0.502, 0.864)	0.067 (0.050, 0.086)	0.055 (0.040, 0.072)
	AD	0.717 (0.539, 0.850)	0.092 (0.068, 0.121)	0.075 (0.055, 0.095)

Note. Values are shown as mean (95% CI) derived from repeated 10-fold cross-validation.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval; ; R², coefficient of determination; RMSE, root mean squared error; MAE, mean absolute error.

Supplementary Table 6. Associations between propagation signatures and regional tau uptake under the Destrieux atlas.

Group	Aβ covariance	Structural connectivity	Functional connectivity
CN Aβ-	0.713 (0.638, 0.775); $P_{spin} < 0.001$	0.648 (0.559, 0.722); $P_{spin} < 0.001$	0.683 (0.602, 0.751) ; $P_{spin} < 0.001$
MCI Aβ-	0.695 (0.616, 0.761); $P_{spin} < 0.001$	0.720 (0.646, 0.781) ; $P_{spin} = 0.001$	0.628 (0.536, 0.705) ; $P_{spin} < 0.001$
CN Aβ+	0.710 (0.634, 0.773); $P_{spin} < 0.001$	0.661 (0.575, 0.732) ; $P_{spin} < 0.001$	0.673 (0.590, 0.743) ; $P_{spin} < 0.001$
MCI Aβ+	0.682 (0.600, 0.750); $P_{spin} < 0.001$	0.706 (0.629, 0.769) ; $P_{spin} < 0.001$	0.659 (0.573, 0.731) ; $P_{spin} < 0.001$
AD	0.734 (0.663, 0.792); $P_{spin} < 0.001$	0.691 (0.611, 0.758) ; $P_{spin} < 0.001$	0.744 (0.675, 0.800) ; $P_{spin} < 0.001$

Note. Values are Pearson's correlation coefficients with 95% CIs and two-tailed P values.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval.

Supplementary Table 7. Predictive performance of models using A β covariance, structural connectivity, and functional connectivity under the Destrieux atlas.

Predictors	Group	R2	RMSE	MAE
Aβ covariance	CN Aβ-	0.437 (0.096, 0.763)	0.058 (0.042, 0.076)	0.045 (0.032, 0.061)
	MCI Aβ-	0.486 (0.130, 0.772)	0.059 (0.043, 0.074)	0.049 (0.035, 0.064)
	CN Aβ+	0.530 (0.198, 0.765)	0.064 (0.048, 0.080)	0.054 (0.040, 0.070)
	MCI Aβ+	0.541 (0.140, 0.810)	0.089 (0.064, 0.118)	0.073 (0.052, 0.097)
	AD	0.504 (0.204, 0.756)	0.136 (0.098, 0.177)	0.112 (0.082, 0.154)
SC	CN Aβ-	0.514 (0.195, 0.756)	0.054 (0.039, 0.069)	0.046 (0.032, 0.060)
	MCI Aβ-	0.459 (0.138, 0.703)	0.061 (0.042, 0.078)	0.050 (0.035, 0.066)
	CN Aβ+	0.524 (0.253, 0.763)	0.065 (0.046, 0.084)	0.054 (0.039, 0.070)
	MCI Aβ+	0.521 (0.130, 0.806)	0.097 (0.062, 0.153)	0.076 (0.048, 0.103)
	AD	0.531 (0.235, 0.762)	0.131 (0.086, 0.176)	0.108 (0.074, 0.151)
FC	CN Aβ-	0.456 (0.081, 0.688)	0.057 (0.043, 0.070)	0.049 (0.035, 0.063)
	MCI Aβ-	0.496 (0.259, 0.736)	0.059 (0.046, 0.075)	0.051 (0.040, 0.065)
	CN Aβ+	0.490 (0.200, 0.703)	0.066 (0.051, 0.080)	0.057 (0.042, 0.071)
	MCI Aβ+	0.556 (0.336, 0.735)	0.088 (0.063, 0.113)	0.075 (0.050, 0.100)
	AD	0.546 (0.321, 0.755)	0.129 (0.092, 0.161)	0.107 (0.074, 0.138)
SC+FC	CN Aβ-	0.533 (0.229, 0.765)	0.053 (0.040, 0.063)	0.046 (0.033, 0.056)
	MCI Aβ-	0.542 (0.304, 0.734)	0.056 (0.044, 0.073)	0.048 (0.034, 0.062)
	CN Aβ+	0.559 (0.289, 0.743)	0.062 (0.047, 0.078)	0.053 (0.041, 0.068)
	MCI Aβ+	0.598 (0.355, 0.797)	0.085 (0.059, 0.109)	0.071 (0.047, 0.093)
	AD	0.602 (0.373, 0.780)	0.121 (0.086, 0.154)	0.100 (0.069, 0.133)
Aβ covariance + SC + FC	CN Aβ-	0.636 (0.342, 0.856)	0.046 (0.033, 0.060)	0.038 (0.027, 0.051)
	MCI Aβ-	0.686 (0.372, 0.855)	0.046 (0.031, 0.060)	0.039 (0.024, 0.053)
	CN Aβ+	0.606 (0.348, 0.806)	0.059 (0.043, 0.073)	0.051 (0.038, 0.066)
	MCI Aβ+	0.652 (0.427, 0.833)	0.078 (0.055, 0.103)	0.067 (0.047, 0.088)
	AD	0.642 (0.417, 0.813)	0.115 (0.079, 0.147)	0.096 (0.066, 0.126)

Note. Values are shown as mean (95% CI) derived from repeated 10-fold cross-validation.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval; ; R², coefficient of determination; RMSE, root mean squared error; MAE, mean absolute error.

Supplementary Table 8. Leave-one-donor-out analysis of gene-weight consistency

Donor left out	CN A β -	MCI A β -	CN A β +	MCI A β +	AD
10021	0.926 (0.923, 0.928); $P < 0.001$	0.878 (0.874, 0.881); $P < 0.001$	0.899 (0.896, 0.902); $P < 0.001$	0.869 (0.865, 0.873); $P < 0.001$	0.867 (0.863, 0.871); $P < 0.001$
12876	0.943 (0.941, 0.944); $P < 0.001$	0.895 (0.892, 0.898); $P < 0.001$	0.914 (0.912, 0.917); $P < 0.001$	0.877 (0.874, 0.881); $P < 0.001$	0.875 (0.871, 0.878); $P < 0.001$
14380	0.934 (0.932, 0.936); $P < 0.001$	0.893 (0.890, 0.896); $P < 0.001$	0.912 (0.910, 0.915); $P < 0.001$	0.869 (0.865, 0.873); $P < 0.001$	0.889 (0.886, 0.892); $P < 0.001$
15496	0.933 (0.931, 0.935); $P < 0.001$	0.899 (0.896, 0.902); $P < 0.001$	0.909 (0.906, 0.911); $P < 0.001$	0.878 (0.874, 0.881); $P < 0.001$	0.867 (0.863, 0.871); $P < 0.001$
15697	0.942 (0.940, 0.944); $P < 0.001$	0.905 (0.902, 0.908); $P < 0.001$	0.910 (0.908, 0.913); $P < 0.001$	0.892 (0.889, 0.895); $P < 0.001$	0.887 (0.884, 0.890); $P < 0.001$
9861	0.906 (0.903, 0.909); $P < 0.001$	0.850 (0.845, 0.854); $P < 0.001$	0.891 (0.887, 0.894); $P < 0.001$	0.843 (0.839, 0.848); $P < 0.001$	0.835 (0.830, 0.840); $P < 0.001$

Note. Values are Pearson's correlation coefficients with 95% CIs and two-tailed P values.

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , amyloid- β ; CI, confidence interval.

Supplementary Table 9. Variance explained by PLS1 in the full-donor and leave-one-donor-out analyses

Donor left out	CN A β -	MCI A β -	CN A β +	MCI A β +	AD
All donors	0.219 (0.194, 0.244)	0.203 (0.180, 0.225)	0.191 (0.165, 0.217)	0.181 (0.165, 0.197)	0.177 (0.160, 0.193)
10021	0.242 (0.219, 0.265)	0.261 (0.238, 0.285)	0.229 (0.202, 0.255)	0.236 (0.216, 0.256)	0.166 (0.147, 0.184)
12876	0.233 (0.206, 0.259)	0.258 (0.235, 0.281)	0.213 (0.189, 0.237)	0.164 (0.147, 0.182)	0.171 (0.154, 0.189)
14380	0.229 (0.204, 0.253)	0.211 (0.189, 0.233)	0.219 (0.195, 0.242)	0.190 (0.170, 0.211)	0.166 (0.147, 0.184)
15496	0.282 (0.252, 0.312)	0.210 (0.183, 0.237)	0.248 (0.222, 0.273)	0.206 (0.186, 0.227)	0.202 (0.182, 0.222)
15697	0.235 (0.210, 0.260)	0.247 (0.222, 0.271)	0.204 (0.179, 0.229)	0.189 (0.167, 0.211)	0.190 (0.167, 0.214)
9861	0.241 (0.217, 0.264)	0.263 (0.241, 0.286)	0.218 (0.195, 0.242)	0.210 (0.184, 0.235)	0.184 (0.168, 0.200)

Note. Values are presented as the proportion of variance in tau topography explained by PLS1 (R^2), with 95% CIs. “All donors” denotes the analysis using the complete AHBA dataset, whereas the remaining rows denote leave-one-donor-out analyses in which the indicated donor was excluded.

Abbreviations: PLS1, first partial least squares component; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer’s disease; A β , amyloid- β ; CI, confidence interval.

Supplementary Table 10. Genes associated with the tau map across the AD continuum.

Gene	<i>r</i> (95%CI)	<i>P</i>_{spin}	Gene	<i>r</i> (95%CI)	<i>P</i>_{spin}
KIRREL3	0.582 (0.482, 0.667)	0.001	SYT6	-0.590 (-0.673, -0.491)	0.001
CARTPT	0.535 (0.428, 0.627)	0.001	INHBA	-0.540 (-0.632, -0.434)	< 0.001
NPPA	0.526 (0.417, 0.619)	0.003	GMPR	-0.524 (-0.618, -0.415)	0.001
EHBP1L1	0.508 (0.397, 0.604)	0.001	IGFLR1	-0.474 (-0.575, -0.358)	< 0.001
PDZD2	0.503 (0.391, 0.600)	0.001	CRISPLD1	-0.472 (-0.573, -0.356)	< 0.001
DUSP5P1	0.504 (0.392, 0.600)	< 0.001	FAM189A1	-0.471 (-0.573, -0.356)	0.003
NPTX2	0.495 (0.383, 0.593)	0.001	TNFRSF12A	-0.465 (-0.568, -0.349)	< 0.001
RFTN1	0.494 (0.381, 0.592)	0.003	CLMP	-0.464 (-0.567, -0.348)	0.001
TNFRSF11A	0.484 (0.370, 0.583)	0.002	ASTN2	-0.447 (-0.551, -0.328)	0.002
CYP1B1	0.474 (0.359, 0.575)	0.01	HSBP1L1	-0.443 (-0.548, -0.324)	0.005
PKD2L1	0.473 (0.358, 0.574)	< 0.001	CRABP1	-0.435 (-0.541, -0.316)	0.006
ST6GALNAC5	0.466 (0.350, 0.568)	0.001	RBKS	-0.433 (-0.539, -0.313)	0.011
ENC1	0.460 (0.343, 0.563)	0.001	PPIL3	-0.430 (-0.537, -0.310)	0.035
UNC13A	0.453 (0.336, 0.557)	< 0.001	CSDC2	-0.428 (-0.535, -0.307)	0.008
DGKB	0.453 (0.335, 0.556)	< 0.001	DSCAML1	-0.425 (-0.532, -0.304)	0.001
GRM8	0.450 (0.332, 0.554)	< 0.001	SH3BGRL	-0.424 (-0.532, -0.303)	0.019
TYRO3	0.450 (0.332, 0.554)	0.001	MICB	-0.420 (-0.528, -0.299)	0.001
TSHZ2	0.448 (0.330, 0.553)	0.002	NXPH3	-0.412 (-0.521, -0.290)	0.005
MKL2	0.445 (0.326, 0.550)	0.028	STK33	-0.397 (-0.508, -0.274)	0.005
GSTM5	0.443 (0.325, 0.548)	0.007	GRM4	-0.381 (-0.494, -0.256)	0.002
BSN	0.442 (0.323, 0.547)	0.001	RHOV	-0.376 (-0.490, -0.251)	0.004
STX1A	0.440 (0.321, 0.546)	0.007	DIP2A	-0.360 (-0.475, -0.233)	0.001
CELF3	0.438 (0.318, 0.544)	0.001	C4orf33	-0.350 (-0.466, -0.222)	0.043
LONRF2	0.438 (0.318, 0.543)	< 0.001	SVIP	-0.349 (-0.465, -0.221)	0.001
LTK	0.425 (0.304, 0.532)	0.001	PDPN	-0.342 (-0.459, -0.214)	< 0.001
LAMB1	0.423 (0.303, 0.531)	0.01	ANTXR2	-0.341 (-0.458, -0.212)	0.005

SLC30A3	0.423 (0.302, 0.531)	0.005	PAQR9	-0.336 (-0.454, -0.207)	0.005
SERPINF1	0.418 (0.296, 0.526)	0.003	RASSF8-AS1	-0.336 (-0.454, -0.207)	0.004
CELF5	0.415 (0.293, 0.523)	0.01	SNRNP48	-0.329 (-0.447, -0.200)	0.002
ONECUT1	0.411 (0.289, 0.520)	0.046	PRDM5	-0.328 (-0.446, -0.198)	0.011
RLBP1	0.410 (0.288, 0.519)	0.002	BHLHE41	-0.327 (-0.445, -0.197)	0.04
EGR3	0.410 (0.287, 0.519)	< 0.001	GADD45B	-0.323 (-0.442, -0.193)	0.01
KCNB2	0.407 (0.284, 0.517)	0.009	MICA	-0.322 (-0.441, -0.192)	0.026
OBSCN	0.401 (0.278, 0.511)	0.014	MAP3K14	-0.321 (-0.441, -0.191)	0.006
SLC25A23	0.399 (0.275, 0.509)	0.013	HIST4H4	-0.320 (-0.439, -0.189)	0.027
EFNB2	0.398 (0.275, 0.509)	0.002	TGFBR1	-0.317 (-0.436, -0.186)	0.01
BEGAIN	0.393 (0.268, 0.504)	0.002	CRYGD	-0.309 (-0.430, -0.178)	0.018
INSM1	0.388 (0.263, 0.499)	0.002	UNC13C	-0.304 (-0.425, -0.173)	0.014
SH2D5	0.386 (0.261, 0.498)	0.01	PSMC3IP	-0.295 (-0.417, -0.163)	0.005
C5orf30	0.377 (0.252, 0.490)	0.033	ZNF684	-0.292 (-0.414, -0.160)	0.041
CNNM4	0.354 (0.227, 0.470)	0.016	MCEE	-0.290 (-0.412, -0.157)	0.012
CERS6	0.346 (0.217, 0.462)	0.045	LMO7	-0.288 (-0.410, -0.155)	0.017
PLXNA1	0.341 (0.212, 0.458)	0.014	TRPM3	-0.282 (-0.405, -0.149)	0.046
OCA2	0.341 (0.212, 0.458)	0.002	TAP1	-0.280 (-0.403, -0.147)	0.012
FAM171A2	0.329 (0.199, 0.447)	0.002	WDR91	-0.280 (-0.403, -0.147)	0.024
DOC2A	0.327 (0.198, 0.446)	0.048	DHRS13	-0.269 (-0.393, -0.136)	0.004
KCNV1	0.327 (0.197, 0.445)	0.005	RUNX2	-0.267 (-0.391, -0.133)	0.011
FIGNL2	0.325 (0.195, 0.444)	0.008	NDUFS4	-0.266 (-0.390, -0.132)	0.012
SEC24D	0.323 (0.193, 0.442)	0.003	GLRX3	-0.266 (-0.390, -0.132)	0.034
CEP170B	0.323 (0.193, 0.442)	0.034	FKBP7	-0.265 (-0.389, -0.131)	0.019
AHR	0.312 (0.181, 0.432)	0.004	B3GAT3	-0.263 (-0.388, -0.129)	0.032
ASS1	0.311 (0.180, 0.431)	0.008	OR7E24	-0.262 (-0.387, -0.128)	0.005
EGR4	0.304 (0.173, 0.425)	0.029	NOB1	-0.258 (-0.383, -0.124)	0.045
CTNND2	0.303 (0.171, 0.424)	0.011	UTRN	-0.257 (-0.382, -0.122)	0.015

LINGO1	0.303 (0.171, 0.424)	0.015	ARHGEF6	-0.252 (-0.377, -0.117)	0.044
IQSEC2	0.294 (0.162, 0.416)	0.013	IQCH-AS1	-0.250 (-0.376, -0.116)	0.013
C1QL2	0.293 (0.161, 0.415)	0.037	DCXR	-0.250 (-0.375, -0.115)	0.035
ZMIZ2	0.284 (0.151, 0.406)	0.004	SCRN2	-0.241 (-0.367, -0.106)	0.022
KIAA1549	0.280 (0.147, 0.403)	0.012	CLIP4	-0.240 (-0.367, -0.105)	0.022
CYB561	0.279 (0.146, 0.402)	0.028	SDHAF3	-0.236 (-0.363, -0.101)	0.018
GPR150	0.278 (0.145, 0.402)	0.018	SEMA3E	-0.230 (-0.357, -0.094)	0.017
LRRC57	0.278 (0.145, 0.401)	0.015	SLC46A3	-0.227 (-0.354, -0.091)	0.034
PJA1	0.267 (0.134, 0.392)	0.02	EAF2	-0.220 (-0.348, -0.084)	0.011
SORCS3	0.266 (0.132, 0.390)	0.011	PLBD2	-0.219 (-0.348, -0.083)	0.036
LOC441666	0.252 (0.118, 0.378)	0.018	ZNF672	-0.209 (-0.338, -0.073)	0.024
SYT1	0.248 (0.113, 0.374)	0.034	HM13	-0.201 (-0.330, -0.064)	0.009
SNAI3-AS1	0.245 (0.110, 0.371)	0.034	MRPL2	-0.199 (-0.329, -0.062)	0.024
ARNT2	0.242 (0.107, 0.368)	0.036	ERI1	-0.194 (-0.324, -0.056)	0.027
RNF38	0.227 (0.091, 0.355)	0.029	GRAMD1A	-0.175 (-0.306, -0.037)	0.029
PIK3R5	0.180 (0.042, 0.311)	0.036			

Note. Values are Pearson's correlation coefficients (r) with 95% CIs. P_{spin} was assessed using spin-test permutations (2000 rotations). Positive r indicates higher gene expression in regions showing higher tau residuals, whereas negative r indicates the opposite.

Abbreviations: CI, confidence interval.

Supplementary Table 11. Pathway and process enrichment analyses for shared gene set across the AD continuum.

GroupID	Category	Description	LogP	Log(q-value)	%InGO	Enrichment	Z-score
1_Summary	GO Biological Processes	synaptic signaling	-5,945360311	-2,091	5.1	3.1	6
1_Member	GO Biological Processes	synaptic signaling	-5,945360311	-2,091	5.1	3.1	6
1_Member	GO Biological Processes	modulation of chemical synaptic transmission	-5,887499352	-2,091	5.3	3	5.9
1_Member	GO Biological Processes	regulation of trans-synaptic signaling	-5,872787169	-2,091	5.3	3	5.9
1_Member	GO Biological Processes	chemical synaptic transmission	-5,272793671	-1,708	4.4	3.1	6
1_Member	GO Biological Processes	anterograde trans-synaptic signaling	-5,272793671	-1,708	4.4	3.1	6
1_Member	GO Biological Processes	trans-synaptic signaling	-4,943484371	-1,445	4.4	3.1	6
2_Summary	GO Biological Processes	rhythmic process	-5,832725678	-2,091	3.6	4	6.3
2_Member	GO Biological Processes	rhythmic process	-5,832725678	-2,091	3.6	4	6.3
2_Member	GO Biological Processes	circadian rhythm	-3,414205189	-0,651	1.9	5.1	5.5
2_Member	GO Biological Processes	circadian regulation of gene expression	-2,390593883	-0,110	1.1	8.8	5.9
2_Member	WikiPathways	Circadian rhythm genes	-2,327114232	-0,077	1.9	5.1	5.5
3_Summary	GO Biological Processes	neuron projection development	-4,763550865	-1,323	5.9	2.4	5
3_Member	GO Biological Processes	neuron projection development	-4,763550865	-1,323	5.9	2.4	5
3_Member	GO Biological Processes	neuron projection morphogenesis	-4,166511976	-0,994	4.4	3.1	6
3_Member	GO Biological Processes	plasma membrane bounded cell projection morphogenesis	-4,106941108	-0,994	4.4	3.1	6
3_Member	GO Biological Processes	cell projection morphogenesis	-4,025032928	-0,960	4.4	3.1	6
3_Member	GO Biological Processes	cell morphogenesis	-3,55381811	-0,716	5.3	3	5.9
4_Summary	GO Biological Processes	cell-cell adhesion	-4,599401007	-1,210	4.8	2.7	5
4_Member	GO Biological Processes	cell-cell adhesion	-4,599401007	-1,210	4.8	2.7	5
5_Summary	GO Biological Processes	response to metal ion	-4,3092673	-0,994	3.6	4	6.3
5_Member	GO Biological Processes	response to metal ion	-4,3092673	-0,994	3.6	4	6.3
5_Member	GO Biological Processes	cellular response to metal ion	-3,117507436	-0,427	2.1	4.1	4.9
5_Member	GO Biological Processes	detection of calcium ion	-2,817388062	-0,312	0.63	21	7.7
5_Member	GO Biological Processes	response to calcium ion	-2,726433181	-0,252	1.7	6	5.8
6_Summary	GO Biological Processes	endothelial cell migration	-4,233480575	-0,994	1.7	6	5.8

6_Member	GO Biological Processes	endothelial cell migration	-4,233480575	-0,994	1.7	6	5.8
6_Member	GO Biological Processes	blood vessel endothelial cell migration	-3,62660126	-0,716	1.1	8.8	5.9
6_Member	GO Biological Processes	cell migration involved in sprouting angiogenesis	-3,232553107	-0,523	0.84	17	7.8
6_Member	GO Biological Processes	sprouting angiogenesis	-2,418745802	-0,110	1.1	8.8	5.9
7_Summary	GO Biological Processes	inorganic ion transmembrane transport	-4,193950689	-0,994	5.9	2.4	5
7_Member	GO Biological Processes	inorganic ion transmembrane transport	-4,193950689	-0,994	5.9	2.4	5
7_Member	GO Biological Processes	monoatomic cation transmembrane transport	-2,989983558	-0,372	4.8	2.7	5
7_Member	GO Biological Processes	inorganic cation transmembrane transport	-2,758580311	-0,273	4.6	2	3.6
7_Member	GO Biological Processes	metal ion transport	-2,652549194	-0,239	4.4	3.1	6
8_Summary	GO Biological Processes	regulation of long-term synaptic depression	-4,1454786	-0,994	0.84	17	7.8
8_Member	GO Biological Processes	regulation of long-term synaptic depression	-4,1454786	-0,994	0.84	17	7.8
8_Member	GO Biological Processes	neuropeptide signaling pathway	-2,680098942	-0,239	1.5	6.9	6
9_Summary	GO Biological Processes	ovulation cycle	-4,144847447	-0,994	1.5	6.9	6
9_Member	GO Biological Processes	ovulation cycle	-4,144847447	-0,994	1.5	6.9	6
10_Summary	GO Biological Processes	chloride transmembrane transport	-4,118341342	-0,994	1.9	5.1	5.5
10_Member	GO Biological Processes	chloride transmembrane transport	-4,118341342	-0,994	1.9	5.1	5.5
10_Member	GO Biological Processes	chloride transport	-3,781664398	-0,751	1.9	5.1	5.5
10_Member	GO Biological Processes	inorganic anion transmembrane transport	-3,579083003	-0,716	1.9	5.1	5.5
10_Member	Reactome Gene Sets	Multifunctional anion exchangers	-3,520633652	-0,705	0.63	21	7.7
10_Member	GO Biological Processes	monoatomic anion transmembrane transport	-3,238364694	-0,523	1.9	5.1	5.5
10_Member	GO Biological Processes	monoatomic anion transport	-2,940105467	-0,372	1.9	5.1	5.5
10_Member	GO Biological Processes	inorganic anion transport	-2,940105467	-0,372	1.9	5.1	5.5
10_Member	GO Biological Processes	dicarboxylic acid transport	-2,000725996	0,000	1.1	8.8	5.9
11_Summary	GO Biological Processes	synapse organization	-4,030059899	-0,960	3.6	4	6.3
11_Member	GO Biological Processes	synapse organization	-4,030059899	-0,960	3.6	4	6.3
11_Member	GO Biological Processes	cell junction organization	-3,476716187	-0,690	4.4	3.1	6
11_Member	GO Biological Processes	cell junction assembly	-2,968025555	-0,372	2.7	2.7	5
11_Member	GO Biological Processes	synapse assembly	-2,907116629	-0,363	1.7	6	5.8
11_Member	GO Biological Processes	presynapse organization	-2,816474745	-0,312	0.84	17	7.8

11_Member	GO Biological Processes	presynapse assembly	-2,38188852	-0,110	0.63	21	7.7
12_Summary	KEGG Pathway	Oxytocin signaling pathway	-3,74493262	-0,751	2.1	4.1	4.9
12_Member	KEGG Pathway	Oxytocin signaling pathway	-3,74493262	-0,751	2.1	4.1	4.9
12_Member	KEGG Pathway	Vascular smooth muscle contraction	-3,554854494	-0,716	1.9	5.1	5.5
12_Member	KEGG Pathway	cGMP-PKG signaling pathway	-3,504639677	-0,705	2.1	4.1	4.9
12_Member	GO Biological Processes	cyclic nucleotide biosynthetic process	-2,164157261	0,000	0.63	21	7.7
13_Summary	GO Biological Processes	learning or memory	-3,743128292	-0,751	2.9	3.1	6
13_Member	GO Biological Processes	learning or memory	-3,743128292	-0,751	2.9	3.1	6
13_Member	GO Biological Processes	memory	-3,628246336	-0,716	1.9	5.1	5.5
13_Member	GO Biological Processes	behavior	-3,443723065	-0,669	4.8	2.7	5
13_Member	GO Biological Processes	cognition	-3,054516502	-0,401	2.9	3.1	6
13_Member	GO Biological Processes	visual learning	-2,803346141	-0,305	1.1	8.8	5.9
13_Member	GO Biological Processes	visual behavior	-2,536814281	-0,175	1.1	8.8	5.9
13_Member	GO Biological Processes	associative learning	-2,386391833	-0,110	1.3	5	4.7
13_Member	GO Biological Processes	learning	-2,374703146	-0,108	1.7	6	5.8
14_Summary	GO Biological Processes	retinal metabolic process	-3,713874663	-0,751	0.84	17	7.8
14_Member	GO Biological Processes	retinal metabolic process	-3,713874663	-0,751	0.84	17	7.8
14_Member	GO Biological Processes	diterpenoid metabolic process	-3,260071801	-0,529	1.5	6.9	6
14_Member	GO Biological Processes	terpenoid metabolic process	-2,936795997	-0,372	1.5	6.9	6
14_Member	GO Biological Processes	retinoid metabolic process	-2,624526272	-0,221	1.3	5	4.7
14_Member	GO Biological Processes	isoprenoid metabolic process	-2,49294705	-0,145	1.5	6.9	6
14_Member	GO Biological Processes	aldehyde metabolic process	-2,309151114	-0,070	1.1	8.8	5.9
15_Summary	GO Biological Processes	white fat cell differentiation	-3,713874663	-0,751	0.84	17	7.8
15_Member	GO Biological Processes	white fat cell differentiation	-3,713874663	-0,751	0.84	17	7.8
16_Summary	GO Biological Processes	brain development	-3,676201691	-0,731	5.5	2.2	4.1
16_Member	GO Biological Processes	brain development	-3,676201691	-0,731	5.5	2.2	4.1
16_Member	GO Biological Processes	forebrain development	-2,165246577	0,000	2.9	3.1	6
16_Member	GO Biological Processes	forebrain neuron differentiation	-2,088747536	0,000	1.1	8.8	5.9
16_Member	GO Biological Processes	neuron migration	-2,026398041	0,000	1.5	6.9	6

17_Summary	GO Biological Processes	export from cell	-3,594556161	-0,716	4.2	2.4	5
17_Member	GO Biological Processes	export from cell	-3,594556161	-0,716	4.2	2.4	5
17_Member	GO Biological Processes	calcium-ion regulated exocytosis	-3,569148466	-0,716	1.1	8.8	5.9
17_Member	GO Biological Processes	secretion by cell	-3,51449704	-0,705	3.8	2.6	4.7
17_Member	GO Biological Processes	positive regulation of catecholamine secretion	-3,117751594	-0,427	0.63	21	7.7
17_Member	GO Biological Processes	secretion	-3,067390527	-0,402	4.2	2.4	5
17_Member	GO Biological Processes	synaptic vesicle docking	-3,008887335	-0,381	0.63	21	7.7
17_Member	GO Biological Processes	signal release	-2,944426116	-0,372	2.1	4.1	4.9
17_Member	Reactome Gene Sets	Uptake and actions of bacterial toxins	-2,923721905	-0,366	0.84	17	7.8
17_Member	GO Biological Processes	positive regulation of calcium ion-dependent exocytosis	-2,578898029	-0,199	0.63	21	7.7
17_Member	GO Biological Processes	neurotransmitter secretion	-2,57418355	-0,199	1.3	5	4.7
17_Member	GO Biological Processes	signal release from synapse	-2,57418355	-0,199	1.3	5	4.7
17_Member	GO Biological Processes	regulation of catecholamine secretion	-2,494659187	-0,145	0.84	17	7.8
17_Member	GO Biological Processes	synaptic vesicle exocytosis	-2,447426355	-0,113	1.1	8.8	5.9
17_Member	GO Biological Processes	regulation of calcium ion-dependent exocytosis	-2,415008534	-0,110	0.84	17	7.8
17_Member	GO Biological Processes	neurotransmitter transport	-2,135660869	0,000	1.5	6.9	6
17_Member	GO Biological Processes	regulation of amine transport	-2,111640481	0,000	1.1	8.8	5.9
17_Member	WikiPathways	Synaptic vesicle pathway	-2,075984579	0,000	0.84	17	7.8
17_Member	Reactome Gene Sets	Protein-protein interactions at synapses	-2,022216865	0,000	1.1	8.8	5.9
17_Member	Reactome Gene Sets	Neurexins and neuroligins	-2,017757825	0,000	0.84	17	7.8
18_Summary	Reactome Gene Sets	Metabolism of lipids	-3,348306392	-0,603	5.3	3	5.9
18_Member	Reactome Gene Sets	Metabolism of lipids	-3,348306392	-0,603	5.3	3	5.9
19_Summary	GO Biological Processes	regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction	-3,344070618	-0,603	2.9	3.1	6
19_Member	GO Biological Processes	regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction	-3,344070618	-0,603	2.9	3.1	6
19_Member	GO Biological Processes	positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction	-2,116011587	0,000	1.9	5.1	5.5
20_Summary	Reactome Gene Sets	CD28 dependent PI3K/Akt signaling	-3,101138493	-0,420	0.84	17	7.8
20_Member	Reactome Gene Sets	CD28 dependent PI3K/Akt signaling	-3,101138493	-0,420	0.84	17	7.8
20_Member	Reactome Gene Sets	Regulation of T cell activation by CD28 family	-2,207054934	-0,007	1.1	8.8	5.9
20_Member	Reactome Gene Sets	Co-stimulation by CD28	-2,168706549	0,000	0.84	17	7.8

Supplementary Table 12. Associations of tau spatial gradient, epicenter segregation, and perivascular diffusion with neuropsychological performance.

Neuropsychology	Spatial gradient	Epicenter segregation (top 5)	Epicenter segregation (top 10)	Epicenter segregation (top 15)	Left DTI-ALPS	Right DTI-ALPS	Whole brain DTI-ALPS
MMSE	0.422 (0.297, 0.532); $P_{FDR} < 0.001$	-0.169 (-0.304, -0.028); $P_{FDR} = 0.027$	-0.180 (-0.314, -0.039); $P_{FDR} = 0.020$	-0.176 (-0.310, -0.035); $P_{FDR} = 0.022$	0.127 (-0.016, 0.264); $P_{FDR} = 0.100$	0.210 (0.070, 0.342); $P_{FDR} = 0.007$	0.182 (0.041, 0.316); $P_{FDR} = 0.018$
MOCA	0.463 (0.343, 0.568); $P_{FDR} < 0.001$	-0.239 (-0.369, -0.099); $P_{FDR} = 0.002$	-0.321 (-0.443, -0.187); $P_{FDR} < 0.001$	-0.291 (-0.417, -0.155); $P_{FDR} < 0.001$	0.230 (0.090, 0.360); $P_{FDR} = 0.002$	0.211 (0.070, 0.343); $P_{FDR} = 0.007$	0.241 (0.102, 0.371); $P_{FDR} = 0.002$
CDR-SB	-0.455 (-0.561, -0.336); $P_{FDR} < 0.001$	0.143 (0.002, 0.279); $P_{FDR} = 0.062$	0.207 (0.068, 0.339); $P_{FDR} = 0.007$	0.239 (0.101, 0.368); $P_{FDR} = 0.002$	-0.190 (-0.323, -0.050); $P_{FDR} = 0.013$	-0.235 (-0.364, -0.096); $P_{FDR} = 0.002$	-0.234 (-0.364, -0.096); $P_{FDR} = 0.002$
ADAS							
ADAS11	-0.452 (-0.559, -0.332); $P_{FDR} < 0.001$	0.159 (0.017, 0.294); $P_{FDR} = 0.038$	0.216 (0.077, 0.348); $P_{FDR} = 0.006$	0.266 (0.129, 0.393); $P_{FDR} < 0.001$	-0.312 (-0.435, -0.178); $P_{FDR} < 0.001$	-0.286 (-0.412, -0.151); $P_{FDR} < 0.001$	-0.329 (-0.450, -0.197); $P_{FDR} < 0.001$
ADAS13	-0.510 (-0.608, -0.397); $P_{FDR} < 0.001$	0.190 (0.049, 0.323); $P_{FDR} = 0.014$	0.269 (0.132, 0.396); $P_{FDR} < 0.001$	0.299 (0.163, 0.423); $P_{FDR} < 0.001$	-0.293 (-0.418, -0.158); $P_{FDR} < 0.001$	-0.307 (-0.431, -0.173); $P_{FDR} < 0.001$	-0.327 (-0.449, -0.194); $P_{FDR} < 0.001$
ADASQ4	-0.550 (-0.642, -0.443); $P_{FDR} < 0.001$	0.229 (0.091, 0.359); $P_{FDR} = 0.002$	0.329 (0.196, 0.449); $P_{FDR} < 0.001$	0.320 (0.187, 0.442); $P_{FDR} < 0.001$	-0.237 (-0.367, -0.099); $P_{FDR} = 0.002$	-0.282 (-0.407, -0.146); $P_{FDR} < 0.001$	-0.278 (-0.403, -0.141); $P_{FDR} < 0.001$
RAVLT							
Immediate	0.489 (0.373, 0.590); $P_{FDR} < 0.001$	-0.180 (-0.315, -0.039); $P_{FDR} = 0.020$	-0.278 (-0.404, -0.141); $P_{FDR} < 0.001$	-0.313 (-0.436, -0.178); $P_{FDR} < 0.001$	0.283 (0.147, 0.409); $P_{FDR} < 0.001$	0.278 (0.141, 0.404); $P_{FDR} < 0.001$	0.309 (0.175, 0.433); $P_{FDR} < 0.001$
Learning	0.427 (0.303, 0.537); $P_{FDR} < 0.001$	-0.123 (-0.260, 0.020); $P_{FDR} = 0.112$	-0.213 (-0.345, -0.073); $P_{FDR} = 0.006$	-0.246 (-0.375, -0.107); $P_{FDR} = 0.002$	0.258 (0.120, 0.386); $P_{FDR} < 0.001$	0.280 (0.143, 0.406); $P_{FDR} < 0.001$	0.293 (0.157, 0.418); $P_{FDR} < 0.001$
Forgetting	-0.192 (-0.325, -0.051); $P_{FDR} = 0.013$	0.221 (0.081, 0.352); $P_{FDR} = 0.004$	0.245 (0.106, 0.374); $P_{FDR} = 0.002$	0.185 (0.043, 0.319); $P_{FDR} = 0.017$	-0.213 (-0.345, -0.073); $P_{FDR} = 0.006$	-0.209 (-0.341, -0.068); $P_{FDR} = 0.007$	-0.233 (-0.364, -0.094); $P_{FDR} = 0.002$
Perc forgetting	-0.415 (-0.526, -0.289); $P_{FDR} < 0.001$	0.267 (0.130, 0.394); $P_{FDR} < 0.001$	0.313 (0.179, 0.436); $P_{FDR} < 0.001$	0.289 (0.152, 0.414); $P_{FDR} < 0.001$	-0.272 (-0.399, -0.135); $P_{FDR} < 0.001$	-0.272 (-0.399, -0.135); $P_{FDR} < 0.001$	-0.302 (-0.426, -0.167); $P_{FDR} < 0.001$
LDELTOTAL	0.447 (0.327, 0.554); $P_{FDR} < 0.001$	-0.197 (-0.329, -0.057); $P_{FDR} = 0.010$	-0.266 (-0.393, -0.129); $P_{FDR} < 0.001$	-0.273 (-0.399, -0.137); $P_{FDR} < 0.001$	0.281 (0.145, 0.406); $P_{FDR} < 0.001$	0.260 (0.123, 0.387); $P_{FDR} < 0.001$	0.298 (0.164, 0.422); $P_{FDR} < 0.001$
mPACC							
Digit	0.523 (0.412, 0.619); $P_{FDR} < 0.001$	-0.208 (-0.339, -0.068); $P_{FDR} = 0.007$	-0.285 (-0.410, -0.149); $P_{FDR} < 0.001$	-0.277 (-0.402, -0.140); $P_{FDR} < 0.001$	0.243 (0.105, 0.372); $P_{FDR} = 0.002$	0.295 (0.160, 0.419); $P_{FDR} < 0.001$	0.292 (0.157, 0.417); $P_{FDR} < 0.001$

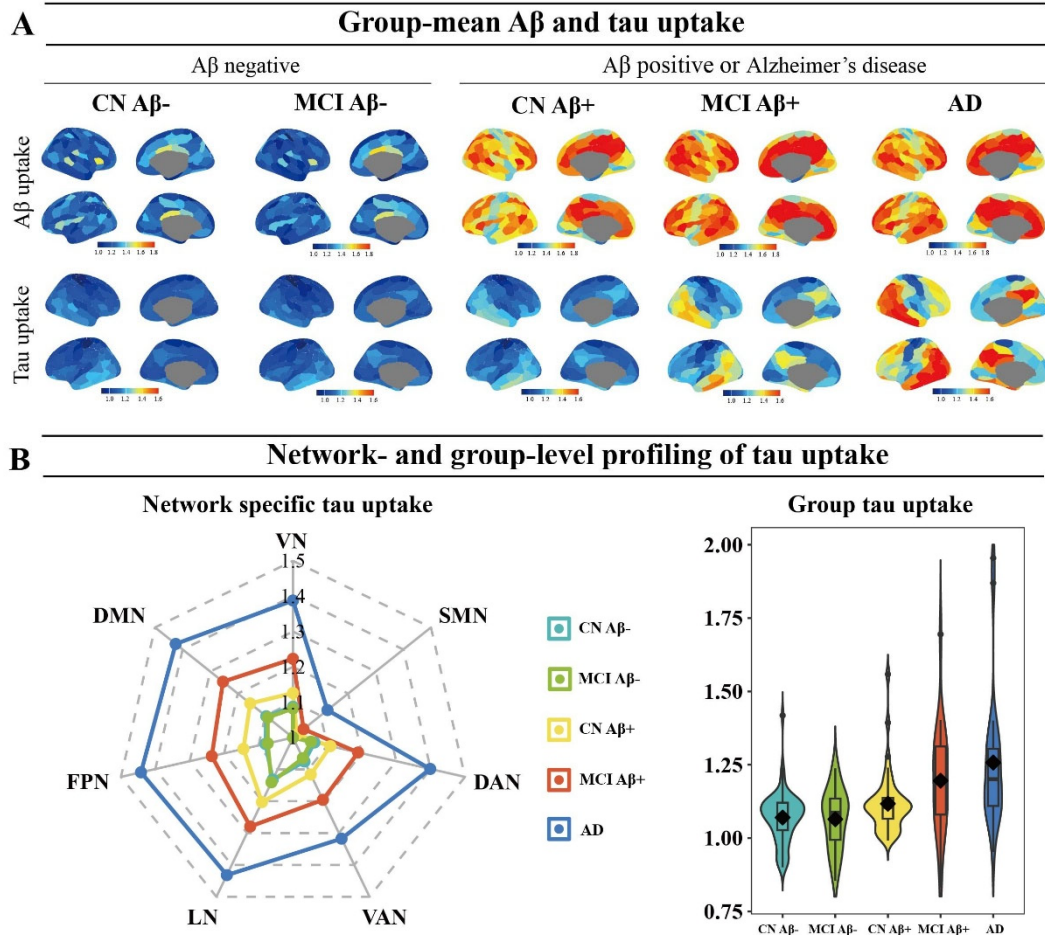
Trails B	0.538 (0.430, 0.632); $P_{FDR} < 0.001$	-0.212 (-0.343, -0.073); $P_{FDR} = 0.006$	-0.294 (-0.419, -0.159); $P_{FDR} < 0.001$	-0.291 (-0.415, -0.155); $P_{FDR} < 0.001$	0.248 (0.110, 0.376); $P_{FDR} = 0.002$	0.298 (0.163, 0.422); $P_{FDR} < 0.001$	0.298 (0.163, 0.422); $P_{FDR} < 0.001$
TRABSCOR	-0.381 (-0.496, -0.252); $P_{FDR} < 0.001$	0.092 (-0.051, 0.231); $P_{FDR} = 0.243$	0.179 (0.037, 0.313); $P_{FDR} = 0.021$	0.215 (0.075, 0.346); $P_{FDR} = 0.006$	-0.207 (-0.339, -0.067); $P_{FDR} = 0.007$	-0.261 (-0.389, -0.124); $P_{FDR} < 0.001$	-0.265 (-0.392, -0.127); $P_{FDR} < 0.001$
EcogPT							
MD	-0.283 (-0.410, -0.146); $P_{FDR} < 0.001$	0.072 (-0.072, 0.213); $P_{FDR} = 0.358$	0.075 (-0.068, 0.216); $P_{FDR} = 0.336$	0.075 (-0.068, 0.216); $P_{FDR} = 0.336$	-0.082 (-0.223, 0.062); $P_{FDR} = 0.298$	-0.178 (-0.313, -0.036); $P_{FDR} = 0.022$	-0.149 (-0.286, -0.006); $P_{FDR} = 0.054$
LD	-0.126 (-0.264, 0.018); $P_{FDR} = 0.105$	0.027 (-0.116, 0.170); $P_{FDR} = 0.733$	0.013 (-0.130, 0.156); $P_{FDR} = 0.859$	0.054 (-0.089, 0.196); $P_{FDR} = 0.492$	-0.051 (-0.193, 0.092); $P_{FDR} = 0.517$	-0.080 (-0.220, 0.064); $P_{FDR} = 0.314$	-0.079 (-0.220, 0.065); $P_{FDR} = 0.314$
VSP	-0.151 (-0.288, -0.008); $P_{FDR} = 0.052$	0.048 (-0.096, 0.190); $P_{FDR} = 0.543$	0.110 (-0.034, 0.250); $P_{FDR} = 0.160$	0.140 (-0.003, 0.278); $P_{FDR} = 0.072$	-0.045 (-0.187, 0.099); $P_{FDR} = 0.565$	-0.137 (-0.275, 0.007); $P_{FDR} = 0.078$	-0.102 (-0.241, 0.043); $P_{FDR} = 0.197$
EF-P	-0.218 (-0.350, -0.077); $P_{FDR} = 0.006$	0.027 (-0.117, 0.169); $P_{FDR} = 0.736$	0.051 (-0.093, 0.192); $P_{FDR} = 0.521$	0.085 (-0.059, 0.225); $P_{FDR} = 0.281$	-0.074 (-0.215, 0.070); $P_{FDR} = 0.343$	-0.150 (-0.287, -0.007); $P_{FDR} = 0.053$	-0.128 (-0.266, 0.016); $P_{FDR} = 0.100$
EF-O	-0.273 (-0.401, -0.134); $P_{FDR} < 0.001$	0.032 (-0.112, 0.175); $P_{FDR} = 0.688$	0.020 (-0.124, 0.163); $P_{FDR} = 0.795$	0.062 (-0.082, 0.204); $P_{FDR} = 0.431$	-0.105 (-0.246, 0.039); $P_{FDR} = 0.180$	-0.192 (-0.326, -0.049); $P_{FDR} = 0.014$	-0.162 (-0.299, -0.019); $P_{FDR} = 0.037$
EF-DA	-0.132 (-0.271, 0.011); $P_{FDR} = 0.088$	-0.010 (-0.153, 0.134); $P_{FDR} = 0.891$	-0.072 (-0.214, 0.072); $P_{FDR} = 0.358$	0.023 (-0.120, 0.166); $P_{FDR} = 0.765$	0.022 (-0.122, 0.165); $P_{FDR} = 0.781$	-0.137 (-0.275, 0.007); $P_{FDR} = 0.078$	-0.068 (-0.210, 0.076); $P_{FDR} = 0.382$
Total	-0.277 (-0.404, -0.139); $P_{FDR} < 0.001$	0.033 (-0.111, 0.175); $P_{FDR} = 0.681$	0.049 (-0.095, 0.191); $P_{FDR} = 0.536$	0.085 (-0.059, 0.225); $P_{FDR} = 0.284$	-0.092 (-0.232, 0.052); $P_{FDR} = 0.245$	-0.204 (-0.338, -0.063); $P_{FDR} = 0.009$	-0.168 (-0.304, -0.025); $P_{FDR} = 0.029$
EcogSP							
MD	-0.525 (-0.620, -0.414); $P_{FDR} < 0.001$	0.155 (0.014, 0.290); $P_{FDR} = 0.044$	0.185 (0.045, 0.319); $P_{FDR} = 0.016$	0.238 (0.099, 0.367); $P_{FDR} = 0.002$	-0.235 (-0.365, -0.097); $P_{FDR} = 0.002$	-0.220 (-0.350, -0.081); $P_{FDR} = 0.004$	-0.253 (-0.381, -0.116); $P_{FDR} < 0.001$
LD	-0.451 (-0.557, -0.331); $P_{FDR} < 0.001$	0.249 (0.112, 0.378); $P_{FDR} < 0.001$	0.180 (0.039, 0.313); $P_{FDR} = 0.020$	0.209 (0.070, 0.341); $P_{FDR} = 0.007$	-0.169 (-0.303, -0.028); $P_{FDR} = 0.027$	-0.164 (-0.298, -0.022); $P_{FDR} = 0.032$	-0.192 (-0.324, -0.051); $P_{FDR} = 0.013$
VSP	-0.475 (-0.579, -0.356); $P_{FDR} < 0.001$	0.139 (-0.004, 0.277); $P_{FDR} = 0.072$	0.199 (0.058, 0.333); $P_{FDR} = 0.010$	0.230 (0.090, 0.362); $P_{FDR} = 0.002$	-0.138 (-0.275, 0.006); $P_{FDR} = 0.077$	-0.171 (-0.307, -0.029); $P_{FDR} = 0.027$	-0.179 (-0.314, -0.037); $P_{FDR} = 0.021$
EF-P	-0.409 (-0.521, -0.282); $P_{FDR} < 0.001$	0.135 (-0.008, 0.273); $P_{FDR} = 0.080$	0.178 (0.036, 0.312); $P_{FDR} = 0.022$	0.205 (0.065, 0.338); $P_{FDR} = 0.009$	-0.185 (-0.319, -0.043); $P_{FDR} = 0.017$	-0.114 (-0.252, 0.029); $P_{FDR} = 0.144$	-0.171 (-0.306, -0.029); $P_{FDR} = 0.027$
EF-O	-0.460 (-0.567, -0.338); $P_{FDR} < 0.001$	0.100 (-0.045, 0.241); $P_{FDR} = 0.204$	0.149 (0.005, 0.287); $P_{FDR} = 0.057$	0.191 (0.048, 0.326); $P_{FDR} = 0.014$	-0.229 (-0.362, -0.088); $P_{FDR} = 0.004$	-0.244 (-0.375, -0.104); $P_{FDR} = 0.002$	-0.267 (-0.396, -0.128); $P_{FDR} < 0.001$
EF-DA	-0.423 (-0.535, -0.297); $P_{FDR} < 0.001$	0.091 (-0.055, 0.232); $P_{FDR} = 0.255$	0.109 (-0.037, 0.249); $P_{FDR} = 0.170$	0.152 (0.008, 0.291); $P_{FDR} = 0.052$	-0.254 (-0.385, -0.114); $P_{FDR} < 0.001$	-0.219 (-0.352, -0.077); $P_{FDR} = 0.006$	-0.266 (-0.396, -0.126); $P_{FDR} < 0.001$
Total	-0.518 (-0.614, -0.406); $P_{FDR} < 0.001$	0.185 (0.044, 0.318); $P_{FDR} = 0.016$	0.185 (0.045, 0.319); $P_{FDR} = 0.016$	0.231 (0.092, 0.361); $P_{FDR} = 0.002$	-0.232 (-0.361, -0.093); $P_{FDR} = 0.002$	-0.206 (-0.338, -0.066); $P_{FDR} = 0.007$	-0.247 (-0.375, -0.109); $P_{FDR} = 0.002$

FAQ	-0.486 (-0.587, -0.370); $P_{FDR} < 0.001$	0.135 (-0.006, 0.272); $P_{FDR} = 0.078$	0.228 (0.090, 0.358); $P_{FDR} = 0.002$	0.246 (0.108, 0.375); $P_{FDR} = 0.002$	-0.232 (-0.361, -0.093); $P_{FDR} = 0.002$	-0.214 (-0.345, -0.075); $P_{FDR} = 0.006$	-0.245 (-0.374, -0.107); $P_{FDR} = 0.002$
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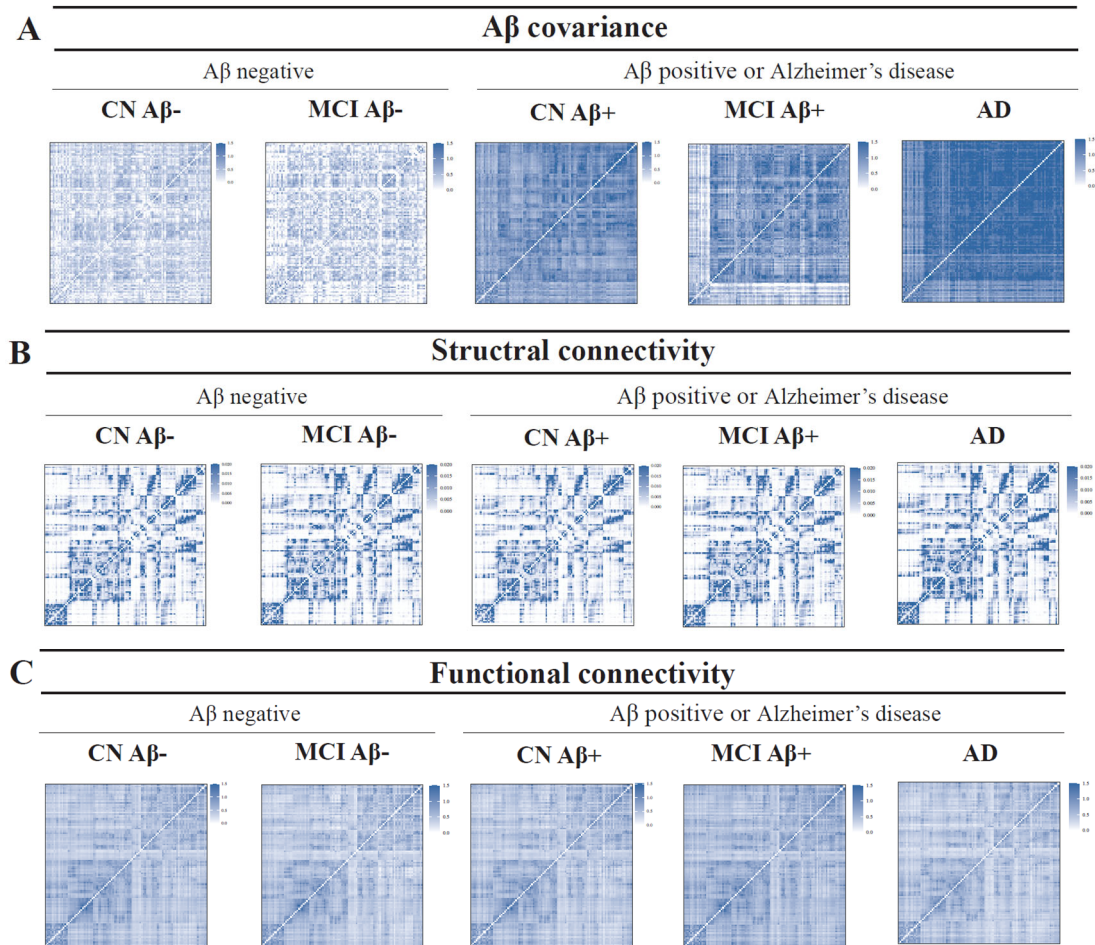
Note. Values are Spearman rank correlation coefficients with 95% CIs. P values were adjusted using the FDR method, and statistical significance after correction was defined as $P_{FDR} < 0.05$

Abbreviations: DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; CI, confidence interval. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS, Alzheimer's Disease Assessment Scale (ADAS-11/ADAS-13/ADAS-Q4); RAVLT, Rey Auditory Verbal Learning Test; LDELTOTAL, Logical Memory delayed recall total score; mPACC, modified Preclinical Alzheimer's Cognitive Composite; TRABSCOR, time to complete Trail Making Test Part B; ECogPT/ECogSP, Everyday Cognition scales completed by participant/study partner; MD, Memory Domain; LD, Language Domain; VSP, Visuospatial Abilities; EF-P, Executive Function-Planning; EF-O, Executive Function-Organization; EF-DA, Executive Function-Divided Attention; FAQ, Functional Activities Questionnaire; FDR, false discovery rate.

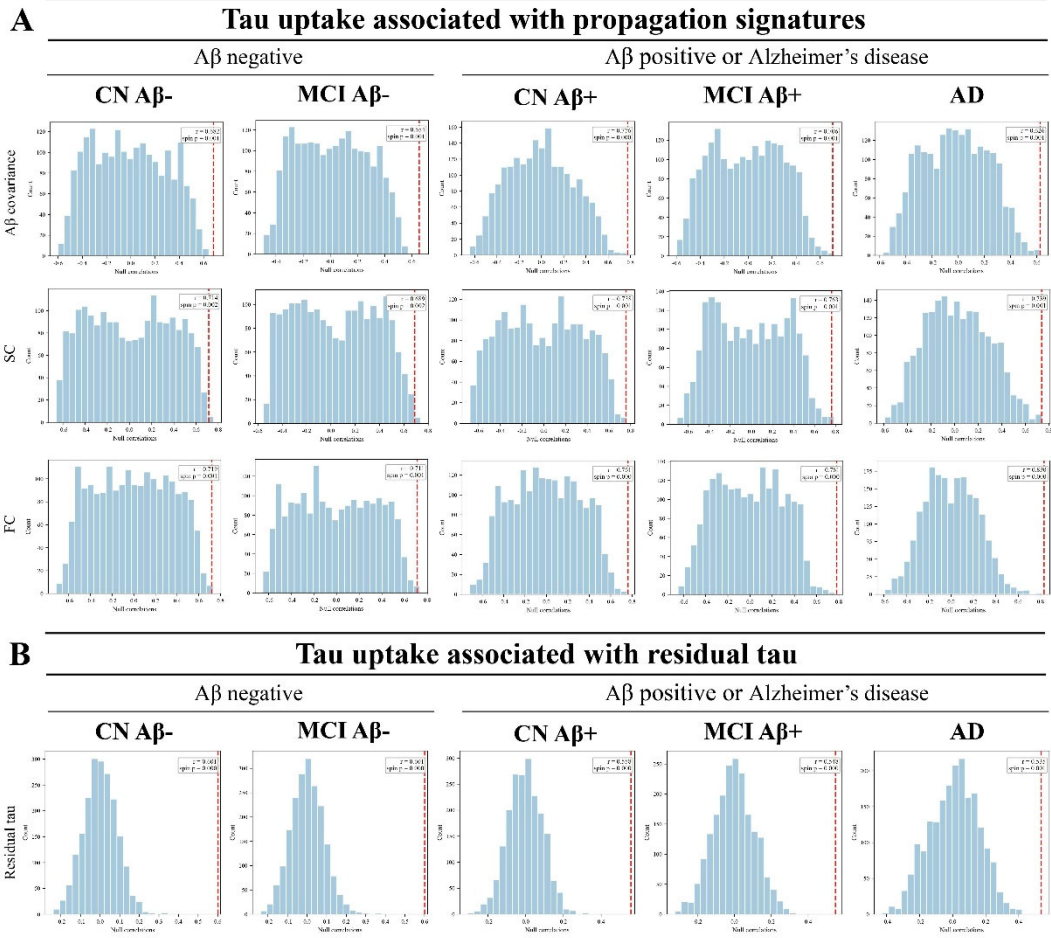
Supplementary Figures



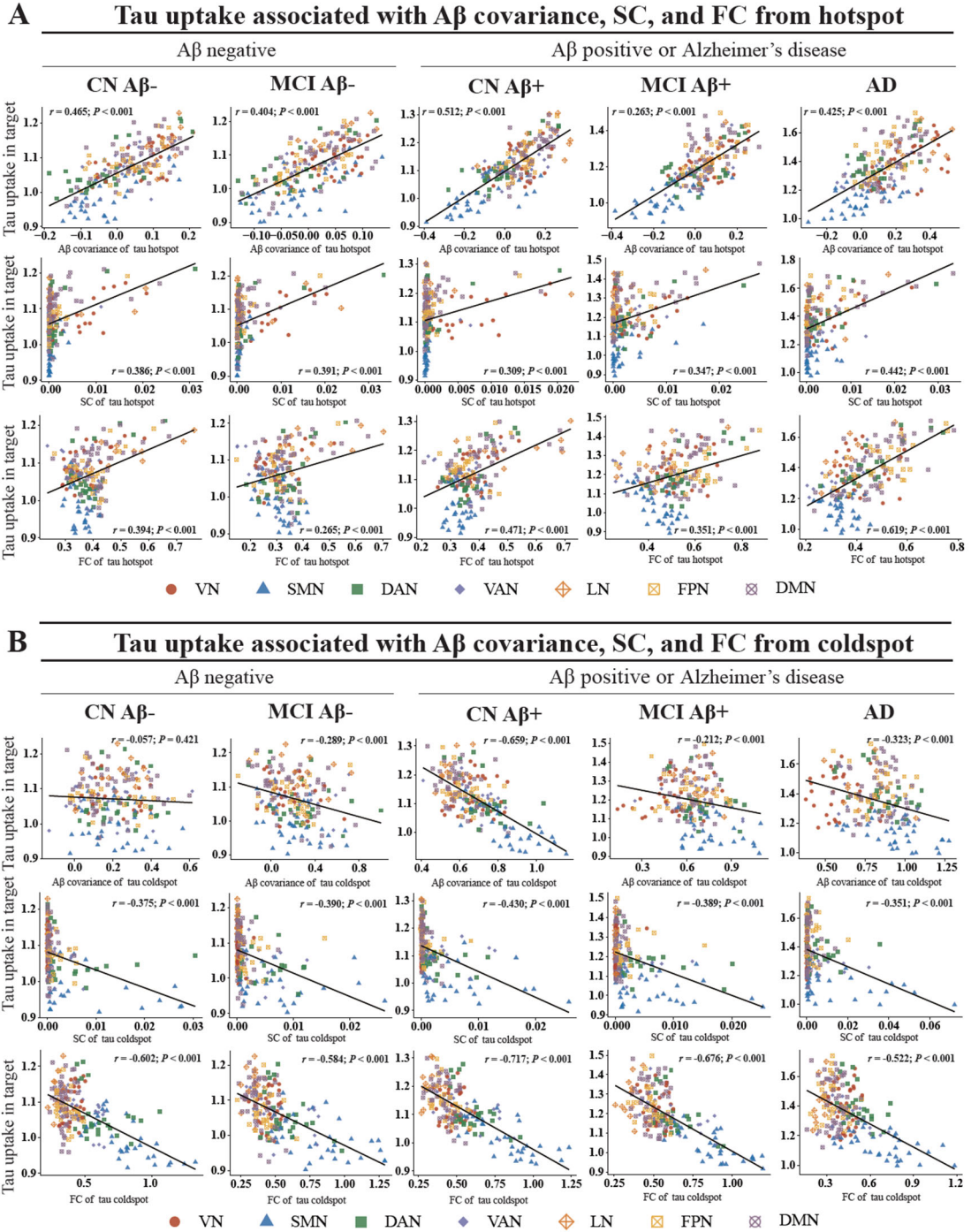
Supplementary Figure 1. Stage-stratified cortical topography of A β and tau across the AD continuum. (A) Group-mean cortical A β -PET and tau-PET uptake maps for CN A β -, MCI A β -, CN A β +, MCI A β +, and AD. A β shows widespread neocortical involvement in A β -positive groups, whereas tau displays a stage-dependent, hierarchical expansion from temporo-limbic regions toward parietal and frontal association cortices. (B) Network- and group-level profiling of tau uptake. Left, radar plot showing mean tau uptake within seven canonical functional systems for each group.



Supplementary Figure 2. Group-mean A β covariance, structural connectivity, and functional connectivity matrices across the AD continuum. (A) **A β covariance.** Group-mean A β covariance matrices were constructed within each subgroup using across-subject Spearman correlations of regional A β -PET uptake (Fisher z-transformed; diagonal set to zero). (B) **Structural connectivity.** Group-average SC matrices derived from DTI tractography, weighted by streamline counts and averaged across participants within each subgroup. (C) **Functional connectivity.** Group-average FC matrices derived from rsfMRI as Fisher z-transformed Pearson correlations between parcel-wise BOLD time series (diagonal set to zero).

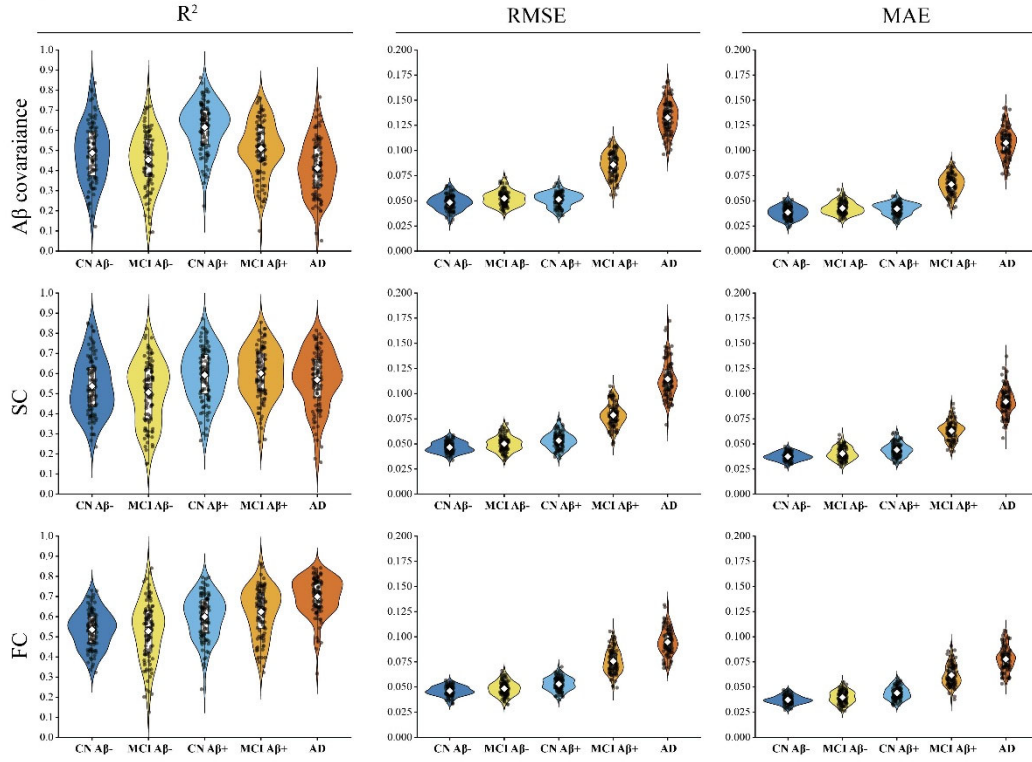


Supplementary Figure 3. Spin-test null distributions for associations between tau uptake and propagation signatures, and between tau uptake and residual tau. (A) The spin-test distributions for propagation-signature associations; **(B)** the corresponding distributions for associations between tau uptake and residual tau. Histograms show null distributions generated from 2000 spin-test permutations for the correlations between regional tau uptake and propagation signatures derived from $\text{A}\beta$ covariance, structural connectivity, and functional connectivity across the five subgroups (CN $\text{A}\beta^-$, MCI $\text{A}\beta^-$, CN $\text{A}\beta^+$, MCI $\text{A}\beta^+$, and AD). Red dashed lines indicate the observed correlation coefficients.

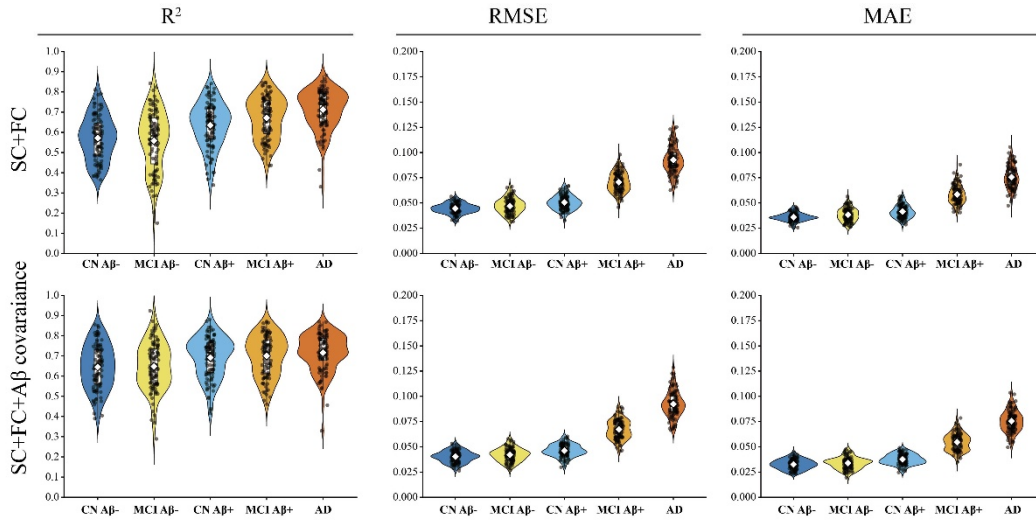


Supplementary Figure 4. Target tau uptake associated with seed-to-target A β covariance, SC, and FC from hot and cold spot. (A) For tau “hotspot” seeds, stronger seed-to-target A β covariance, SC, and FC, is associated with higher tau uptake in target regions across subgroups. (B) For tau “cold-spot” seeds, stronger seed-to-target A β covariance, SC, and FC is associated with lower target tau uptake in target regions across subgroups. Scatterplots are shown by subgroup, with points representing cortical parcels colored by functional system and lines indicating linear fits; Pearson's r and P values are displayed in each panel.

A Model performance for single-modality propagation signature predictors

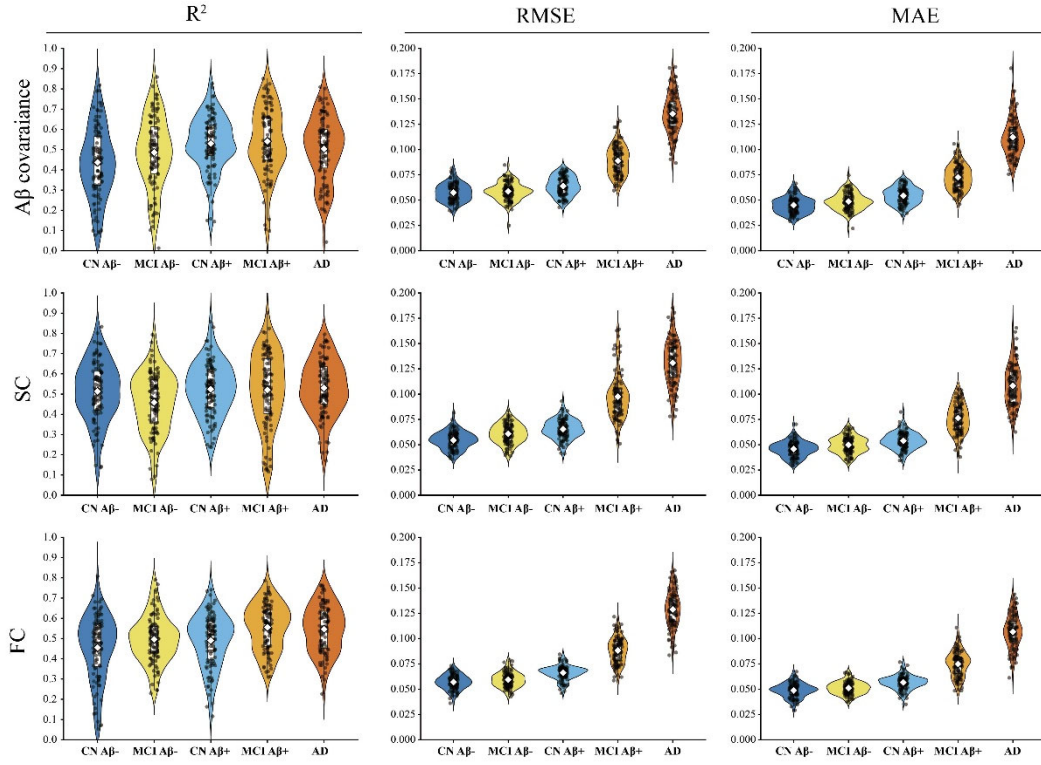


B Model performance for multimodal propagation signature predictors

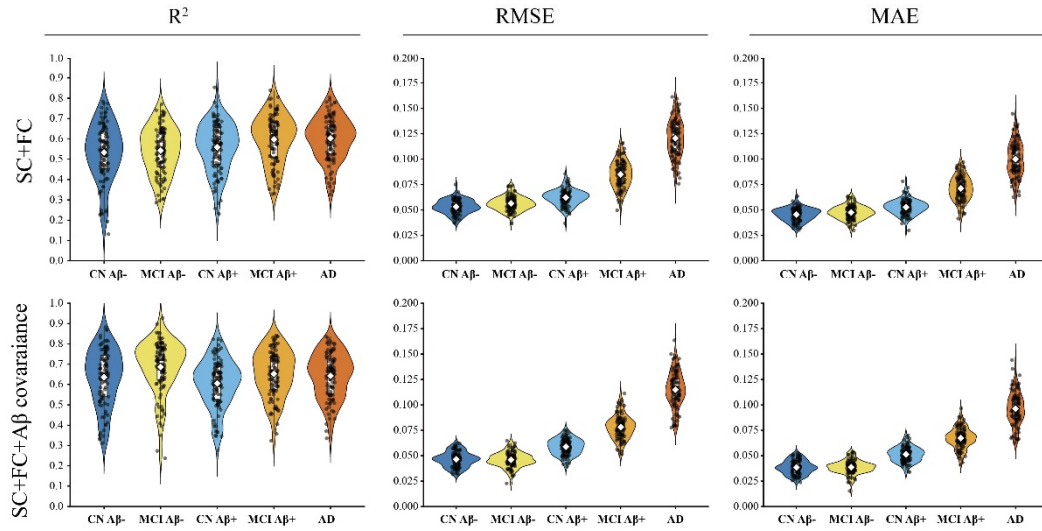


Supplementary Figure 5. Predicting regional tau uptake from propagation signatures across the AD continuum. (A) Model performance for single-modality propagation signature predictors, including A β covariance, SC, and FC. **(B)** Model performance for multimodal propagation signature predictors, including SC+FC and A β covariance+SC+FC. For each model, performance is summarized using R², RMSE, and MAE.

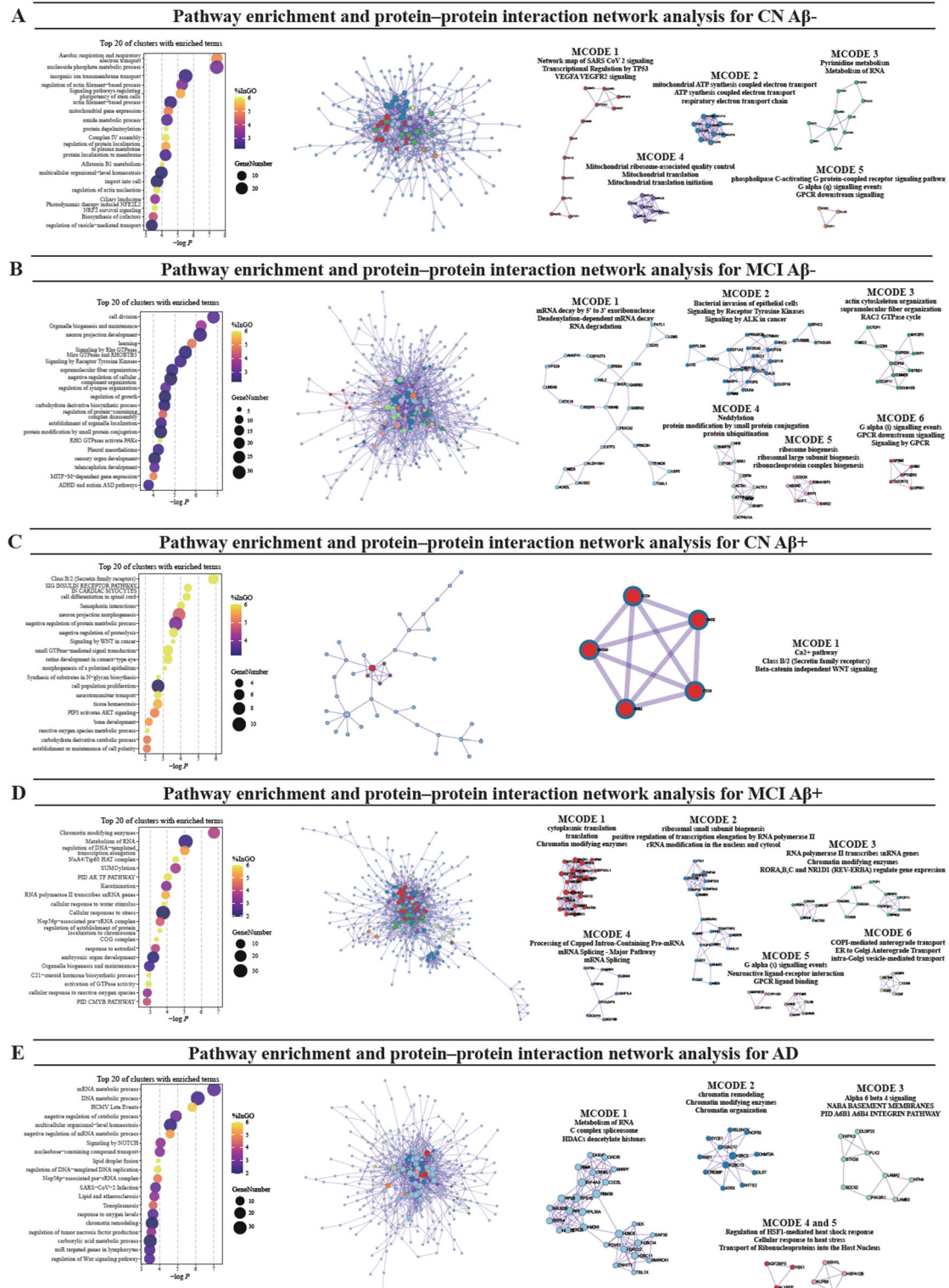
A Model performance for single-modality propagation signature predictors



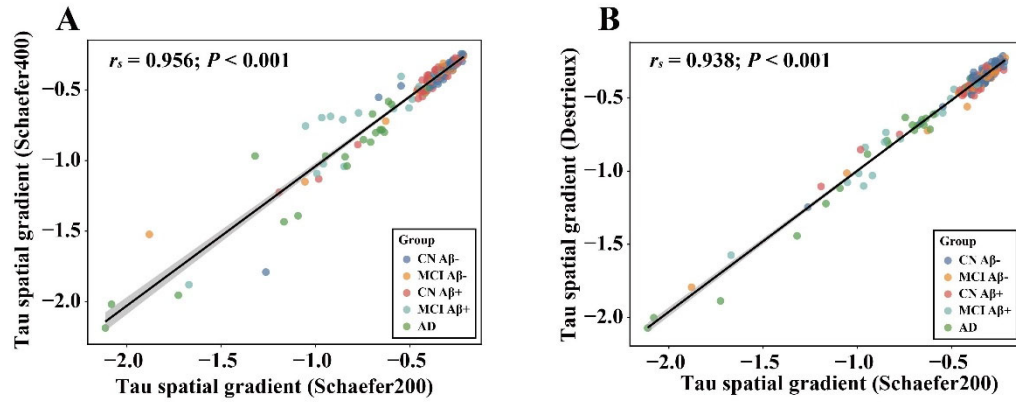
B Model performance for multimodal propagation signature predictors



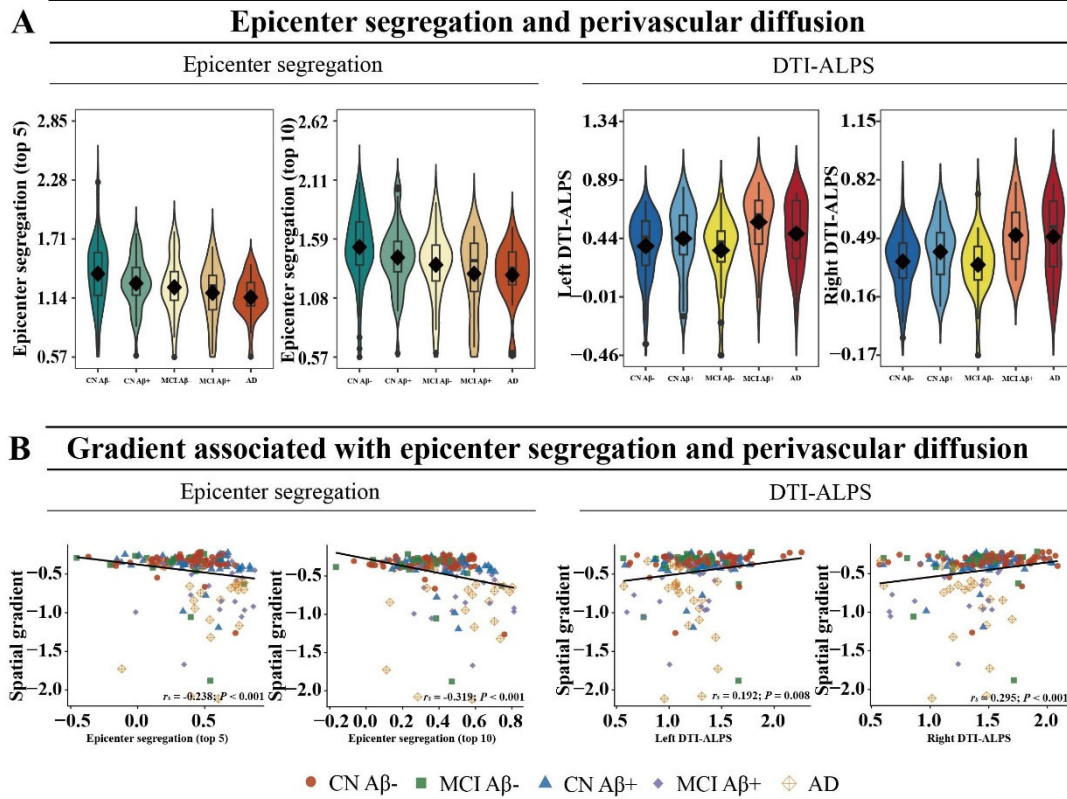
Supplementary Figure 6. Predicting regional tau uptake from propagation signatures across the AD continuum under the Destrieux atlas. (A) Model performance for single-modality propagation signature predictors, including A β covariance, SC, and FC. **(B)** Model performance for multimodal propagation signature predictors, including SC+FC and A β covariance+SC+FC. For each model, performance is summarized using R², RMSE, and MAE.



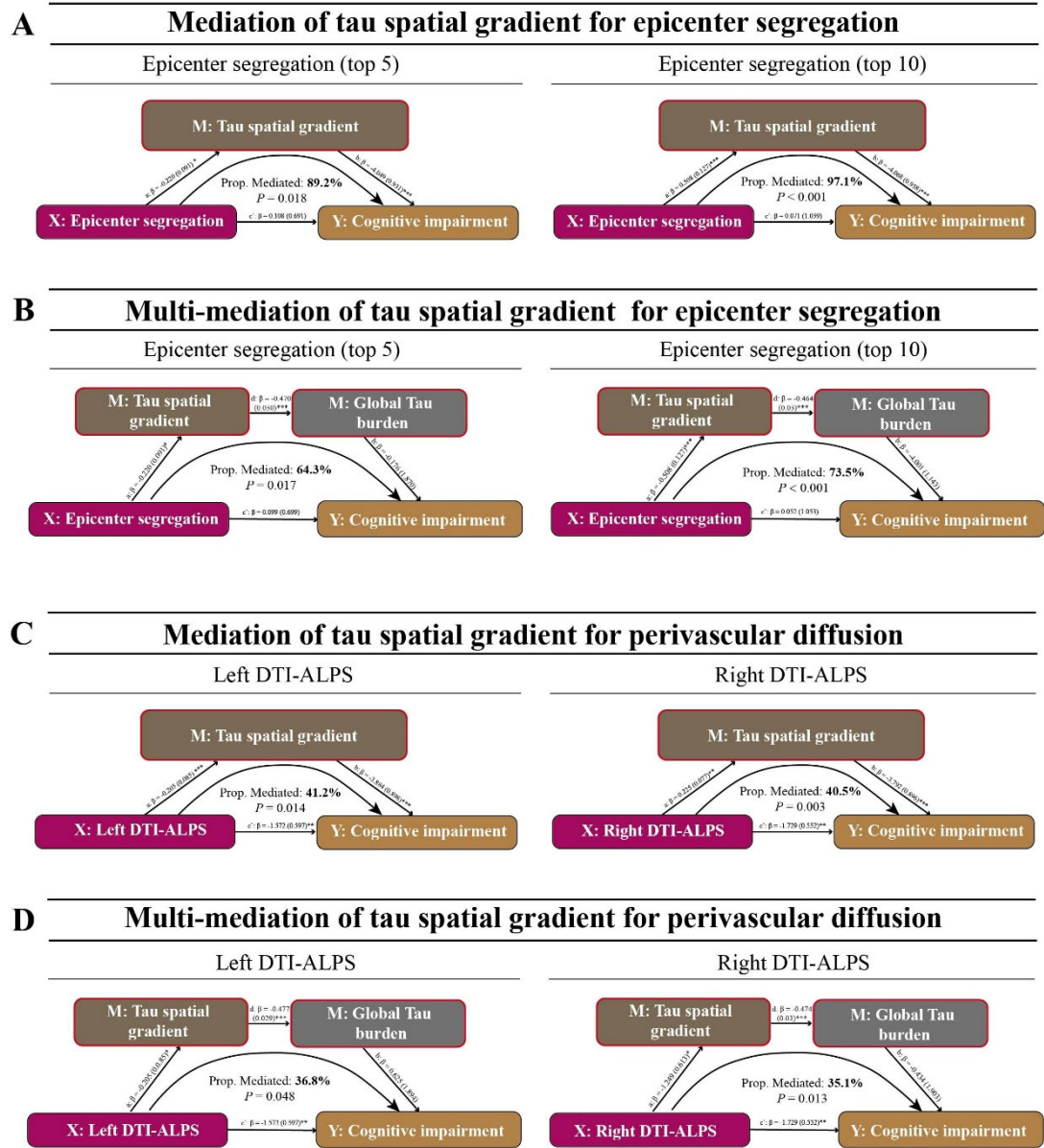
Supplementary Figure 7. Stage-specific pathway enrichment and PPI networks of residual tau across the AD continuum. (A) Pathway enrichment and PPI network analyses for CN Aβ⁻. (B) Pathway enrichment and PPI network analyses for MCI Aβ⁻. (C) Pathway enrichment and PPI network analyses for CN Aβ⁺. (D) Pathway enrichment and PPI network analyses for MCI Aβ⁺. (E) Pathway enrichment and PPI network analyses for AD.



Supplementary Figure 8. Sensitivity analysis of tau spatial gradient across alternative cortical parcellation schemes. (A) Correlation between tau spatial gradient values derived from the Schaefer200 and Schaefer400 atlases. (B) Correlation between tau spatial gradient values derived from the Schaefer200 and Destrieux atlases.



Supplementary Figure 9. Associations between epicenter segregation, glymphatic function, and tau spatial gradient across alternative epicenter definitions and DTI-ALPS indices. (A) Group comparisons of epicenter segregation defined using the top 5 and top 10 regions, alongside left- and right-hemisphere DTI-ALPS indices. **(B)** Correlations between tau spatial gradient and alternative epicenter segregation and hemispheric DTI-ALPS measures.



Supplementary Figure 10. Mediation and multi-mediation effects of tau spatial gradient linking epicenter segregation, perivascular diffusion, and cognition. (A) Mediation of tau spatial gradient for epicenter segregation. **(B)** Multi-mediation of tau spatial gradient for epicenter segregation. **(C)** Mediation of tau spatial gradient for GS function. **(D)** Multi-mediation of tau spatial gradient for GS function.