

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY MATERIAL AND METHODS

Head-plate surgical procedures

At 3 M (N=27), 5/8 M (N=4/13), or 19 M (N=30), all animals undergo a surgical procedure where an in-house built glass head-plate is affixed to the skull. The surgical procedure is based on the design we have described previously³⁷. Since this description, we eliminated the agarose layer and plastic border. We find that these amendments improve the longevity of the preparation. The implants reduce susceptibility artifacts in the cortex and head-motion. The head-plates are well tolerated and the signal-to-noise ratio (SNR) in the cortex shows no change over time (data not shown, non-significant differences in SNR across sessions). The head-plate yields permanent optical access to the cortex (for WF-Ca²⁺ imaging) and immobilizes the head. Animals are initially anesthetized with 5% isoflurane (70/30 medical air/O₂) and secured in a stereotaxic frame (KOPF) using ear-bars and an incisor-bar. Isoflurane is then reduced to 2%. Ointment is applied to the eyes to prevent dryness; meloxicam (2mg/kg body weight) is administered subcutaneously, and bupivacaine (0.1%) injected locally at the incision site. After hair removal (Nair), the scalp is washed (3×) with betadine followed by ethanol 70%. The skin and soft tissue overlying the skull surface is surgically removed. The skull is cleaned and dried. Antibiotic powder (Neo-Predef) is applied to the incision site, and isoflurane reduced further to 1.5%. Skull-thinning of the frontal and parietal skull plates is performed with a hand-held drill (FST), tip diameters 1.4 and 0.7mm, to translucency whilst remaining intact. Superglue (Locite) is applied to the exposed skull, followed by transparent dental cement C&B Metabond (Parkell). The pre-cut (Omax 5555 with Tilt-A-Jet, Fisher Finest, Fisher Scientific, PA) head-plate is attached to the dental cement prior to its solidification. Animals are allotted 3-4 weeks to recovered from the procedure before any imaging data are collected.

Creation of out-of-sample MRI template

All operations are executed using BioImage Suite (BIS). We generate the out-of-sample template from N=162 isotropic (0.2×0.2×0.2mm³) MSME images from N=64 mice (each animal is imaged up to three times during separate imaging sessions with a minimum of 7 days between sessions). Data are skull stripped using an in-house algorithm. After brains are isolated, two images, selected at random, are registered using non-linear registration. The registered images are merged to create an interim reference image. A third image, selected at

random from those remaining in the pool, is registered, and merged with the interim reference image using the same approach. This procedure is repeated until no images remain in the pool (i.e., all 162 images are merged). This final merged image is split along the midline and the two halves (hemispheres) are registered and merged. These data are then duplicated, and one 'side' is flipped to create a bilaterally symmetric brain image. Using non-linear registration, this template is registered to the annotated CCFv3 data and ontology downloaded from the Allen Institute^{43,44}. We modulated the contrast and smoothed the histological data to better match the MR data prior to this registration step.

Structural MRI data acquisition

Besides the 3D isotropic MSME image, two other structural images are acquired, for registration purposes to the WF-Ca²⁺ data, however these are not used in this study. (2) A multi-spin-multi-echo (MSME) image sharing the same field-of-view (FOV) as the fMRI data. Acquired with a repetition time (TR) of 2500ms and echo time (TE) of 20ms, 28 slices, two averages, and resolution of 0.1×0.1×0.4 mm³ (10mins and 40s). (3) A fast-low-angle-shot (FLASH) time-of-flight (TOF) angiogram (FOV, 2.0×1.0×2.5cm³, covering the cortex), TR/TE of 130/4ms, and resolution of 0.05×0.05×0.05mm³ (18mins). Of note, the FLASH-TOF was not acquired in the animals that did not undergo multimodal imaging (i.e., animals in experiments 2 and 3).

Automated skull stripping for template creation

We use a 2D U-Net-like framework from the deep learning library deep-image. For training data, we manually segmented the brains of five mice selected at random (balanced by session). The binarized masks and MSME images constitute the training set. To make efficient use of the small number of images included in the training data, we implement augmentation methods including image rotation, deformation, cropping, scaling, and padding. Quantile normalization is used for data normalization. Our neural network is based on a three level U-Net architecture. The number of channels in the contracting path are 64, 128 and 256 from top-to-bottom. Each level consists of two padded convolutions with filter size three and stride size one using a ReLU activation function. A max pooling layer of stride size two is applied after the top two levels. In the expansive path, up-convolution of stride size two is conducted between levels. Concatenation is performed by concatenating the up-sampled feature map and the feature map of the corresponding level within the contracting path. Finally, training is performed using the Adam Optimizer with a Cross Entropy loss function.

Functional MRI pre-processing and registration to common space

The pre-processed fMRI data from each mouse at each imaging session are averaged to create a representative mean image that is itself corrected for intensity inhomogeneity and then non-linearly registered to the isotropic structural MSME image acquired during the same imaging session. This procedure minimizes the effects of distortions caused by susceptibility artifacts⁸⁸. Then, four transforms - (1) the framewise rigid head motion correction, (2) representative mean fMRI to individual mouse/session isotropic MSME image, (3) individual mouse/session isotropic MSME image to within-dataset template, and (4) within-dataset template to out-of-sample template – are concatenated and applied to the fMRI data to normalize timeseries in the out-of-sample template space. As part of this step, the native resolution of the functional data ($0.31 \times 0.31 \times 0.31 \text{mm}^3$) is resampled to the template resolution ($0.2 \times 0.2 \times 0.2 \text{mm}^3$). The Allen Atlas (which resides in the out-of-sample template space) can then be applied to the fMRI data to compute connectomes. Registration performance is visually inspected using the RABIES quality control report. Following timeseries normalization, the six-parameters motion estimates are regressed from the timeseries data and used to compute framewise-displacement (FD). Frame scrubbing for motion using a conservative 0.075mm threshold is applied. Cerebrospinal fluid (CSF) and white matter (WM) are also used as nuisance regressors for the final timeseries analyses. Data are smoothed with 0.4mm sigma.

Example of methods files

See supplementary files 'BrukerMethods_EPI' and 'BrukerMethods_MSME'.

Exclusion criteria

From experiment 1 (**Supplementary Table 1**), N=25 are imaged at the first imaging session (4 M) and no animals or data are excluded. Before the second imaging session (6 M), N=4 mice (all in the AD group) recovered poorly after the first imaging session and were thus excluded from the 6M imaging session. An additional N=2 were not imaged at the second imaging session (6 M) due to scanner hardware issues (but were imaged at the third imaging session). Thus, in total, N=18 are imaged at the second imaging session. Between the second (6 M) and third (9 M) imaging session, N=9 are allocated to a separate study leaving N=8 for the third imaging session (9 M). None of these data are excluded. To augment the number of mice at 6 M and 9 M (N=18 and N=8, respectively) we conducted experiment 2 (**Supplementary Table 1**) where N=4 are imaged at 6 M and N=13 are imaged at 9 M. Thus, between experiment 1 and 2, N=22 at 6 M and N=21 at 9 M.

For experiment 3, N=27 are imaged at 20 M. Of these, N=3 are not scanned at the following imaging session (22 M), N=1 due to head-implant detachment, N=1 was euthanized due to an eye infection and N=1 recovered poorly from anesthesia after the first imaging session. Of note, the animals that experience implant detachment received head-implants (unlike the rest) made with coated glass (Fisher Scientific, same brand as used throughout the other experiments, but with an additional coating that decreased glue-to-glass adherence, thus leading to implant detachment). The remaining N=23 are imaged at 22 M, and no animals or data are excluded.

Treatment with a silent allosteric mGluR5 (metabotropic glutamate receptor 5) modulator

A subgroup of AD mice (N=10) is treated between 20 and 22 M with a silent allosteric mGluR5 (metabotropic glutamate receptor 5) modulator (SAM, BMS-984923/ALX001). Drug synthesis is as previously described (compound 16)³² with simplifications that accommodate 5-10 kg scale preparations by Aptuit-Verona³¹. Purity and composition are confirmed to be >97%³². The SAM compound is incorporated into OpenStandard Diet with 15% kCal Fat purified diet pellets by Research Diets, Inc. at 50mg SAM per kg food. Vehicle pellets are the same purified diet without any additives (Research Diets, Inc. D11112201i)³¹. The drug dosage in food is calculated based on the average amount eaten in a day per kg of body weight⁸⁹ and adjusted to be equivalent to ingesting 7.5 mg/kg per day. Previous studies verified plasma levels of BMS-984923 corresponding to those associated with greater than 85% brain mGluR5 receptor occupancy in PET studies. Throughout the treatment period, body weight is monitored to ensure drug/food intake.

Triple-network model

From the 172-ROI Allen Atlas, we select ROIs that belong to a DMN based on the description by Whitesell and colleagues⁴⁹ (Fig. 1a,b). Additionally, ROIs belonging to a SN and LCN are selected based on the triple-network model^{34,35}. Within our template space, these correspond to: DMN [2:3,18:19,28:31, 38:40], SN [2:3, 28:29, 35:37, 59:61, 63, 70:71, 74:75] and LCN [2:11, 41, 62].

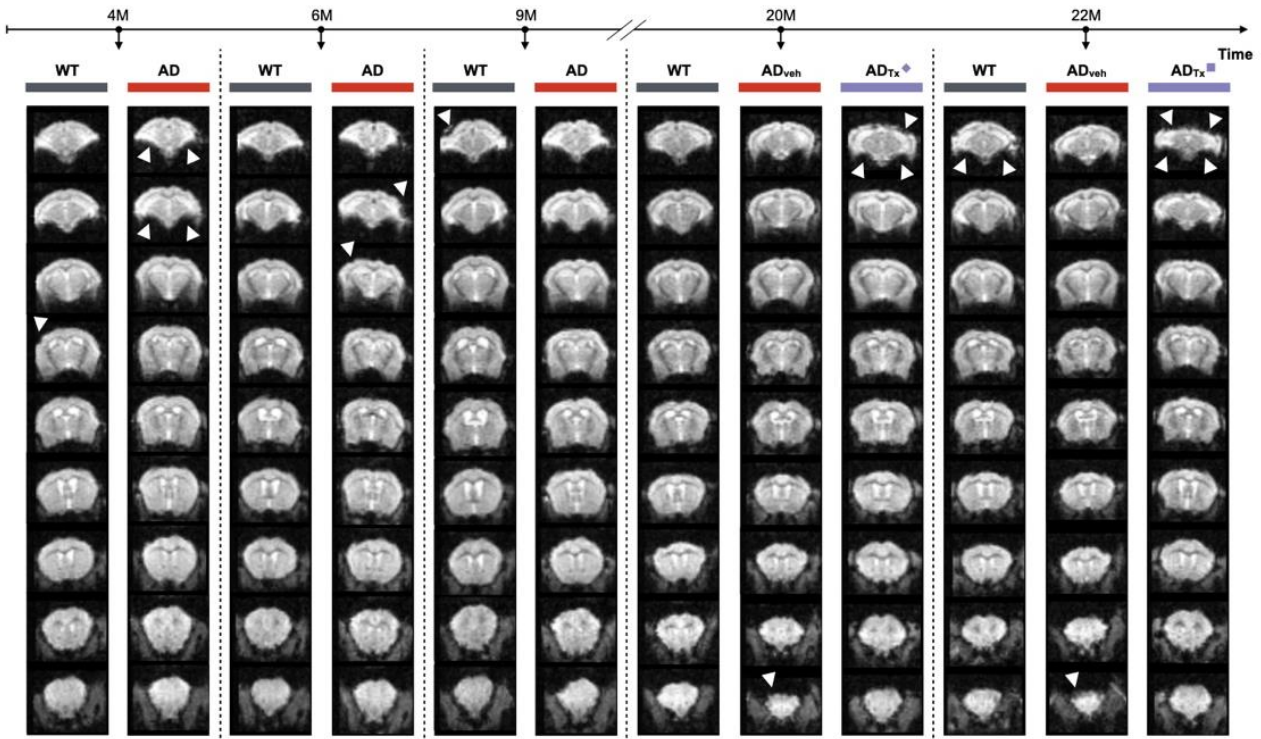
Data-derived networks

In this study, we investigate four main contrasts: aging (WT-aging and AD-aging), pathology (AD vs WT) and treatment (AD_{treated} vs AD_{vehicle}). For each of these, we generate a 'data-derived' network: a binarized mask of the 172x172 matrix, where each value=1/-1 corresponds to all surviving positive/negative edges from the *t*-tests

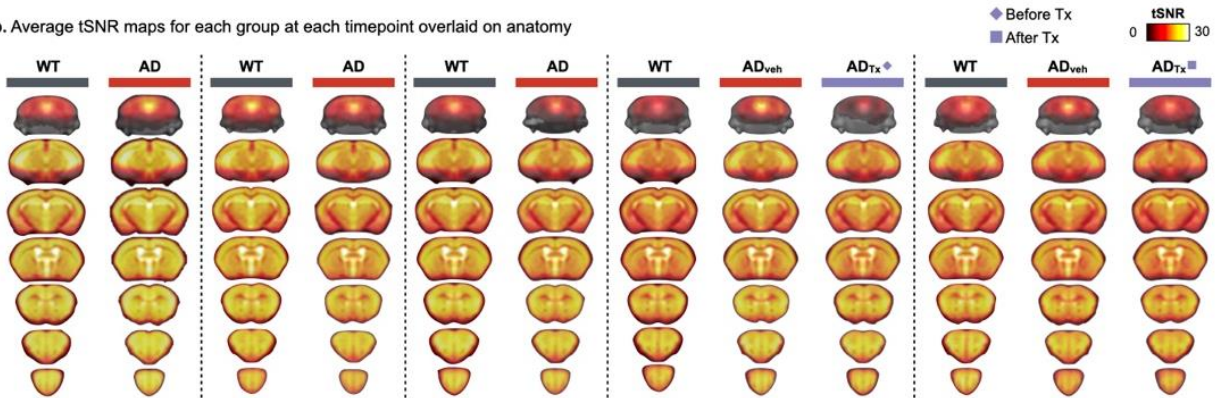
(positive/negative t -values, respectively generating a positive network and a negative network) computed for that specific condition (see Fig. 3, 4 and 5 and Material and Methods, Analyses and Statistics section). For example, the WT-aging network is obtained by (first) computing t -tests at 4 M > 9 M and 4 M > 20 M timepoints, and then creating binarized matrices for both t -test results. Finally, the two matrices obtained (two positive and two negative) are combined either by sum or by intersect to obtain a more extensive or a more stringent data-derived network.

SUPPLEMENTARY FIGURES

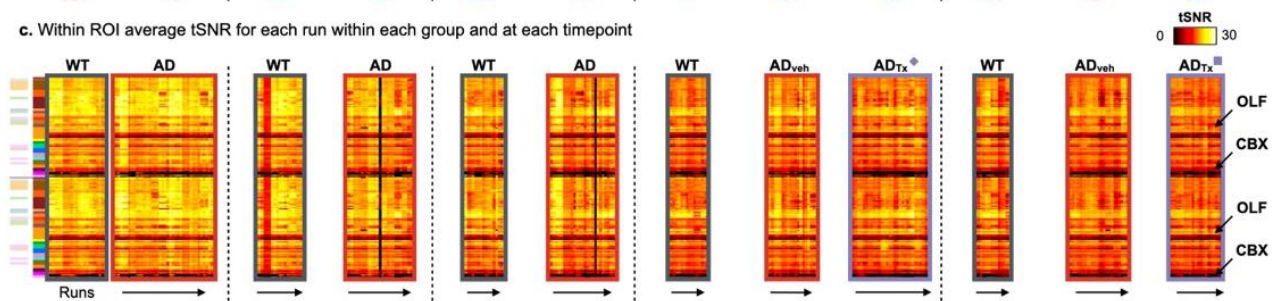
a. Representative raw GE-EPI data for each group and at each timepoint



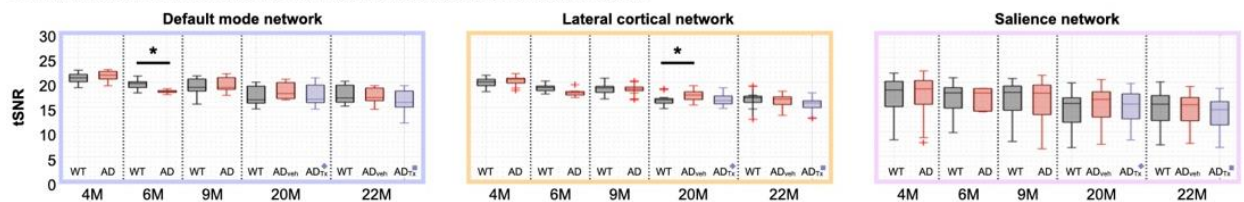
b. Average tSNR maps for each group at each timepoint overlaid on anatomy



c. Within ROI average tSNR for each run within each group and at each timepoint

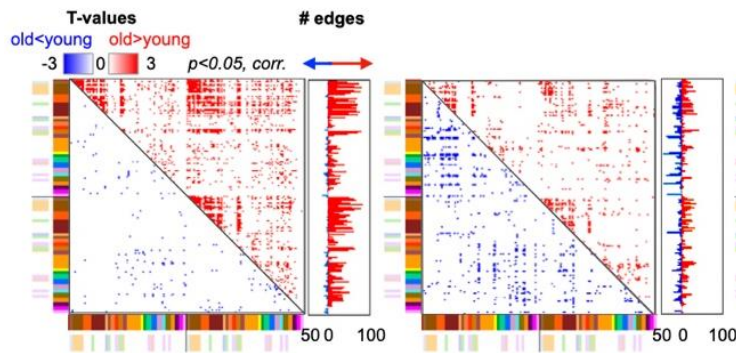


d. Within network tSNR for triple network model for each group atn at each timepoint

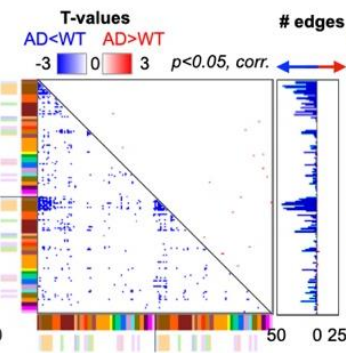


Supplementary Fig. 1: Quality metrics for fMRI data preprocessing. a. Example of raw images for each group/timepoint with artifacts (e.g. due to the ear canals) indicated by white triangles). Group-averaged temporal signal-to-noise ratio (tSNR) for each group/timepoint in hot colors overlaid on a grey-scale template (b.) or shown as a ROI-based matrices (c.). d. Quantification of tSNR (mean $\pm$ standard deviation) within the triple network model, in each group/timepoint shows relatively stable tSNR across the lifespan. OLF: olfactory, CBX: cerebellum.

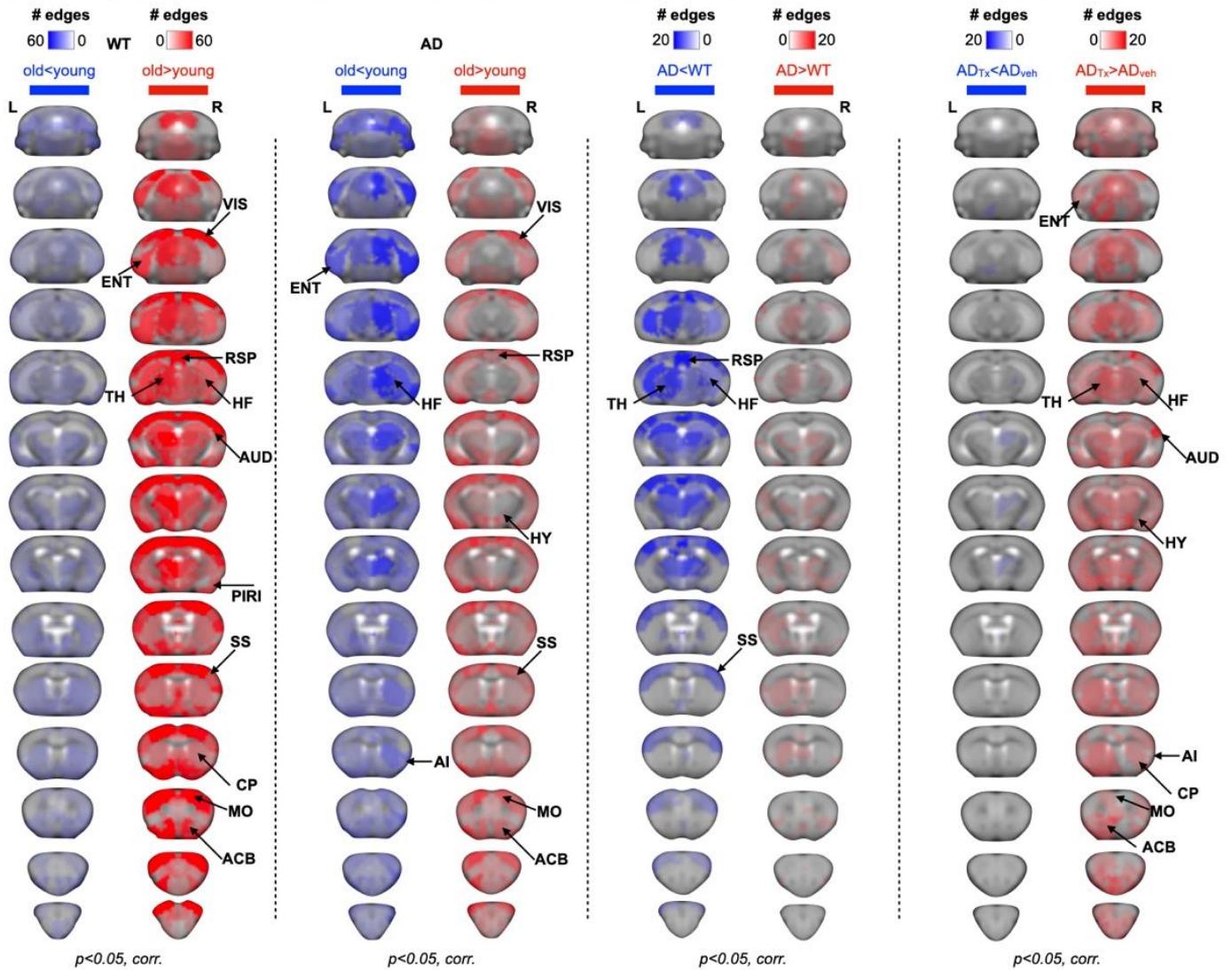
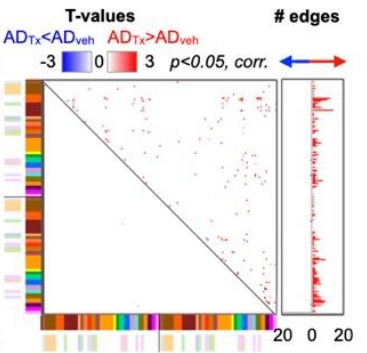
a. Aging networks, WT (left) & AD (right)



b. AD-like networks

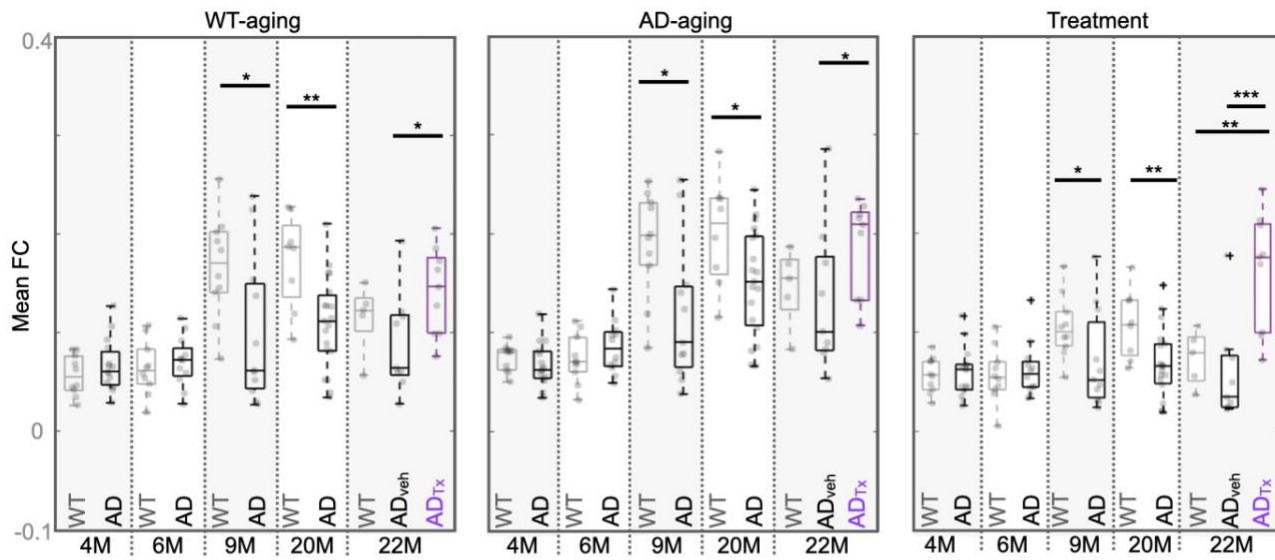


c. Treatment networks

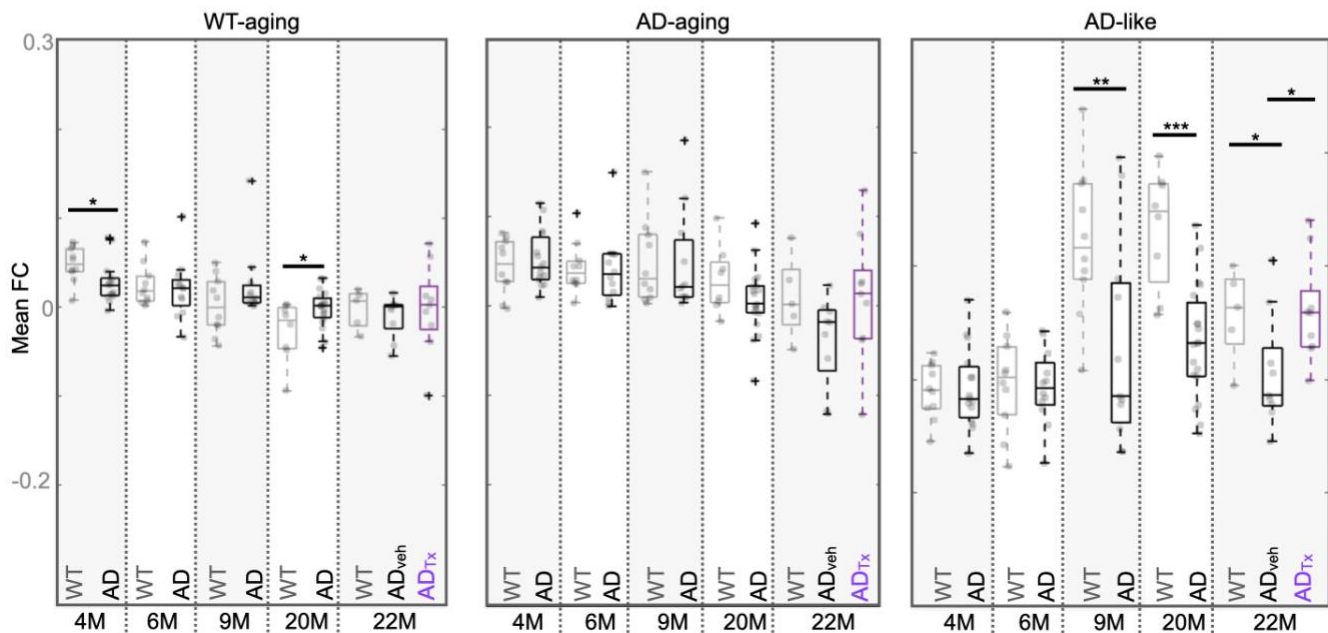


Supplementary Fig. 3: Summaries of data-derived networks. Data-derived networks are displayed as connectomes (172 x 172 ROIs, see Fig. 1a) and summarized as vertical histograms (upper sections). **a.** Aging networks for WT (left) and AD (right): Red indicates greater FC in older mice vs younger (upper-right in connectomes). Blue shows the opposite direction (lower-left in connectomes). **b.** AD-like networks: Red indicates greater FC in AD mice vs WT (upper-right in connectomes). Blue shows the opposite direction (lower-left in connectomes). **c.** Treatment networks: Red indicates greater FC in AD_{Tx} (after treatment, Tx) mice vs vehicle (veh, upper-right in connectomes). Blue shows the opposite direction (lower-left in connectomes). For all networks, data are also shown as node degree maps displayed on anatomical reference images (greyscale) bottom panels. Here the sum (less stringent) is adopted. All results have a statistical threshold (corrected, $p < 0.05$) applied.

a. Positive edges - SUM

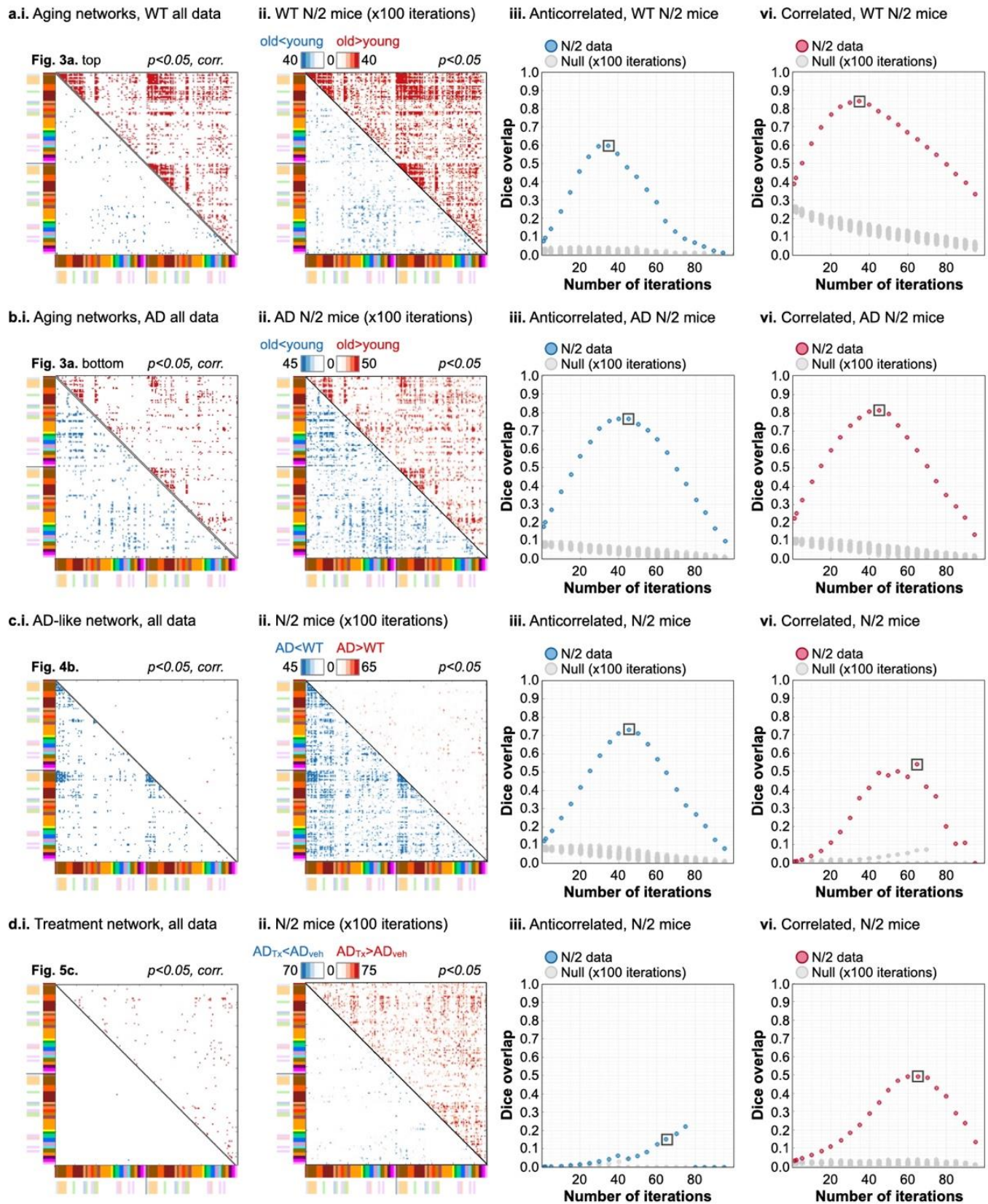


b. Negative edges - SUM

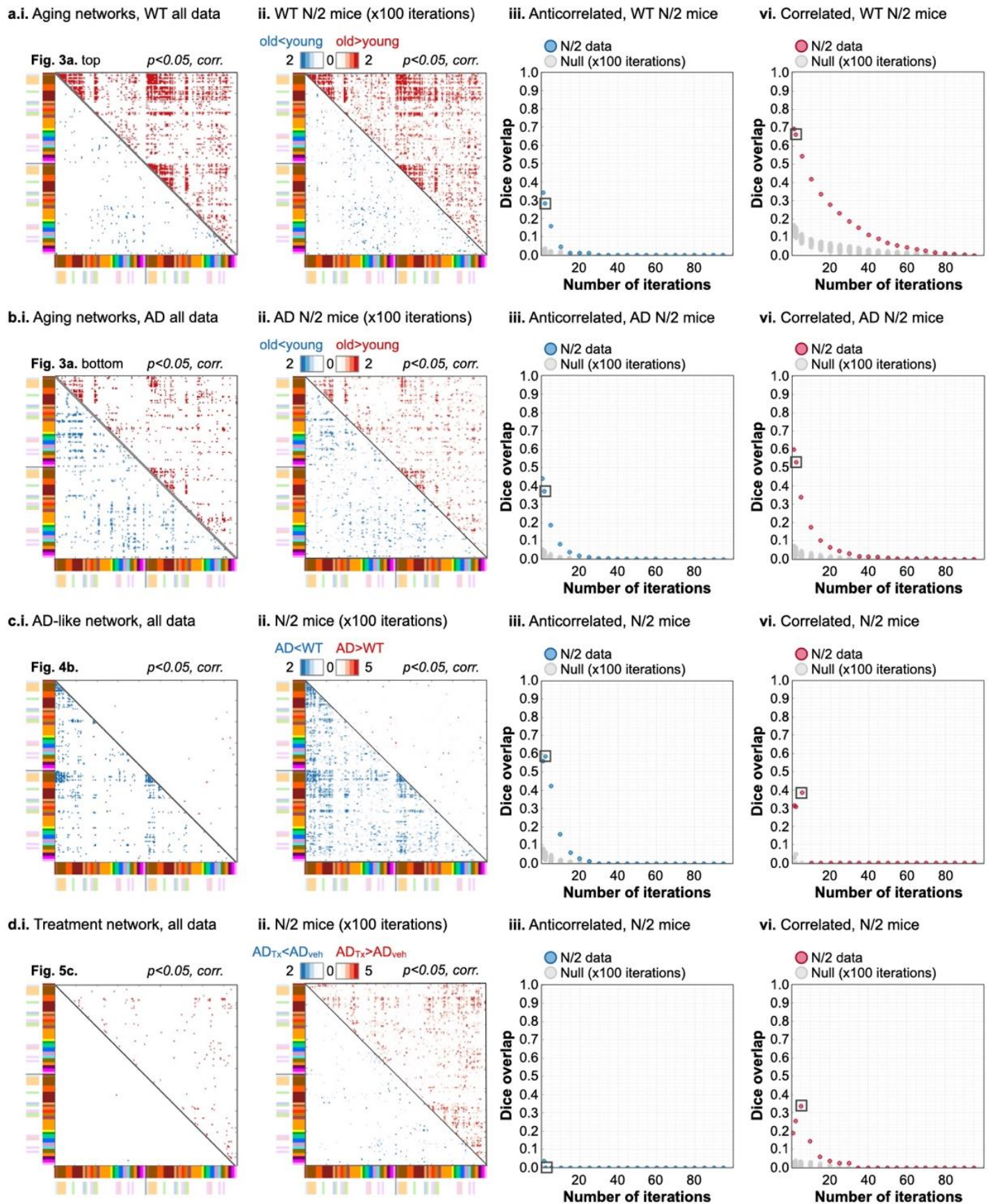


* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.001$

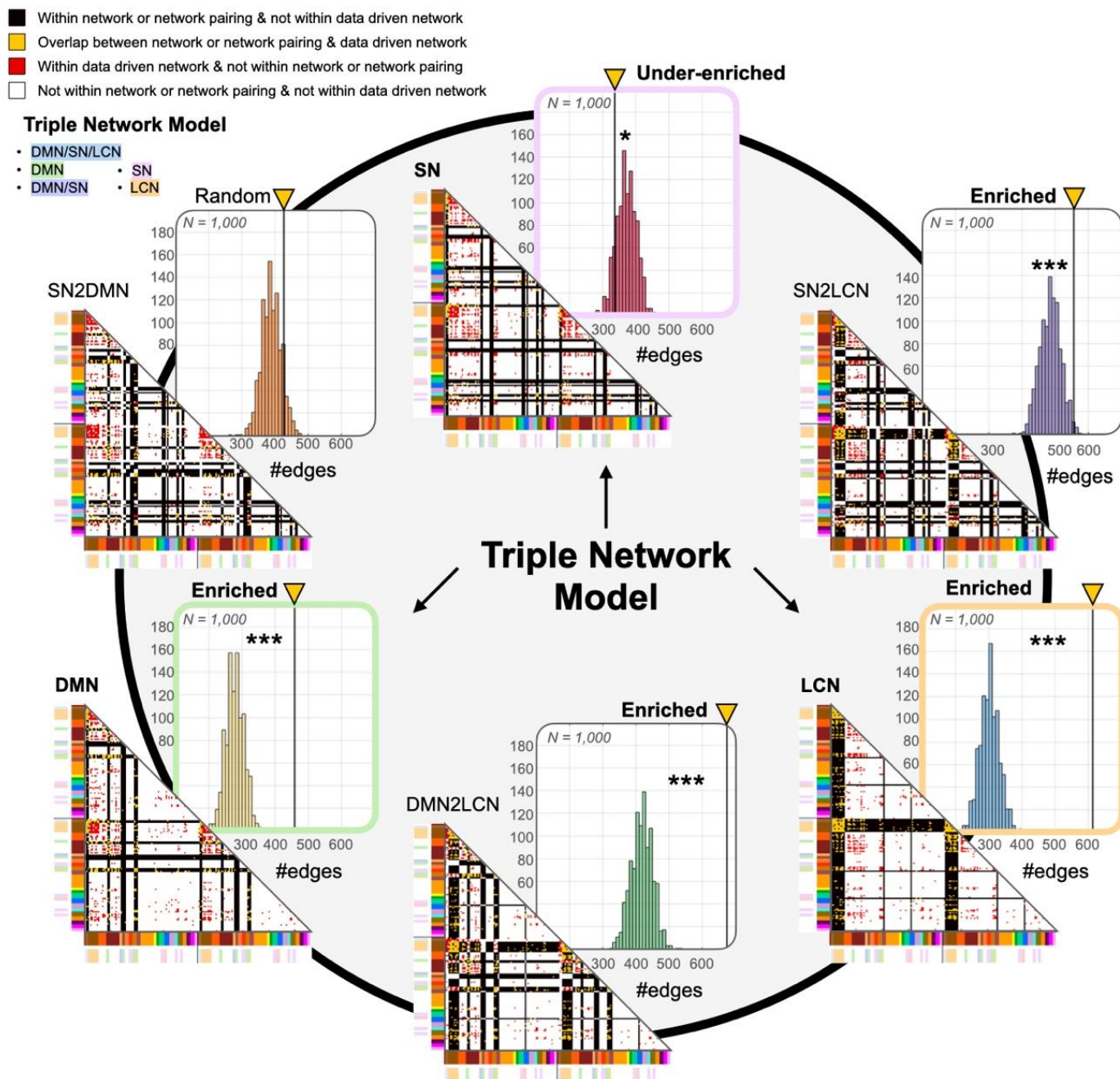
Supplementary Fig. 6: Mean FC within data-derived networks (sum). Of the four data-derived networks (reproduced in **Supplementary Fig. 3**, for the sum), the positive networks for WT-aging, AD-aging and treatment (**a.**), and the negative networks for WT-aging, AD-aging and AD-like (**b.**) are used as binary masks to threshold the raw functional connectome data, and to plot FC values corresponding to each network. As such, the functional connectomes are thresholded for only the edges belonging to each of the selected networks, for all time points and for both WT (grey), AD (vehicle/treated black/purple) animals, for positive (**a.**) and negative (**b.**) edges. The correlation values within each run are summed, and the three runs per mouse averaged. Each data point in the boxplots above represent a mouse average. The mean FC values are used in a t -test to compare across genotypes, at each time point. Horizontal lines show the median within each group. Significant differences between WT and AD mice are reported as * for $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$. Mean FC values are shown for positive and negative-edges networks (**a**, **b**, respectively).



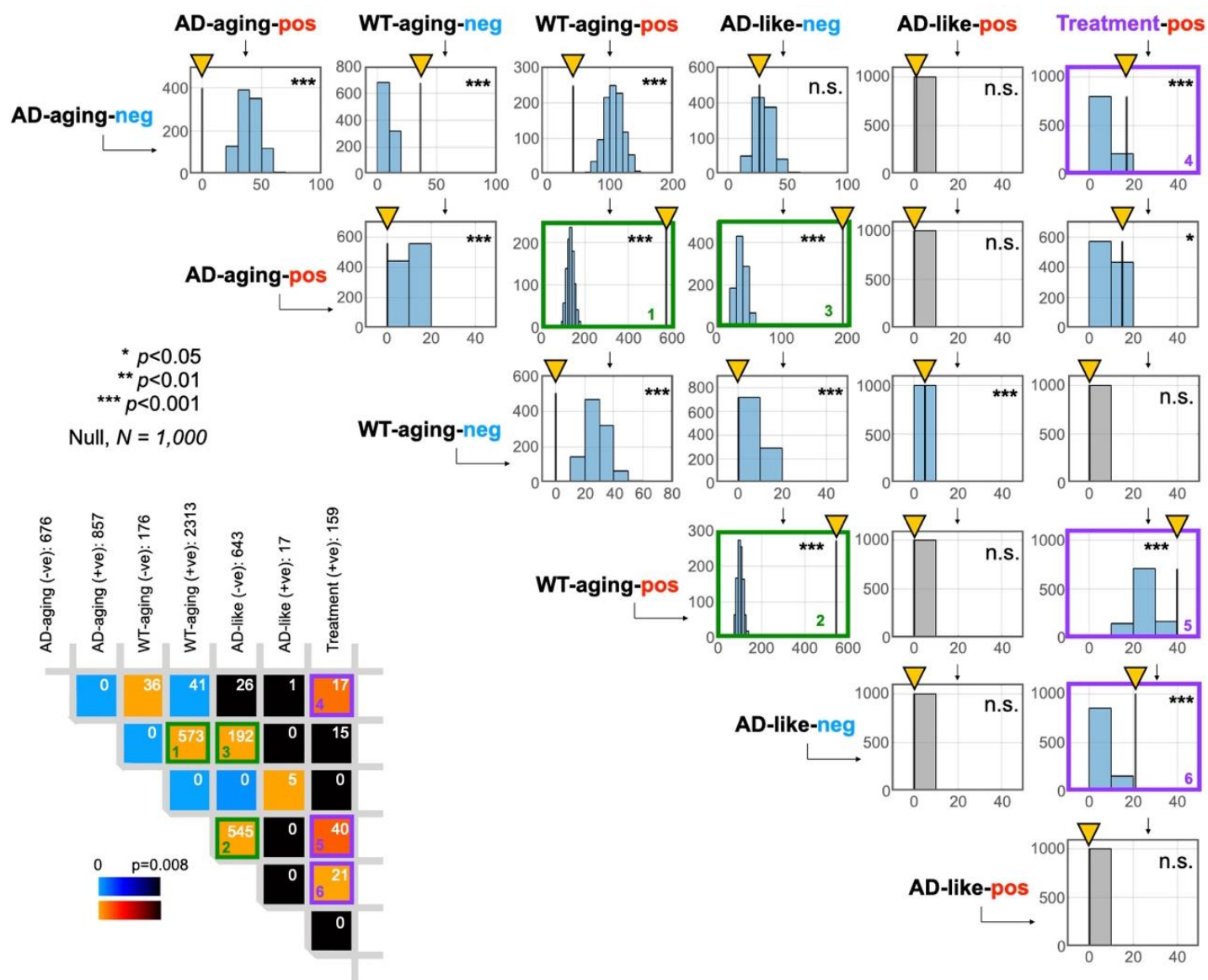
Supplementary Fig. 7: N/2 results without correction for multiple comparison compared to full-N (main findings). For WT (a.), and AD (b.) aging, as well as pathology (c.), and treatment (d.), we recapitulate our main findings using half of the mice we imaged (x100 iterations). For ease of comparison, main findings are reproduced in (i.) for each contrast. N/2 results (summed across iterations as indicated by the squares in iii. and iv.) are shown in (ii.). N/2 findings are summed across iterations and compared to the full-N results using dice overlap for both (-ve) networks, blue data points, (iii.) and (+ve) networks, red data points, (iv.). Null-distributions are shown in greyscale. Here, a statistical threshold $p < 0.05$ is applied to the results of each iteration but not corrected for multiple comparisons.



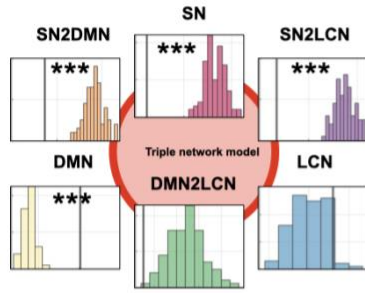
Supplementary Fig. 8: N/2 results with correction for multiple comparison compared to full-N (main findings). As in **Supplementary Fig. 7** with a statistical threshold $p < 0.05$ applied to the results of each iteration and correction for multiple comparisons.



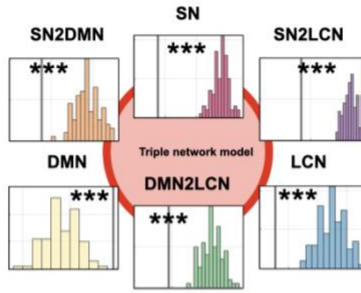
Supplementary Fig. 9: Summary of triple network model quantification of data-derived networks. Each *a priori* canonical network (DMN, LCN, and SN) as well as inter-network pairs are shown as a matrix. Edges within each are shown in color (black, red, and orange). For the example data-driven network, edges that appear in both the data-driven network and the canonical network are shown in orange, edges that are within the data-driven network only are in red, and edges that are only in the canonical network are in black. The histograms show the number of shared edges (black line) relative to a null distribution (color).



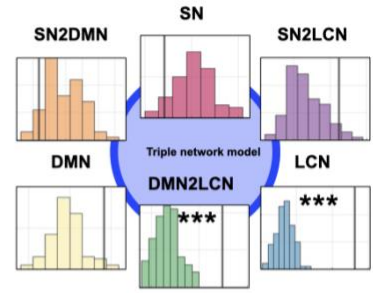
Supplementary Fig. 10: Break-down of shared circuits across data-driven networks. Histograms (as described in Supplementary Fig. 9) for overlap between data-driven networks (Fig. 6).



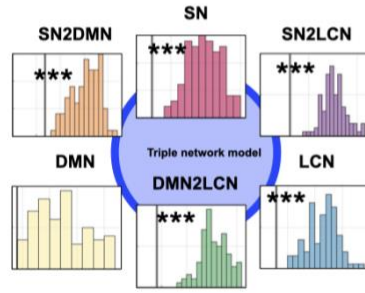
a.ii. Aging networks, WT - negative, N/2



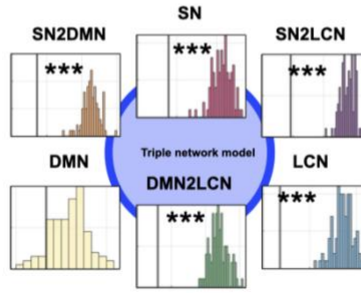
b.ii. Aging networks, AD - negative, N/2



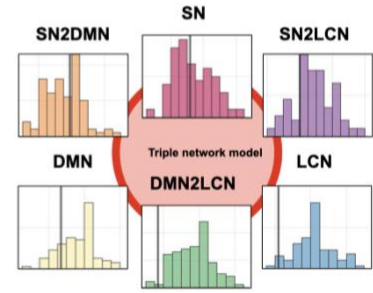
d. Treatment network, positive, N/2



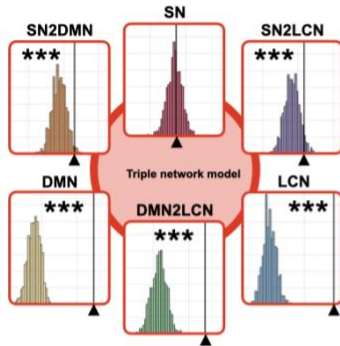
e.i. Aging networks, WT - positive



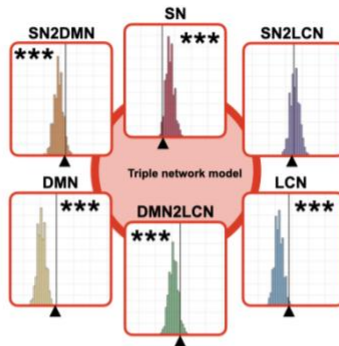
f.i. Aging networks, AD - positive



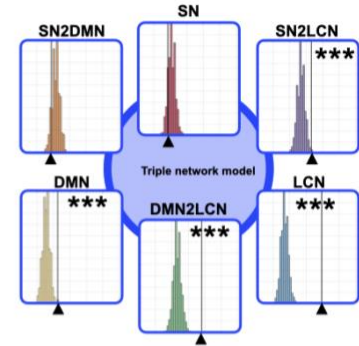
g. AD-like network, negative



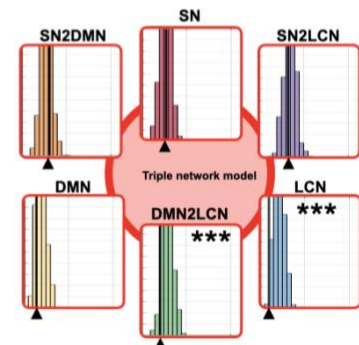
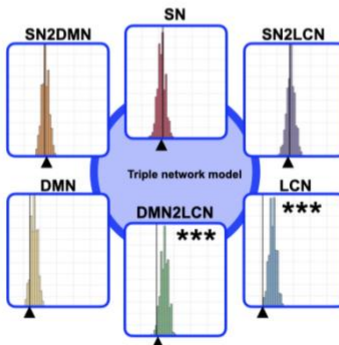
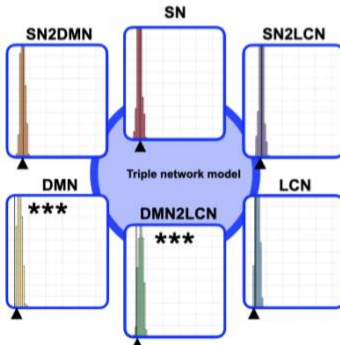
e.ii. Aging networks, WT - negative



f.ii. Aging networks, AD - negative

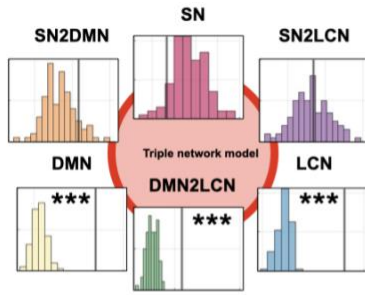


h. Treatment network, positive

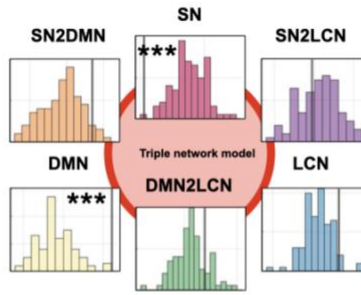


Supplementary Fig. 11: Break-down of data-derived networks from N/2 (uncorrected) findings. Histograms (as described in **Supplementary Fig. 9**) for overlap between N/2 data-derived networks and a priori canonical networks (above the dotted line). Main findings from full-N analyses are reproduced from the main figures below the dotted line. N/2 results are summed across iterations as indicated in **Supplementary Fig. 7** (squares in **iii.** and **iv.**, for -ve and +ve, respectively).

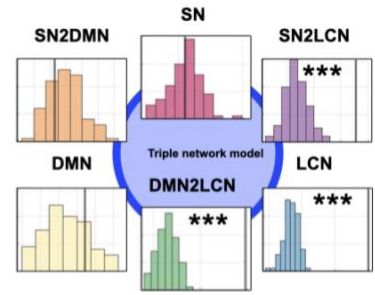
a.i. Aging networks, WT - positive, N/2



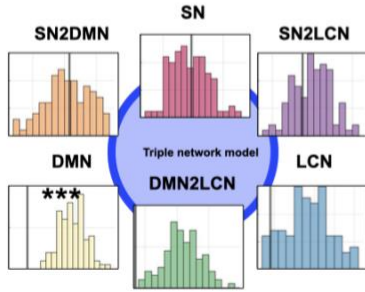
b.i. Aging networks, AD - positive, N/2



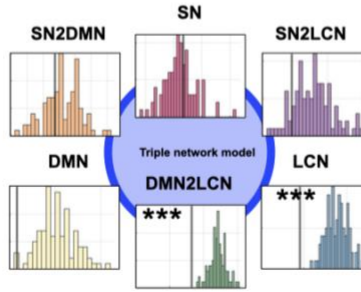
c. AD-like network, negative, N/2



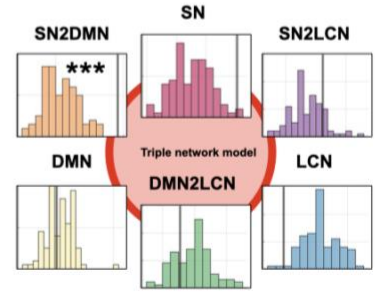
a.ii. Aging networks, WT - negative, N/2



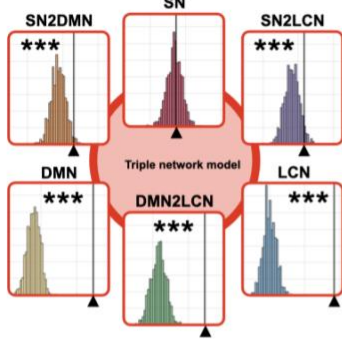
b.ii. Aging networks, AD - negative, N/2



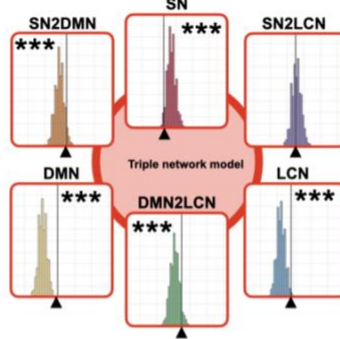
d. Treatment network, positive, N/2



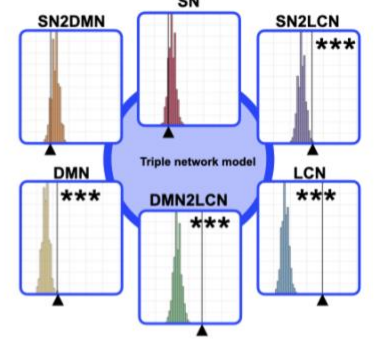
e.i. Aging networks, WT - positive



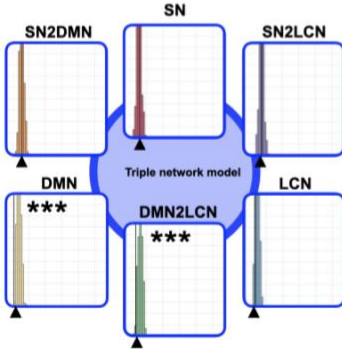
f.i. Aging networks, AD - positive



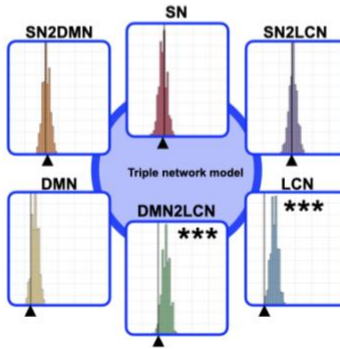
g. AD-like network, negative



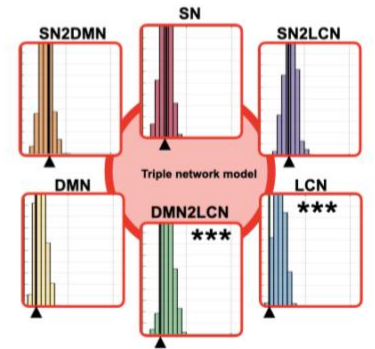
e.ii. Aging networks, WT - negative



f.ii. Aging networks, AD - negative



h. Treatment network, positive



Supplementary Fig. 12: Break-down of data-derived networks from N/2 (corrected) findings. Histograms (as described in **Supplementary Fig. 9**) for overlap between N/2 data-derived networks and a priori canonical networks (above the dotted line). Main findings from full-N analyses are reproduced from the main figures below the dotted line. N/2 results are summed across iterations as indicated in **Supplementary Fig. 8** (squares in **iii.** and **iv.**, for -ve and +ve, respectively).

SUPPLEMENTARY TABLES

Supplementary Table 1: Overview of datasets

Procedure	Experiment 1				Experiment 2				Experiment 3			
												
	WT	AD	WT	AD	WT	AD	WT	AD	WT	AD	WT	AD
Transverse sinus injection	5	8	6	8								
Head-plate at 3M	5	8	6	8								
Head-plate at 5M					-	-	-	4				
Head-plate at 8M					6	4	2	1				
Head-plate at 19M									5	12	5	8
Multimodal imaging at 4M	5	7+1 ^{\$}	5+1 ^{\$}	8								
Multimodal imaging at 6M	5	5+1 ^{\$}	5	3								
Multimodal imaging at 9M	-	2	2	4								
Unimodal* imaging at 6M								4				
Unimodal* imaging at 9M					6	4	2	1				
Unimodal* imaging at 20M									5	12	3	7+1 ^{\$}
Allocated to treatment									-	5	-	4
Unimodal* imaging at 22M									5	6/5 [†]	0	3/4 [†]

* Unimodal is always MRI-only

^{\$} excluded

[†] Vehicle/drug-treated

Abbreviations: wild-type (WT), double knock in (AD), months of age (M).

Supplementary Table 2: Change in FC strength with age in healthy mice

Age	This study	Egimendia	Vasilkovska	Morrissey	Albertson*		
2-4M	Baseline	Baseline	Baseline	Baseline	Baseline		
4-6M	•	•		•			
6-8M			↑				
8-10M	↑	↑		↑			
10-12M			↓				
12-14M		↓					
14-16M				↑			
16-18M						↓	
18-20M	↑						
20-22M	↓						

* Optical imaging of Thy-1-GCaMP6f mice.

Supplementary Table 3: Brain areas showing changes in FC strength with age in WT-mice

Network/Region	This study	Egimendia	Vasilkovska	Morrissey*	Albertson**
DMN	•	•	•		•
RSP [†]	•	(part of DMN)	•		•
VIS [†]	•		•		•
MO [†]	•				•
AUD	(Fig. 5d)		•		•
ACA [†]	•		•		•
SS [†]	•	•			
HF [†]				•	
LCN	•				
HY	•				
TH [†]	•				
ACB [†]	•				
MB	•				
PTL [‡]					•

* Only hippocampal region investigated

** Optical imaging cannot access subsurface areas.

[†] Areas in our Neurosynth analysis
(**Supplementary Fig. 4**).

[‡] PTL: Posterior parietal association area⁶¹.

Refer to **Fig. 1** for abbreviations.

Supplementary Table 4: Brain areas showing changes in FC strength across comparisons in this study

Network/Region		WT-Aging	AD-Aging	WT vs. AD	Shared (Fig. 6)
DMN:		↑ (+ve); ↓ (-ve)	↑ (+ve)	↑ (-ve)	★
VIS [†]		↑ (+ve)	↑ (-ve)	↑ (-ve)	★
RSP [‡] (PREC)		↑ (+ve)	•	↑ (-ve)	★
MO [†]		↑ (+ve)	•	↑ (-ve)	★
ACA ^{†‡}		↑ (+ve)	•	↑ (-ve)	•
LCN:		↑ (+ve)	↑ (+ve); ↓ (-ve)	↑ (-ve)	★
SS [†]		↑ (+ve)	•	↑ (-ve)	★
TeA		•	•	↑ (-ve)	•
MO [†]		↑ (+ve)	•	↑ (-ve)	★
SN:		•	↓ (+ve)	•	•
HY		↑ (+ve)	•	•	•
TH [†]		↑ (+ve)	↑ (-ve)	↑ (-ve)	•
INS ^{†‡}		•	↑ (-ve)	•	•
MO [†]		↑ (+ve)	•	↑ (-ve)	★
ACA ^{†‡}		↑ (+ve)	•	↑ (-ve)	•
DMN-LCN		↑ (+ve); ↓ (-ve)	↑ (+ve); ↓ (-ve)	↑ (-ve)	★
DMN-SN		↑ (+ve)	↑ (+ve)	•	•
LCN-SN		↑ (+ve)	•	↑ (-ve)	★
Other	MB	↑ (+ve)	•	↑ (-ve)	•
	ECT	•	↑ (-ve)	•	•
	PERI	•	↑ (-ve)	•	•
	HF [†]	•	↑ (-ve)	↑ (-ve)	•
	CP	•	↑ (-ve)	•	•
	PIR	•	↑ (-ve)	•	•
	PPA	•	•	↑ (-ve)	•
	ACB [†]	↑ (+ve)	•	•	•
	ENT	•	•	↑ (-ve)	•
	HF [‡]	•	•	↑ (-ve)	•
	AUD	•	•	•	★
	AA	•	•	•	★

ACB: Nucleus accumbens, ENT: entorhinal cortex.

[†] Neurosynth results for 'Age' (**Supplementary Fig. 4**).

[‡] Neurosynth results for 'Alzheimer' (**Supplementary Fig. 4**).

PREC: precuneus (human) to RSP (mouse).

Refer to **Fig. 1** for abbreviations.

SUPPLEMENTARY DISCUSSION

BMS-984923 mechanism of action

The cellular prion protein (PrP^C) is a specific and high affinity receptor for amyloid- β oligomers (A β o)⁹¹⁻⁹⁸. mGluR5 links the A β o/PrP^C complex to the intracellular tyrosine kinases Fyn (a neuronally-enriched cytoplasmic tyrosine kinase) and Pyk2 (PTK2B)^{97, 99-107}. These kinases are in turn associated with tau¹⁰⁸⁻¹¹², and are implicated in AD-risk¹¹³. At the nexus of this AD-pathway, mGluR5 is a promising target. Indeed, reduction of mGluR5 activity alleviates synaptic and memory deficits in multiple AD models^{99, 101-105, 114-122}. Further, BMS-984923 spares glutamate signaling¹²³⁻¹²⁵ while still inhibiting the mGluR5 activation by pathological A β o/PrP^C complexes³³. This mechanism of action greatly expands the potential therapeutic window for mGluR5 as a disease-modifying target.

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