

# Segregation of functional networks confers cognitive reserve against amyloid-associated cognitive decline

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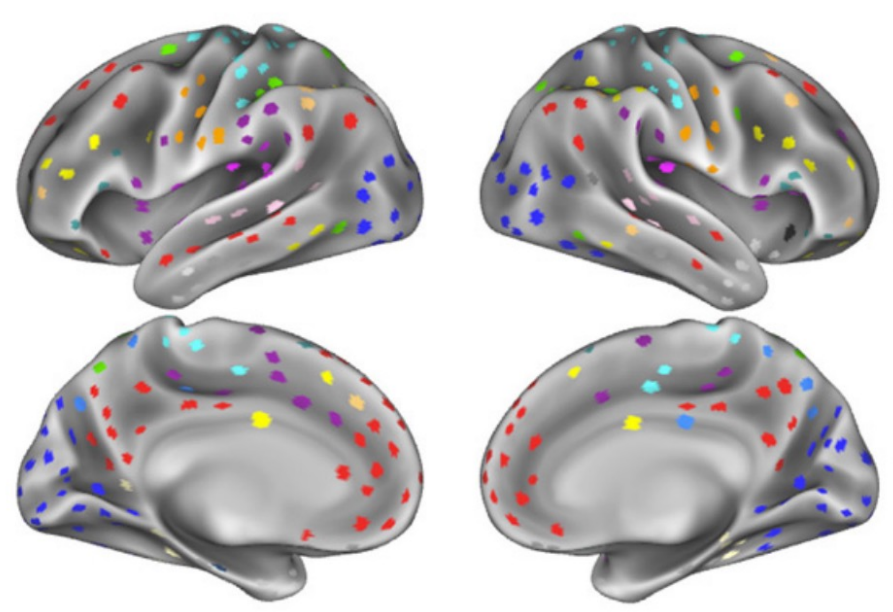
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**Objective:** Increasing evidence suggests that **system segregation** may serve as a **neural substrate** of **cognitive reserve**. This study examined whether baseline global system segregation **moderates** the adverse effects of **Aβ burden** on **both baseline** cognitive performance and **longitudinal** cognitive decline.

## System segregation



$$\text{System Segregation} = \frac{\bar{Z}_{\text{within}} - \bar{Z}_{\text{between}}}{\bar{Z}_{\text{within}}}$$

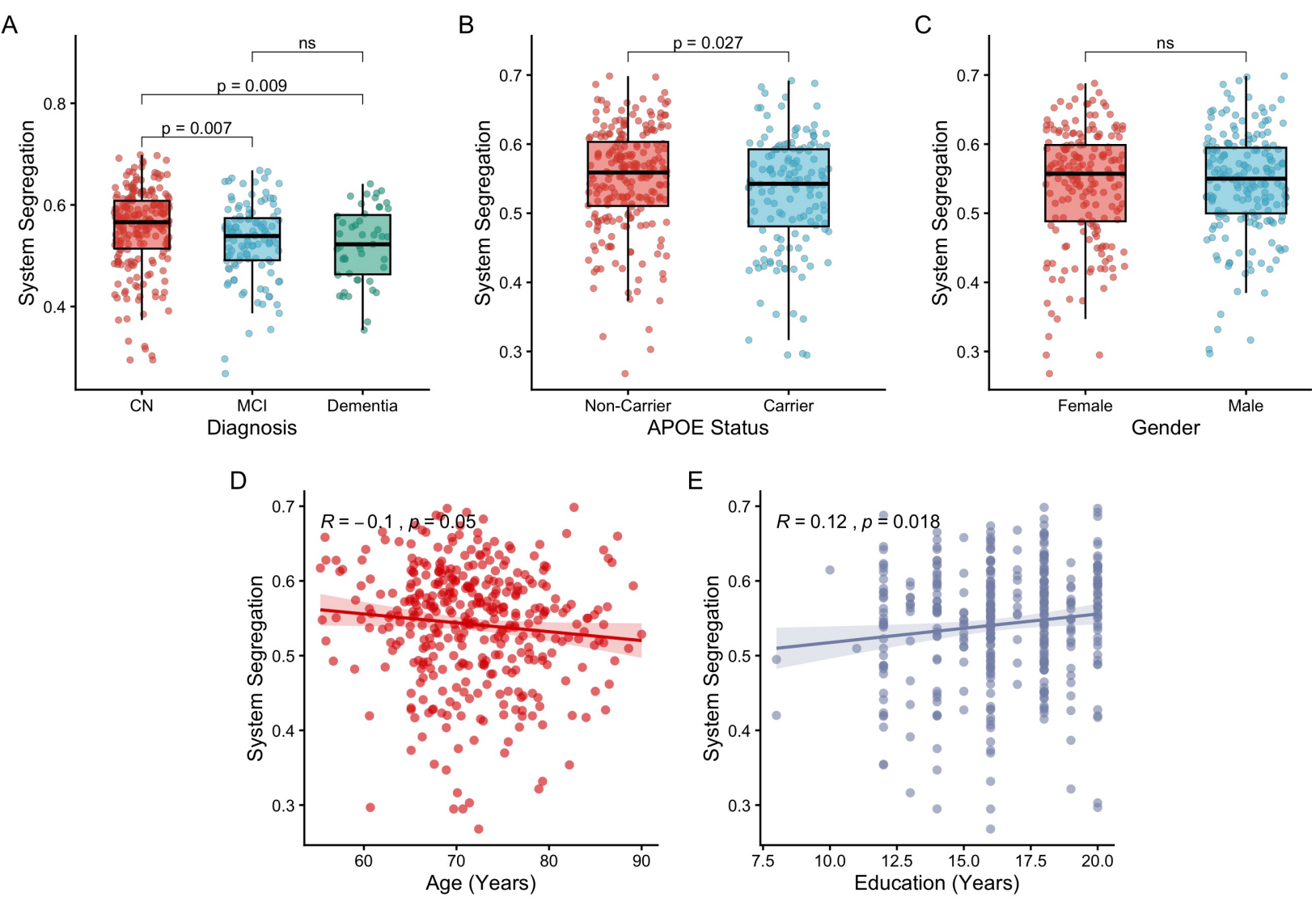
- **441 cortex nodes**
- **61 subcortex nodes**

- System segregation was calculated as the **difference** between mean **within-system** connectivity and mean **between-system** connectivity, normalized by mean within-system connectivity.
- Cognitive reserve (CR) is a property of the brain that allows for cognitive performance that is **better than expected** given the degree of brain changes and brain injury or disease.

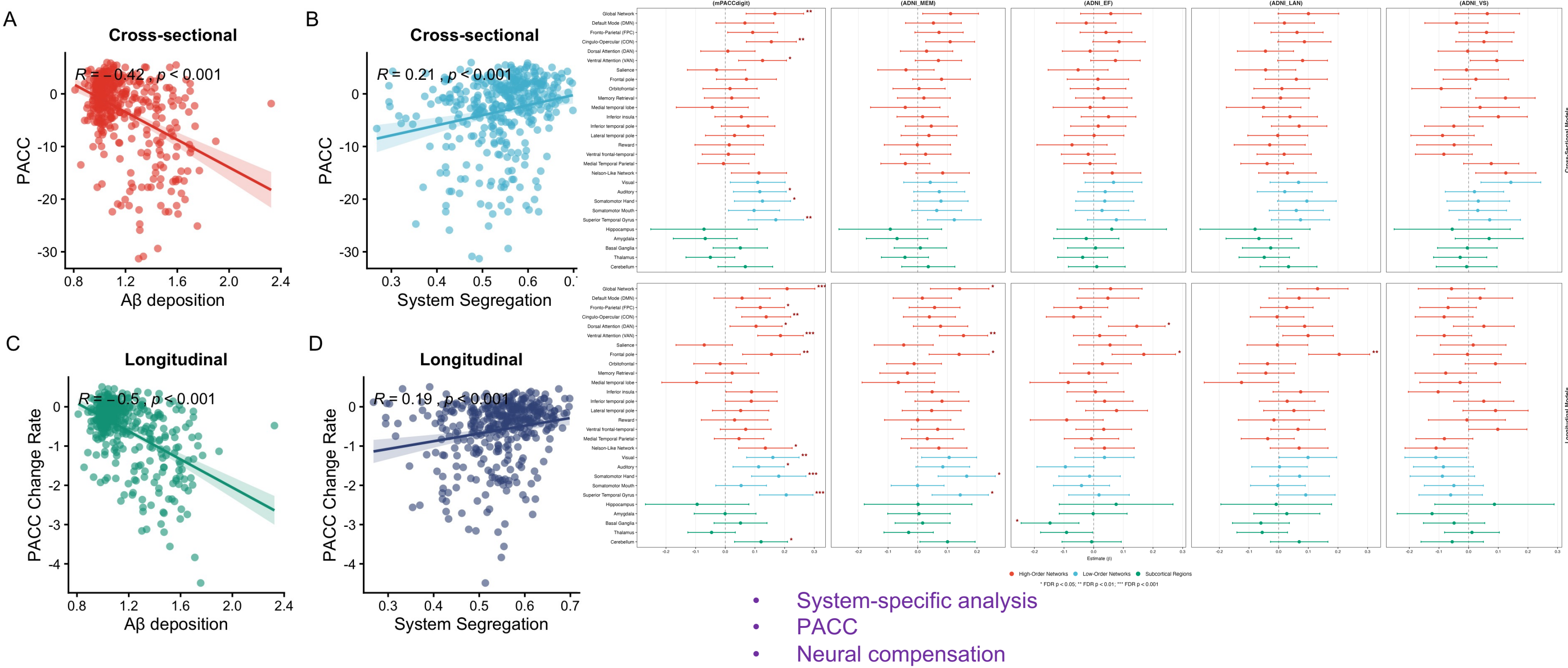
- ❖ **Dataset: ADNI**
- ❖ **216 CN**
- ❖ **112 MCI**
- ❖ **47 dementia**
- **Aβ burden: SUVR of AV45 PET**
- **Cognitive function: PACC, ADNI\_MEM, EF, LAN, VS**
- **Covariates: age, gender, education, APOE ε4 Status**

## Demographic statistics

| Characteristic            | Overall<br>N = 375 <sup>1</sup> | CN<br>N = 216 <sup>1</sup> | MCI<br>N = 112 <sup>1</sup> | Dementia<br>N = 47 <sup>1</sup> | p-value <sup>2</sup> |
|---------------------------|---------------------------------|----------------------------|-----------------------------|---------------------------------|----------------------|
| Age                       | 72 (7)                          | 71 (6)                     | 72 (6)                      | 74 (9)                          | 0.019                |
| Gender                    |                                 |                            |                             |                                 | 0.058                |
| Female                    | 187 (50%)                       | 119 (55%)                  | 49 (44%)                    | 19 (40%)                        |                      |
| Male                      | 188 (50%)                       | 97 (45%)                   | 63 (56%)                    | 28 (60%)                        |                      |
| Education                 | 16.37 (2.54)                    | 16.72 (2.34)               | 15.90 (2.80)                | 15.89 (2.54)                    | 0.017                |
| APOE ε4 status            |                                 |                            |                             |                                 | 0.004                |
| Non-Carrier               | 231 (62%)                       | 146 (68%)                  | 65 (58%)                    | 20 (43%)                        |                      |
| Carrier                   | 144 (38%)                       | 70 (32%)                   | 47 (42%)                    | 27 (57%)                        |                      |
| AV45                      | 1.19 (0.23)                     | 1.12 (0.17)                | 1.22 (0.26)                 | 1.41 (0.21)                     | <0.001               |
| Baseline ACC              | -3 (7)                          | 1 (3)                      | -5 (5)                      | -18 (6)                         | <0.001               |
| Annual change in PACC     | -0.54 (2.27)                    | -0.12 (1.14)               | -0.73 (2.36)                | -2.68 (4.90)                    | <0.001               |
| Global system segregation | 0.54 (0.08)                     | 0.55 (0.08)                | 0.53 (0.08)                 | 0.52 (0.07)                     | <0.001               |

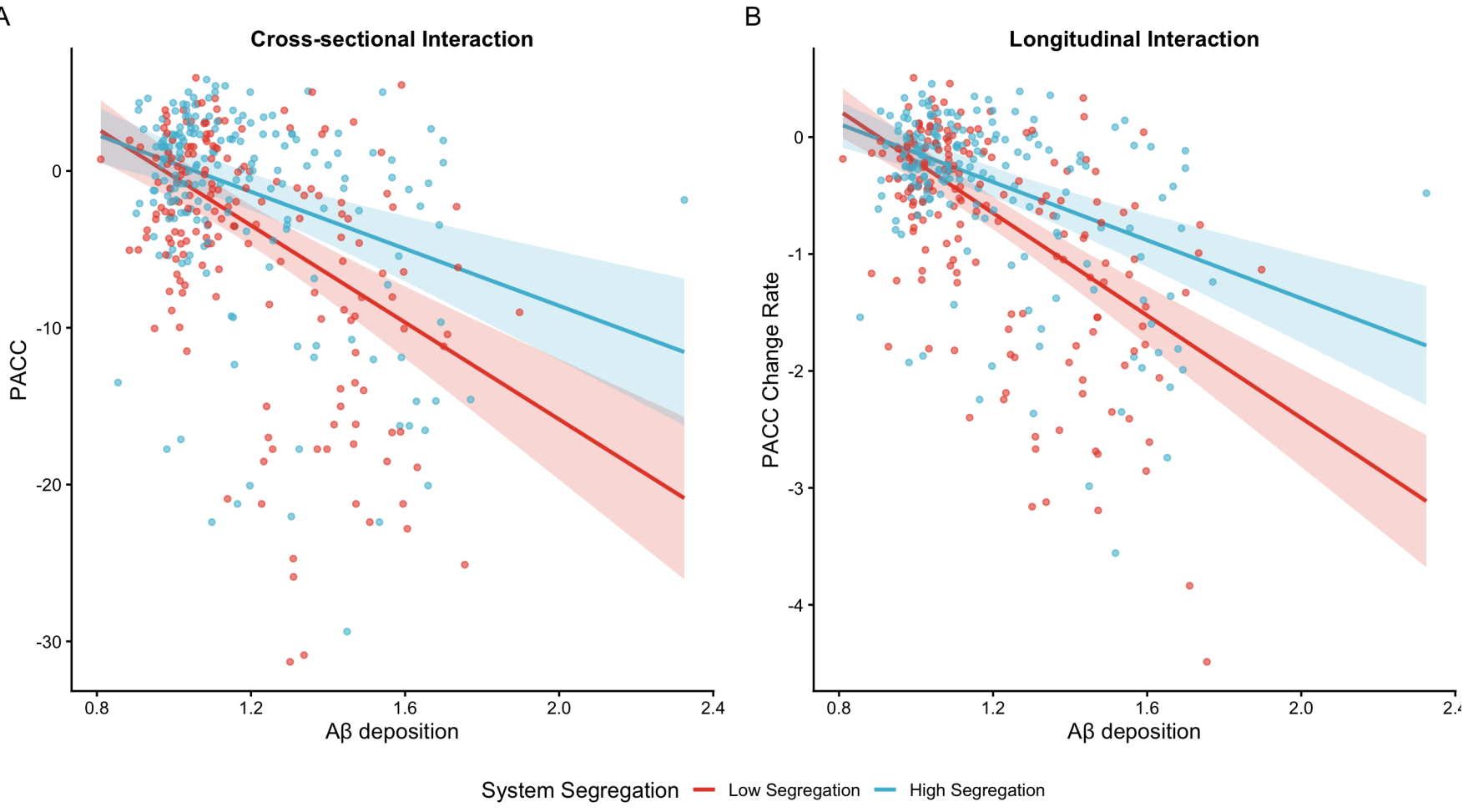


## Results

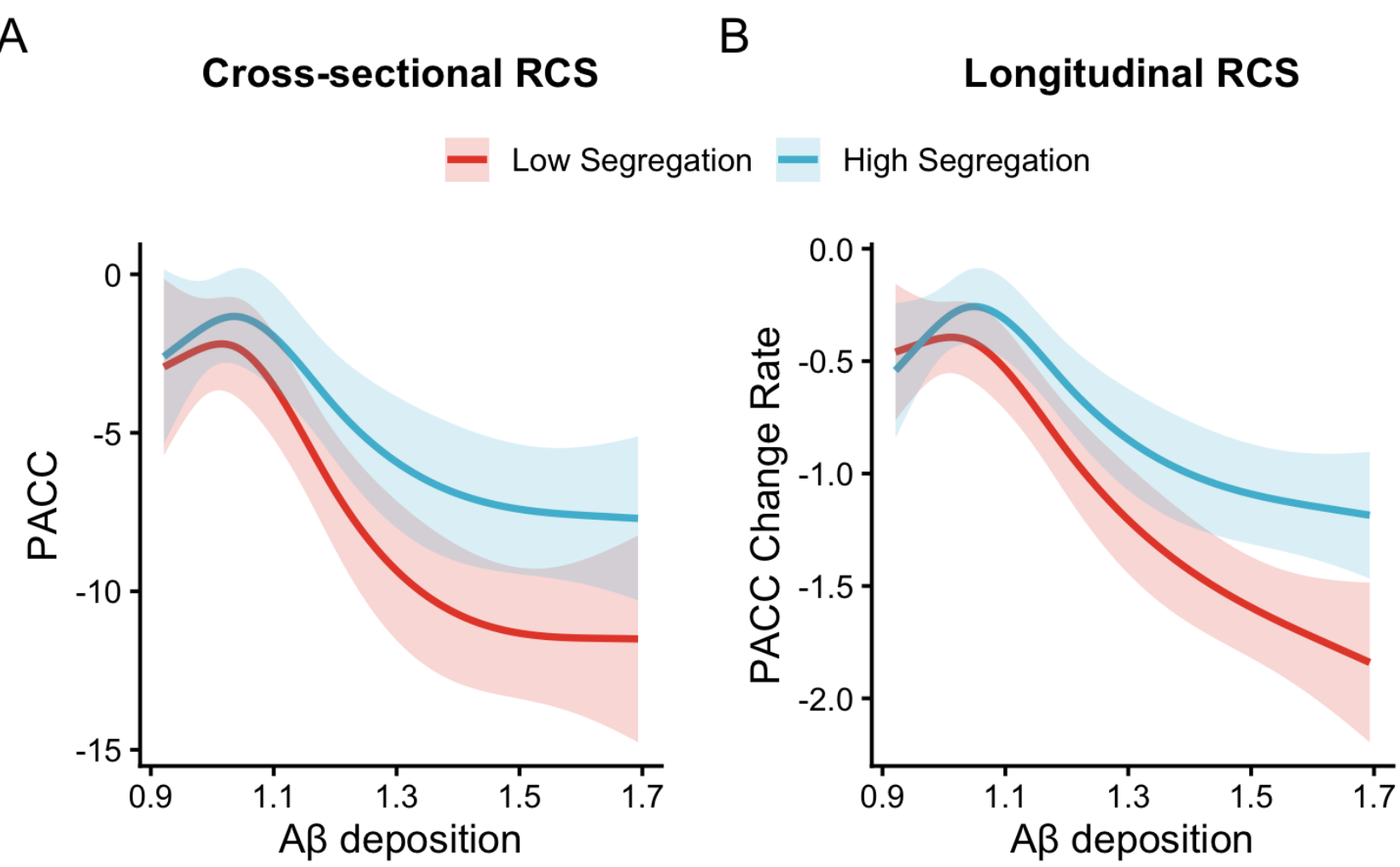


- System-specific analysis
- PACC
- Neural compensation

| Characteristic           | Cross-sectional |        | Longitudinal |        |
|--------------------------|-----------------|--------|--------------|--------|
|                          | B               | p      | B            | p      |
| Aβ                       | -49.0           | <0.001 | -6.89        | <0.001 |
| Global segregation       | -62.2           | 0.008  | -9.33        | <0.001 |
| Age                      | -0.074          | 0.132  | -0.006       | 0.296  |
| Gender (ref. female)     | -2.21           | <0.001 | -0.209       | 0.003  |
| APOE ε4 Status (ref. no) | 0.019           | 0.979  | -0.024       | 0.758  |
| Education                | 0.548           | <0.001 | 0.036        | 0.010  |
| Aβ * global segregation  | 66.9            | <0.001 | 9.44         | <0.001 |



## RCS



- Rightward shift of the change point in the high-segregation group
- No steeper cognitive decline in higher segregation group
- Aβ: **upstream** of AD
- Change point below the Aβ positivity cutoff
- Neural reserve: Higher system segregation reflects a more **modular** functional architecture that supports specialized processing by **minimizing cross-network interference**
- Neural compensation: preserved network **distinctiveness** may provide the **topological basis** for flexible **compensatory recruitment** when primary circuits are disrupted.

## Summary

- **Greater Aβ burden** was associated with **poorer baseline PACC performance** and **steeper longitudinal cognitive decline**.
- **Higher global system segregation** was associated with **better** cognitive performance and slower decline.
- The association between Aβ burden and cognitive decline was **weaker** among participants with **higher system segregation**.
- These findings support global system segregation as a **potential neural substrate of cognitive reserve** in the context of Alzheimer’s disease pathology.

## References

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[2] Ewers, M., Luan, Y., Frontzkowski, L., Neitzel, J., Rubinski, A., Dichgans, M., Hassenstab, J., Gordon, B. A., Chhatwal, J. P., Levin, J., Schofield, P., Benzinger, T. L. S., Morris, J. C., Goate, A., Karch, C. M., Fagan, A. M., McDade, E., Allegri, R., Berman, S.,...Network, t. D. I. A. (2021). Segregation of functional networks is associated with cognitive resilience in Alzheimer’s disease. *Brain*, 144(7), 2176-2185.

[3] Zhang, Z., Chan, M. Y., Han, L., Carreno, C. A., Winter-Nelson, E., Wig, G. S., & Initiative, f. t. A. s. D. N. (2023). Dissociable Effects of Alzheimer's Disease-Related Cognitive Dysfunction and Aging on Functional Brain Network Segregation. *The Journal of Neuroscience*, 43(46), 7879-7892.