

Dissociable Network Topologies Are Linked to Cognitive and Hippocampal Resilience in Ageing and Preclinical Alzheimer's Disease

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Background

In preclinical Alzheimer's disease (AD), **cognitive and hippocampal volume trajectories** begin to **diverge** among individuals of similar age or pathology.

Resilience is exhibiting better-than-expected cognition or brain volume despite disease-adverse factors. **Brain functional connectivity (FC)** (Fig. 1) may confer resilience.

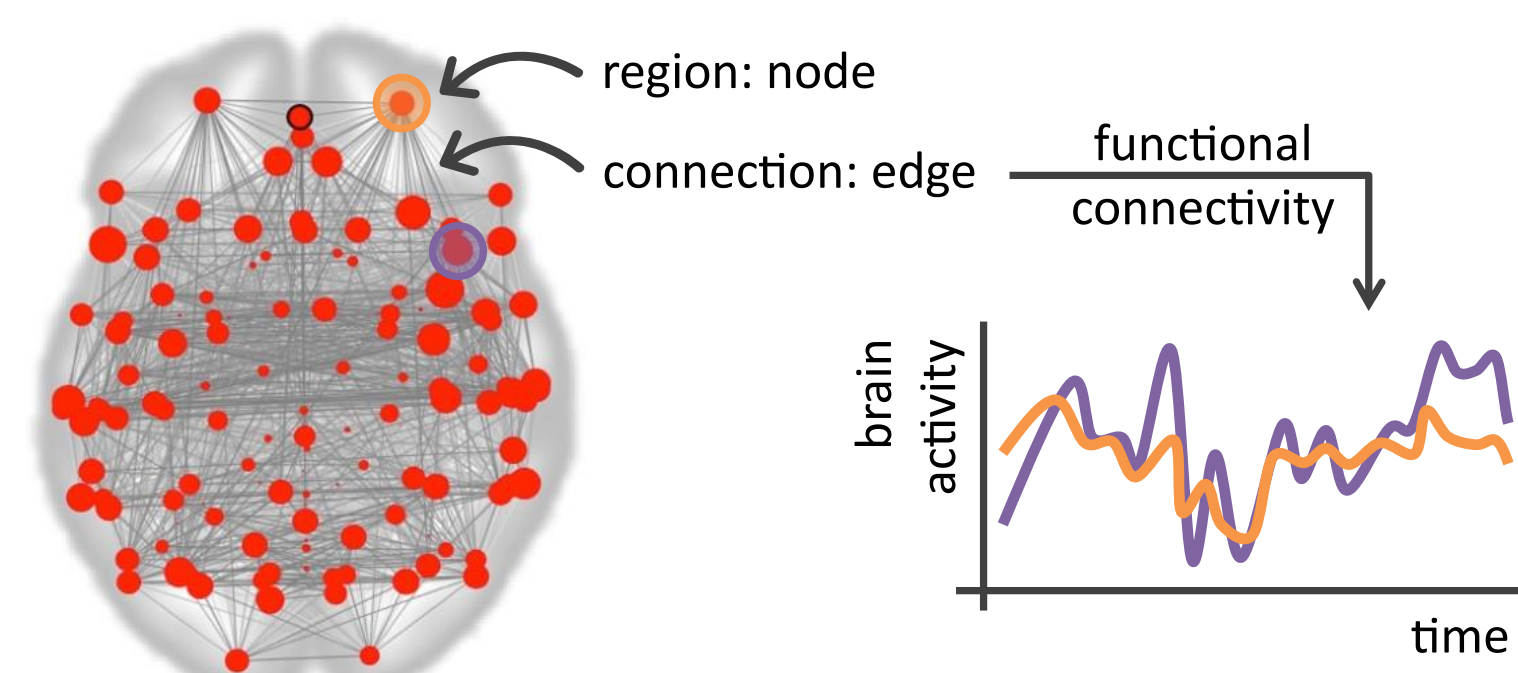


Fig. 1. Brain network diagram. In FC, an edge represents the temporal synchrony of brain activity of two regions.

FC is **disrupted** in individuals with amyloid- β (A β) pathology and AD, and A β tends to accumulate in hubs of the **default mode network (DMN)** [2].

Previous studies lack longitudinal data and sensitive preclinical biomarkers [3, 4]. Importantly, there is not a clear distinction of brain correlates of resilience to different vulnerability factors.

Aim

Identify functional network topologies that attenuate cognitive decline and hippocampal atrophy associated with ageing and A β pathology.

Methods

We analyzed **326** cognitively unimpaired participants at risk of AD from the **ALFA+** cohort.

A β and tau positivity (A+, T+) were defined using **CSF A β 42/40** and **p-tau181** with established cut-offs [5].

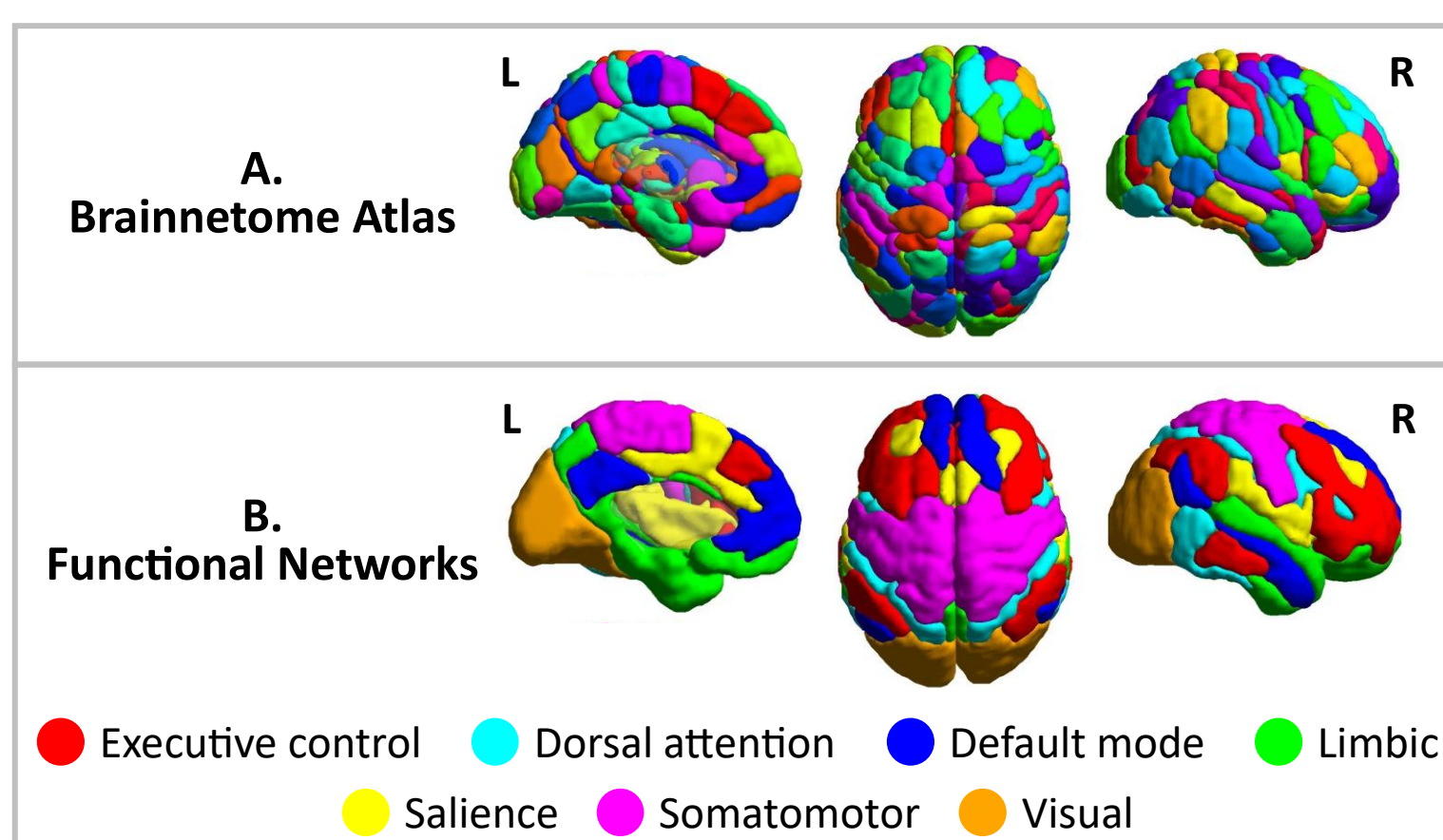


Fig. 2. A) 218 cortical regions of interest (ROIs) of the Brainnetome Atlas. B) ROIs assigned to seven functional networks [6].

Resting-state functional MRI (rs-fMRI) data were used to compute FC between Brainnetome Atlas regions (Fig. 2A). Regions were assigned to seven functional networks (Fig. 2B) [6], and graph metrics of **segregation** (specialization into modules), **integration** (information exchange across distributed regions) and **centrality** (importance of regions) were computed for each network.

Longitudinal outcomes were **cognitive composite scores** and **hippocampal subfield volumes** derived from ASHS (mean follow-up: 3.36 years).

Linear mixed-effect models first tested whether age and baseline A β status predict cognitive and hippocampal volume decline over time: $\text{Outcome}_{it} \sim \text{Time}_{it} \times \text{AdverseFactor}_i + \text{Covariates}_i + (1|\text{Subject}_i)$.

Then, we tested whether network topology moderated significant associations between adverse factors and outcome trajectories: $\text{Outcome}_{it} \sim \text{Time}_{it} \times \text{AdverseFactor}_i \times \text{NetworkTopology}_i + \text{Covariates}_i + (1|\text{Subject}_i)$.

Results

Sample demographics and functional networks

Mean age was 60.62 years (Table 1). Overall, functional networks were well defined, with high within-network connectivity (Fig. 3).

	Total (N=326)	A-T ₋ (n=215)	A+T ₋ (n=83)	A+T ₊ (n=28)	p-value
Age, y	60.62 ± 4.65	60.10 ± 4.41	60.95 ± 4.90	63.61 ± 4.57	< 0.001
Sex, f	205 (62.9%)	136 (63.3%)	50 (60.2%)	19 (67.9%)	0.76
Education, y	13.45 ± 3.56	13.53 ± 3.43	13.88 ± 3.71	11.61 ± 3.58	0.01
APOE- ϵ 4 carrier, n	174 (53.4%)	87 (40.5%)	70 (84.3%)	17 (60.7%)	< 0.001

Table 1. Baseline sample demographics by AT status.

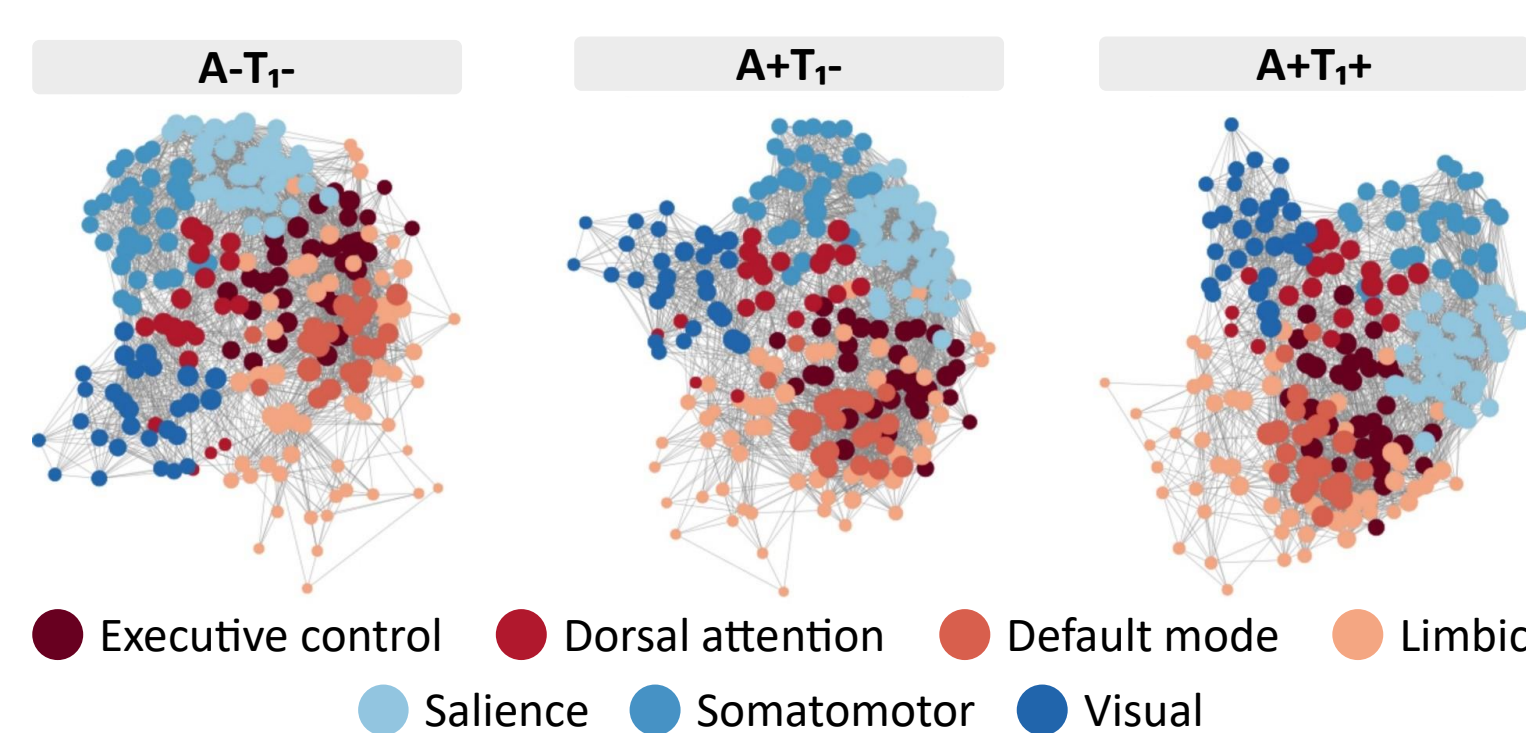


Fig. 3. Graph representation of the participants' functional networks (color-coded) by AT status. Closer regions have higher connectivity.

Age and A β pathology predict cognitive and hippocampal decline

Older age predicted steeper executive function decline and greater atrophy in the right CA1 and subiculum (SUB). **A β +** predicted steeper decline in executive function, episodic memory, and the Preclinical Alzheimer's Cognitive Composite (PACC), as well as greater right SUB atrophy.

Functional network organization moderates the relationship between adverse factors and decline

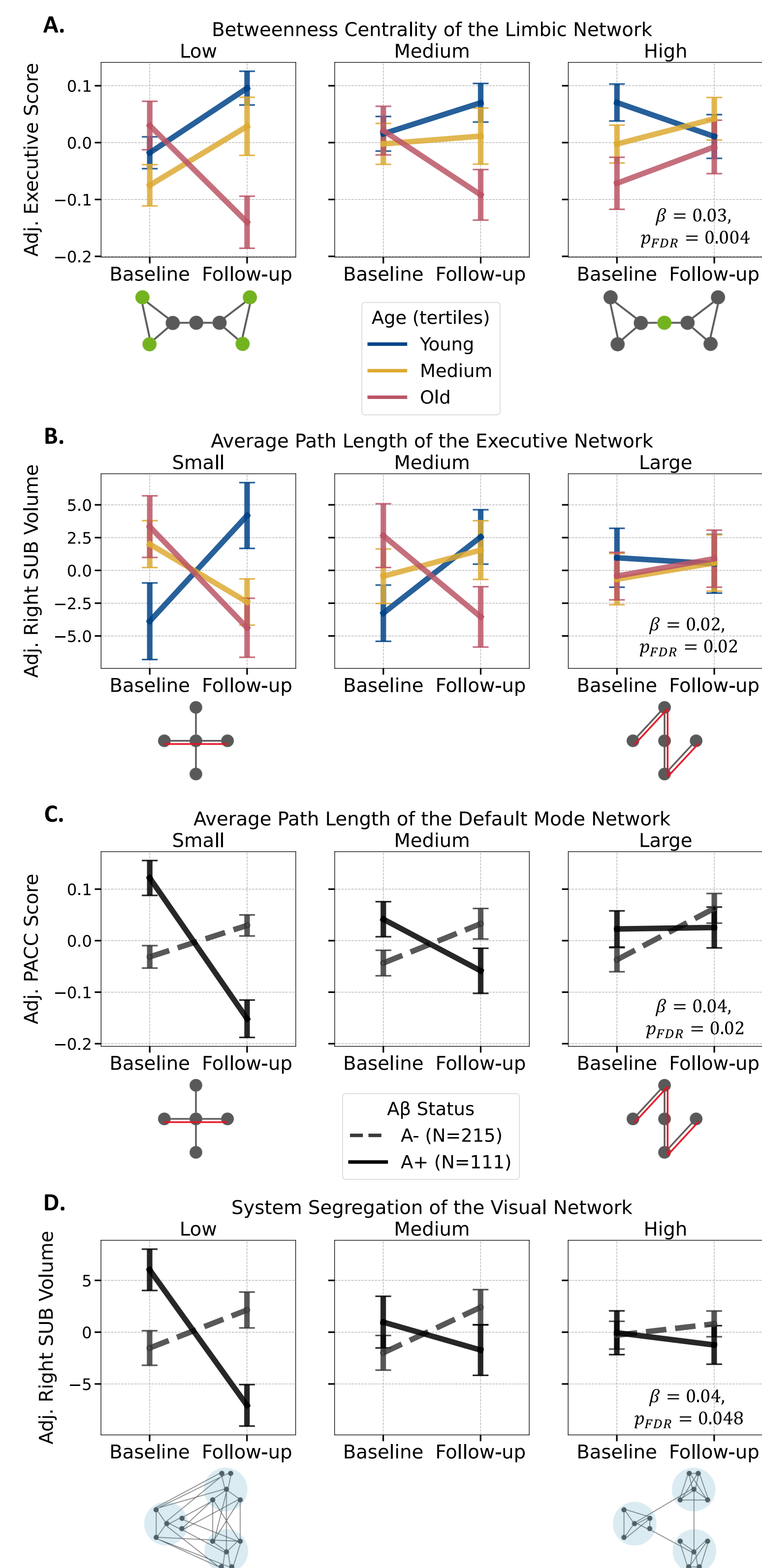


Fig. 4. Cognitive and hippocampal volume outcomes (adjusted for covariates) as a function of time, stratified by levels of network topology (boxes, from left to right) and adverse factors (lines).

Higher betweenness centrality of the limbic network (presence of bridging regions) moderated the **age-related decline in executive function** (Fig. 4A). Longer average path length (APL) between regions of the executive network (lower integration), moderated the age-related atrophy in the **right SUB** (Fig. 4B). Longer APL within the DMN moderated the **A β -related decline in PACC** (Fig. 4C). Higher segregation of the visual network moderated the **A β -related atrophy in the right SUB** (Fig. 4D). Fig. 5 includes the remaining significant results.

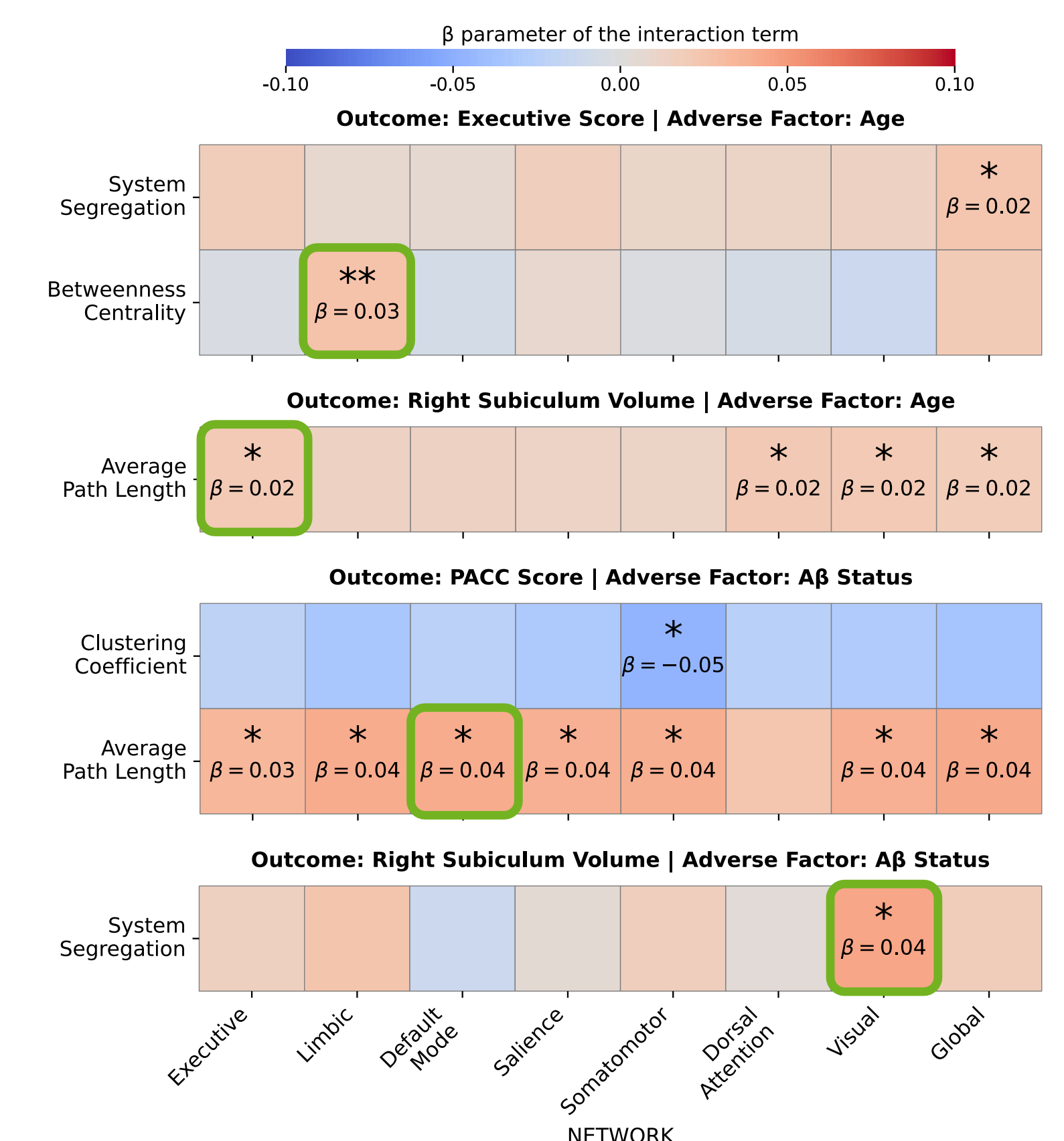


Fig. 5. Summary of all significant graph measures (rows) of each network (columns). Green squares highlight the results in Fig 4.

Conclusions

- Our findings suggest that **brain functional organization**, including longer paths between regions and greater network segregation, may **buffer decline** due to vulnerability factors.
- The identified network topologies were **dissociable** across **outcomes** (cognition vs. hippocampal volumes) and **adverse factors** (age vs. A β pathology).
- These measures may serve as **in vivo markers** of **cognitive and neurodegenerative resilience** in individuals at risk of AD.

References

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