Supplemental Material

Alzheimer's pathology is associated with dedifferentiation of intrinsic functional memory networks in aging

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AT and PM networks are less segregated with older age regardless of analysis approaches

The relationship between age group and segregation was assessed across multiple analysis approaches related to matrix thresholding, bivariate vs. semi-partial correlations, various network metrics of intersystem relationships, and network labeling.

To assess the influence of matrix thresholding on age group differences in network segregation, this supplementary analysis was identical to the original analysis (in the main text) except we retained both positive and negative correlations in each subject's z-matrix (Figure S1A). Similarly, to assess the influence of type of correlation analysis on age group differences in network segregation, this supplementary analysis was identical to the original one except we calculated bivariate correlations instead of semi-partial correlations (Figure S1B).

To examine the influence of network labeling on age group differences in network segregation, we used two different labeling schemes (in addition to our original one). First, we used the Brainnetome Atlas[1], using all ROIs from amygdala (4 ROIs), FuG (6 ROIs), ITG (14 ROIs), PHC (12 ROIs), RSC (4 ROIs), and precuneus (8 ROIs). To create these ROIs, we produced 4mm-radius spheres centered around each MNI coordinate from the literature (Figure S1C). To create AT and PM networks based on the same AT and PM regions used in one of the seminal papers defining AT and PM systems[2], we added 4 FreeSurfer ROIs each to our original AT and PM networks. These additional FreeSurfer regions included bilateral lateral orbitofrontal cortex and temporal pole for the AT network and medial orbitofrontal and posterior cingulate cortices for the PM network, creating a total of 10 ROIs for each network (Figure S1D).

To assess the influence of various network metrics of intersystem relationships, we used the Brain Connectivity Toolbox in Matlab to calculate participation coefficient and modularity values for each subject. The participation coefficient of a given ROI measures to what extent an

ROI interacts with ROIs in other networks in relation to the total number of connections it contains in its own network. Each subject's participation coefficient value was calculated from their respective z-matrix. Participation coefficients for each ROI were computed based on the following formula:

$$P(i) = 1 - \sum_{m=1}^{M} \left[\frac{k_i(m)}{k_i}\right]^2$$

where $k_i(m)$ is the weighted connections of ROI i with nodes in network m and k_i is the total weighted connections ROI i exhibits. Thus, higher participation coefficient values indicate proportionally greater communication with ROIs in other networks (Figure S1E).

Similar to network segregation, modularity assesses the strength of module (i.e., network) segregation. Specifically, the modularity index (Q) compares the observed intra-module functional connectivity with that which is expected by chance. Thus, higher modularity values reflect stronger separation of the system's modules. The modularity index is formally defined as:

$$Q = \frac{1}{2E}\sum_{ij}\left[A_{ij} - \gamma e_{ij}\right]\delta(m_i, m_j)$$

where E is the number of graph connections (i.e., edges), A is the adjacency matrix, γ is the resolution parameter, e is the null model, and δ is an indicator that equals 1 if ROIs i and j belong to the same module and 0 otherwise (Figure S1F).

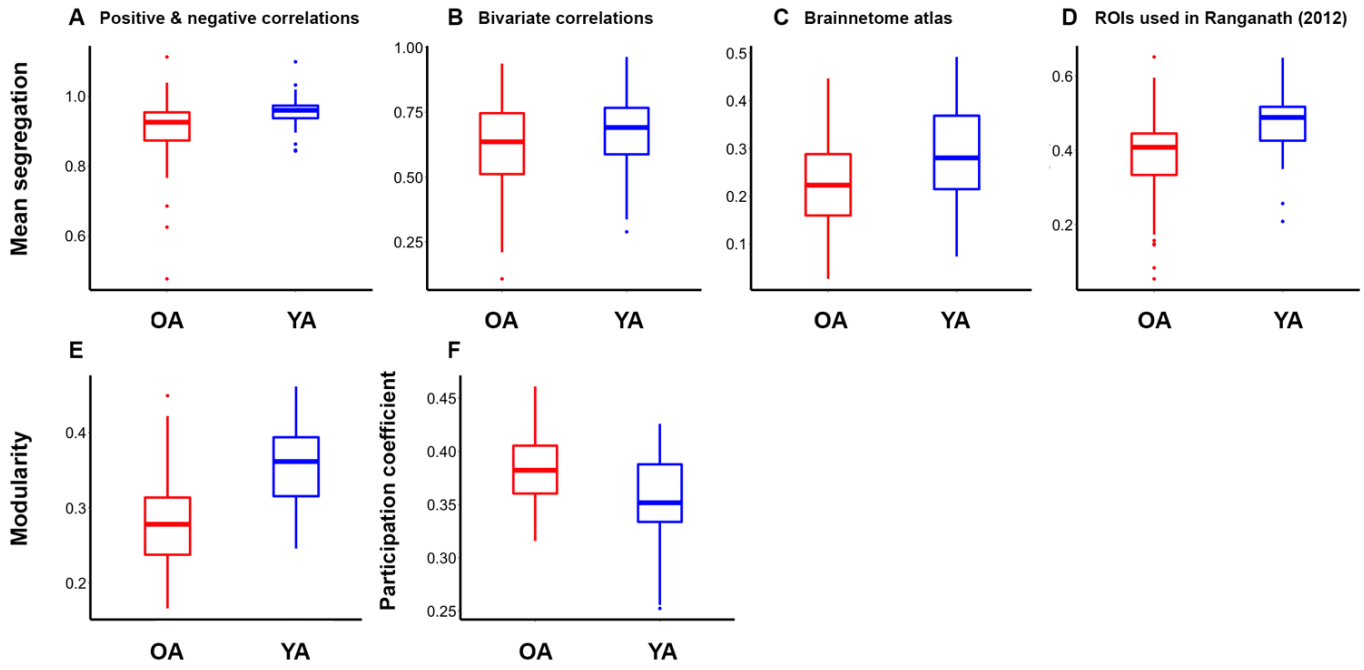

Figure S1. Older adults show significantly less segregated networks compared to younger adults across multiple analysis approaches related to A) matrix thresholding: inclusion of positive and negative correlations ($t = 2.8, p = 0.006$), B) bivariate correlations ($t = 2.4, p = 0.019$), network labeling: C) Brainnetome Atlas ($t = 3.4, p = 0.001$) and D) inclusion of 20 FreeSurfer ROIs used in Ranganath et al. 2012. ($t = 5.7, p < 0.001$), and various network metrics of intersystem relationships: E) participation coefficient ($t = -4.7, p < 0.001$), and F) modularity ($t = 7.9, p < 0.001$).

AD pathology moderates the association between segregation and episodic memory in AT and PM networks

To examine the association between network segregation and episodic memory in the main text, we computed a single segregation measure by averaging the AT and PM segregation values because our episodic memory composite measure included both object- and spatial-related

memory domains. Figure S2 below shows that the results were essentially the same in both the AT and PM networks separately.

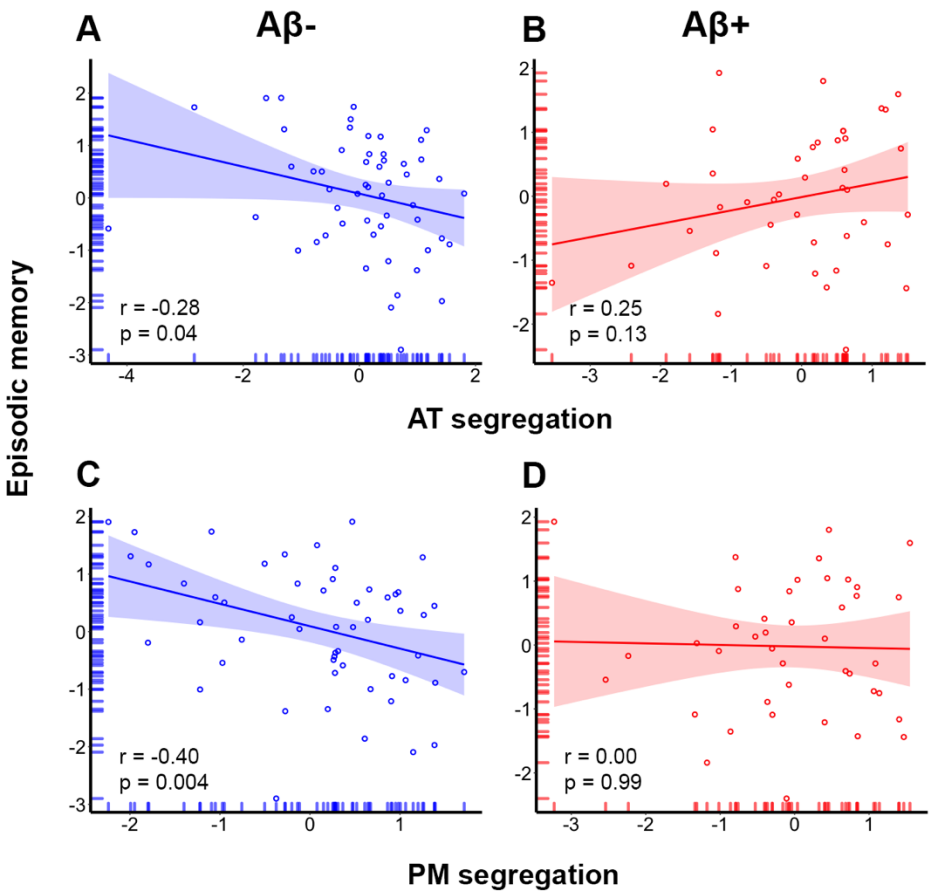

Figure S2. Alzheimer's disease pathology moderates the association between network segregation and episodic memory performance in AT and PM systems. (**A**) Less segregated AT networks are associated with better performance in Aβ- older adults whereas **(B)** AT segregation is not associated with performance in Aβ+ older adults. (**C**) Similarly, less segregated PM networks are associated with better performance in Aβ- older adults whereas **(D)** PM segregation is not associated with performance in Aβ+ older adults.

Baseline segregation predicts longitudinal memory decline using various measures of pathology

In order to examine the relationship between baseline segregation, baseline Aβ and tau, and change in cognitive performance, we used a linear mixed model that included two-way interactions between baseline segregation and time, global Aβ and time, and tau and time. In the main text, we report the results using continuous measures of global Aβ and $Braak_{III-IV}$ tau as they retain more statistical power in the model. The results were very similar whether we used $Braak_{III-IV}$ tau (Table 3 in main text), AT-tau (Table S4) or PM tau (Table S5) and whether we used dichotomous (Table S6) or continuous Aβ and tau (Table 3 in main text) in the model. All models were adjusted for age, sex, and education.

Tables

Table S1. Multiple regression results for AT-Tau predicting AT-segregation and Global Aβ predicting PM-segregation (while controlling for mean motion).

	AT-seg		**PM-seg**	
Predictor	**t**	**p**	**t**	**p**
Age	-0.33	0.75	-1.3	0.2
Aβ	-0.33	0.74	-3.1	0.003
Sex	-0.51	0.61	0.19	0.85
Tau	-2.1	0.047	1.1	0.26
Aβ x Tau	0.39	0.69	1.5	0.15
Mean motion	-0.23	0.82	-0.29	0.78

*AT-tau was used for the regression predicting AT-segregation whereas PM-tau was used for predicting PM-segregation.

Table S2. Multiple regression results for mean segregation and its interaction with Aβ-status predicting episodic memory at baseline (while controlling for mean motion).

Predictor	**t**	**p**
Age	-2.8	0.007
Aβ-status	-2.5	0.016
Sex	0.88	0.38
Education	1.2	0.22
Mean Segregation	-2.8	0.006
Aβ-status x Seg	2.4	0.017
Mean motion	1.2	0.23

Table S3. Multiple regression results for mean segregation and its interaction with Tau-status predicting episodic memory at baseline (while controlling for mean motion).

Predictor	**t**	**p**
Age	-2.5	0.015
Tau-status	-1.4	0.18
Sex	0.8	0.43
Education	1.1	0.28
Mean Segregation	-2.1	0.043
Tau-status x Seg	1.4	0.16
Mean motion	1.3	0.18

Table S4. Linear mixed model results for segregation and pathology predicting longitudinal episodic memory change (while controlling for mean motion).

Predictor	Estimate	p
Age	-0.18	0.04
Sex	-0.03	0.69
Education	0.14	0.1
Segregation	-0.2	0.016
Time	-0.07	0.05
Tau	-0.17	0.09
Aβ	0.03	0.75
Tau x Time	-0.15	0.001
Aβ x Time	-0.001	0.98
Segregation x Time	0.08	0.028
Mean motion	-0.13	0.12

Table S5. Movement parameters for each age group.

Movement Parameter	YA (n = 55)	OA (n = 97)
Framewise displacement (mm)	0.10 ± 0.04 (0.05-0.31)	0.15 ± 0.10 (0.06-0.76)
Percentage of outliers	5 ± 3.5 (1-19)	3.4 ± 2.5 (1-15)

Table S6. Older adult cohort demographics split by Aβ- and tau-status.

	PiB- (N = 54)	PiB+ (N = 42)	t, p	Tau- (N = 66)	Tau+ (N
Age	75.9 ± 7.4 (60-93)	77 ± 4 (69-86)	t = -0.88, p = .38	76 ± 6.7 (60-93)	77.3 ± 4.4 (6
Sex (M/F)	18/36	17/25	t = 0.72, p = 0.48	20/46	16/14
Education (Yrs)	17 ± 0.32	16.5 ± 1.8	t = 1.2, p = 0.23	16.8 ± 1.9	16.8 ± 1.8
APOE ε4 (C/NC)	6/46 (2 N/A)	22/19 (1 N/A)	t = -4.6, p < 0.001	15/48 (1 N/A)	13/17
Global PiB DVR	1.01 ± 0.03 (0.92-1.06)	1.37 ± 0.27 (1.07-1.89)	t = -8.8, p < 0.001	1.09 ± 0.17 (0.92-1.76)	1.32 ± 0.3 (1
AT FTP SUVR	1.21 ± 0.10 (0.98-1.5)	1.39 ± 0.24 (1.11-2.3)	t = -4.5, p < 0.001	1.2 ± 0.08 (0.98-1.3)	1.47 ± 0.25 (
PM FTP SUVR	1.13 ± 0.10 (0.94-1.3)	1.24 ± 0.13 (1.05-1.63)	t = -4.6, p < 0.001	1.12 ± 0.08 (0.94-1.25)	1.3 ± 0.10 (1 1.63)

Table S7. Linear mixed model results for segregation and pathology (including AT-tau) predicting longitudinal episodic memory change.

Predictor	Estimate	p
Age	-0.20	0.02
Sex	-0.003	0.97
Education	0.13	0.12
Segregation	-0.23	0.007
Time	-0.07	0.051
AT-tau	-0.11	0.4
Aβ	0.03	0.79
AT-tau x Time	-0.19	<0.001
Aβ x Time	0.007	0.87
Segregation x Time	0.07	0.049

Table S8. Linear mixed model results for segregation and pathology (including PM-tau) predicting longitudinal episodic memory change.

Predictor	Estimate	p
Age	-0.20	0.03
Sex	0.02	0.84
Education	0.13	0.13
Segregation	-0.18	0.036
Time	-0.07	0.071
PM-tau	-0.11	0.29
Aβ	0.03	0.79
PM-tau x Time	-0.08	0.073
Aβ x Time	-0.05	0.25
Segregation x Time	0.07	0.05

Table S9. Linear mixed model results for segregation and (dichotomous) pathology predicting longitudinal episodic memory change.

Predictor	Estimate	p
Age	-0.20	0.02
Sex	0.007	0.94
Education	0.13	0.15
Segregation	-0.18	0.032
Time	-0.06	0.09
Tau-status	0.009	0.93
Aβ-status	0.03	0.78
Tau-status x Time	-0.09	0.03
Aβ-status x Time	-0.01	0.78
Segregation x Time	0.07	0.05

References

1. Fan, L. *et al*. The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cereb Cortex* **26**, 3508–3526 (2016).
2. Ranganath, C. & Ritchey, M. Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience* **13**, 713–726 (2012).