

Stage-dependent Neural Reconfiguration Of Cognitive Reserve

: From Efficiency To Selective Preservation

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INTRODUCTION

Cognitive reserve (CR) explains the discrepancy between neuropathological burden and cognitive function, yet its underlying mechanisms remain paradoxical—manifesting as neural efficiency in health but compensatory activation in disease. We hypothesized that CR is not a static buffer but operates through stage-dependent neural reconfiguration across the aging-dementia continuum.

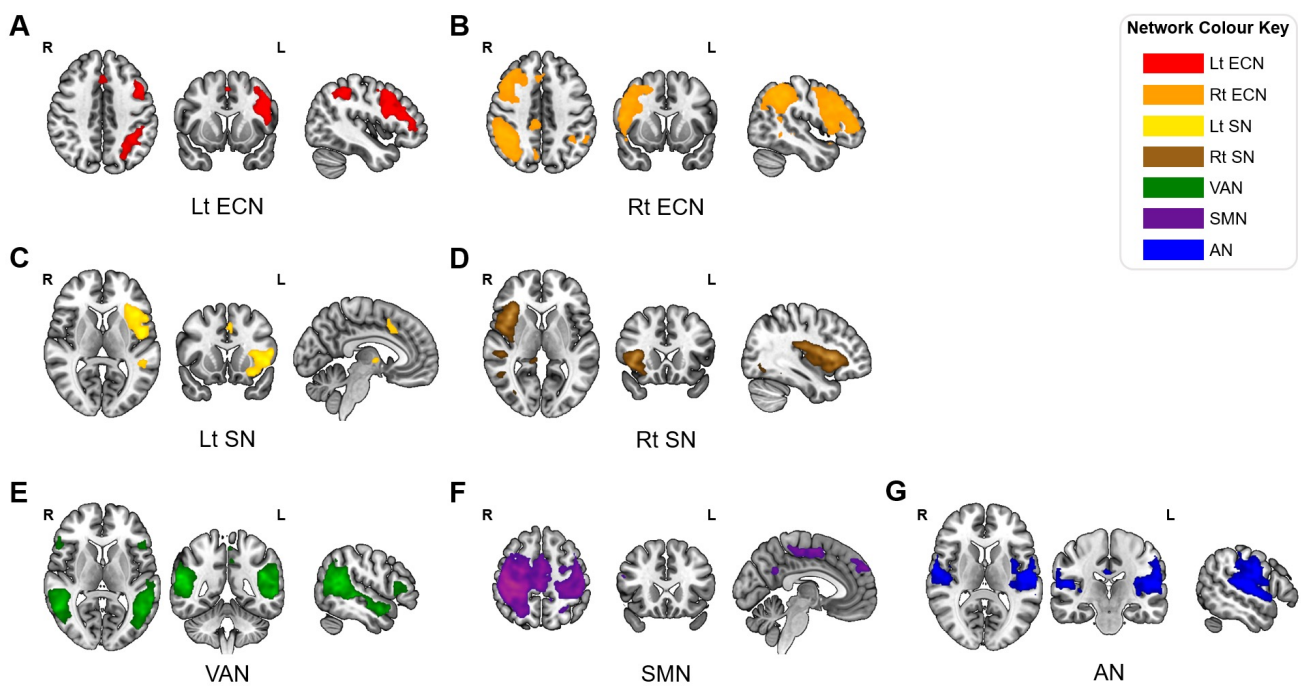


Figure 1 Spatial topography of the seven resting-state networks. Group-level spatial maps of the seven independent components are shown. The maps were derived by applying one-sample *t*-tests (family-wise error [FWE]-corrected $P < 0.05$, cluster size ≥ 64) to the component maps obtained from the cognitively normal (CN) group ($n = 37$). These thresholded maps demonstrate canonical resting-state network topography and served as the basis for defining the network pairs in subsequent functional connectivity (FC) interaction analyses. **The seven networks shown are:** (A) Lt ECN, (B) Rt ECN, (C) Lt SN, (D) Rt SN, (E) VAN, (F) SMN and (G) AN. AN = auditory network; CN = cognitively normal; ECN = executive control network; FC = functional connectivity; FWE = family-wise error; Lt = left; Rt = right; SMN = sensorimotor network; SN = salience network; VAN = ventral attention network.

METHODS

- Resting-state fMRI data from 120 participants representing the full cognitive spectrum (Table 1).
- Independent component analysis (ICA) was used to extract connectivity between seven canonical networks (Figure 1)
- Hierarchical linear models adjusted for age, sex, and APOE $\epsilon 4$ status to test three-way interactions (Disease Stage $\times$ CR $\times$ Connectivity) on cognitive performance.

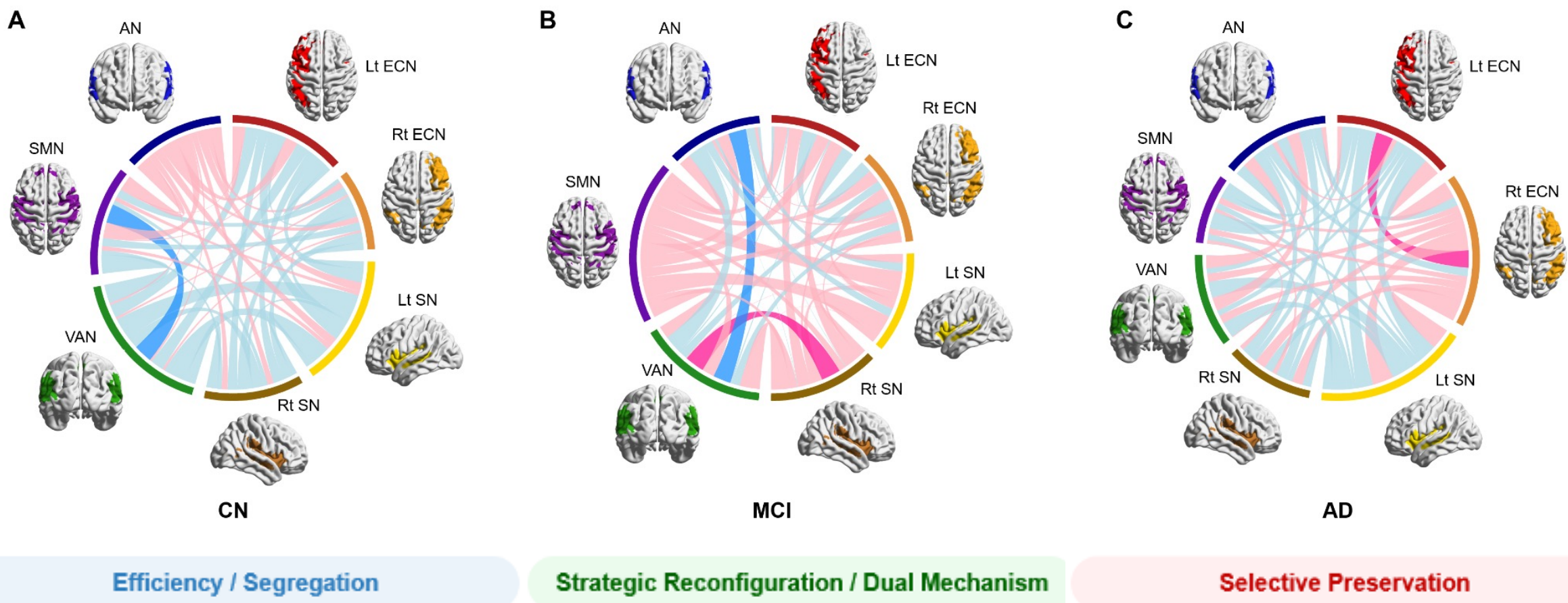
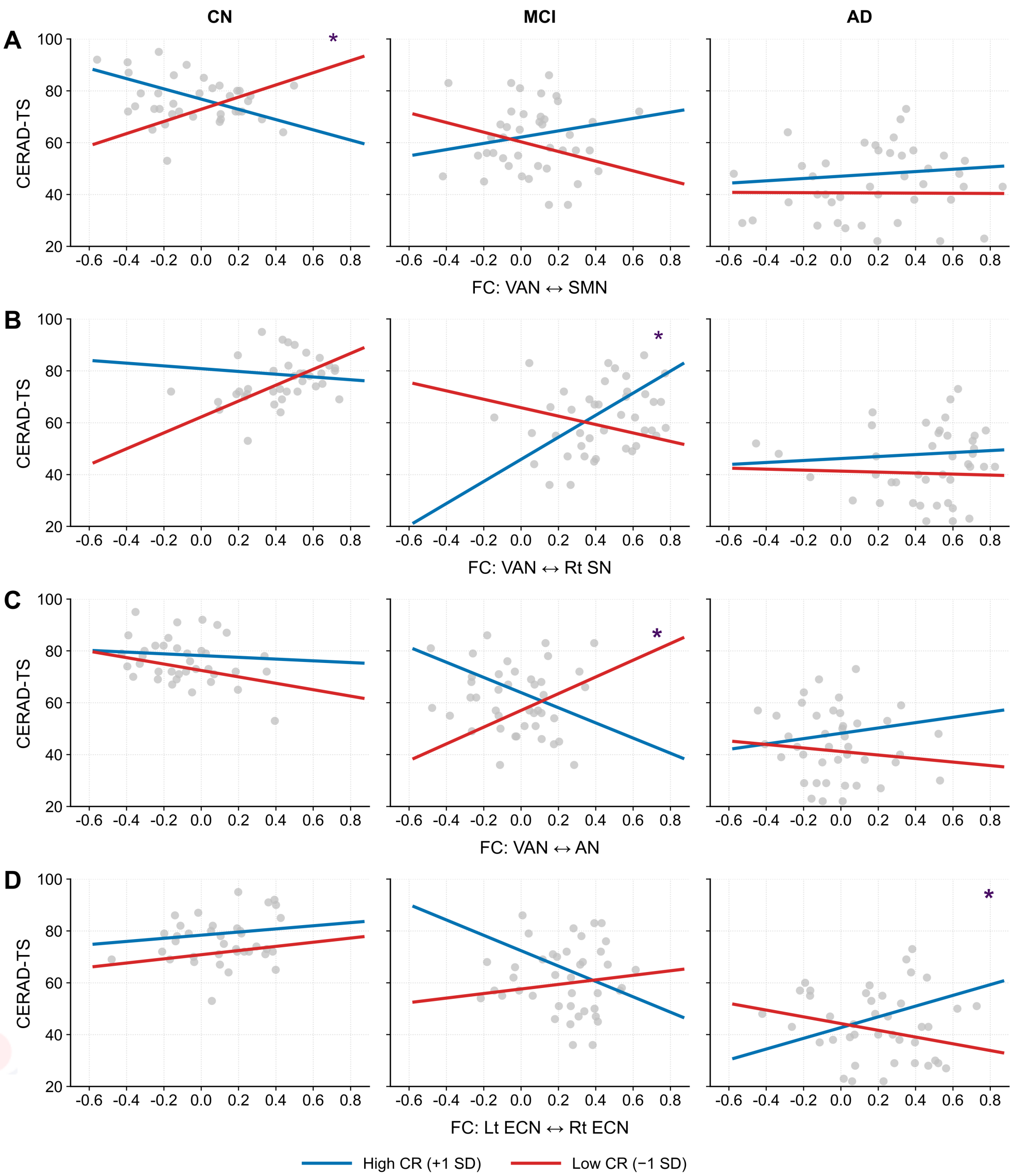


Figure 2 Visualisation of stage-dependent cognitive reserve (CR) modulation on functional connectivity (FC). Chord diagrams illustrate how cognitive reserve differentially modulates the association between inter-network functional connectivity (FC) and cognitive performance (CERAD-TS)

RESULTS

- Four network pairs demonstrated significant three-way interactions (all $p < .05$), revealing distinct CR strategies. (Table 2, Figure 2-3)

Figure 3 Cognitive reserve moderates the association between functional connectivity and cognitive performance in a stage-dependent manner. Interaction plots depict the relationship between x-axis [functional connectivity (FC)] and y-axis [cognitive performance (CERAD-TS)] at high and low levels of cognitive reserve (CR), defined as one standard deviation (SD) above (high) and below (low) the mean. Blue and red lines indicate predicted values at high and low CR, respectively, and grey dots represent individual data points. (A) VAN $\leftrightarrow$ SMN, (B) VAN $\leftrightarrow$ Rt SN, (C) VAN $\leftrightarrow$ AN and (D) Lt ECN $\leftrightarrow$ Rt ECN.



CONCLUSIONS

CR operates through stage-dependent neural mechanisms, transitioning from efficiency to strategic reconfiguration to selective preservation across the disease continuum.

The MCI stage emerges as a critical therapeutic window characterized by maximal network flexibility, informing the development of precision interventions.

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	CN (n = 37)	MCI (n = 41)	AD (n = 42)	Total (n = 120)	Statistics ^a		Post-hoc ^b
					F or χ^2	P	
Age, y, mean (SD)	72.51 (8.28)	75.02 (5.75)	75.33 (6.45)	74.36 (6.91)	1.96	0.145	
Sex, female, n (%)	24 (64.9)	31 (75.6)	33 (78.6)	88 (73.3)	2.05	0.358	
Education, y, mean (SD)	13.11 (3.85)	12.15 (3.73)	11.00 (4.80)	12.04 (4.22)	2.53	0.084	
MMSE, mean (SD)	27.95 (2.31)	25.27 (3.96)	18.17 (5.00)	23.61 (5.72)	65.13	< 0.001	CN > MCI > AD
CERAD-TS, mean (SD)	76.27 (8.70)	61.34 (12.88)	43.45 (13.93)	59.68 (18.03)	72.17	< 0.001	CN > MCI > AD
GDS, mean (SD)	1.86 (0.35)	2.90 (0.66)	4.21 (0.78)	3.04 (1.15)	136.63	< 0.001	CN < MCI < AD
APOE $\epsilon 4$ carriers, n (%)	6 (16.2)	17 (41.5)	25 (59.5)	48 (40.0)	15.43	< 0.001	CN < MCI, CN < AD
Amyloid PET positive, n (%)	12 (32.4)	27 (65.9)	42 (100.0)	81 (67.5)	-	< 0.001	CN < MCI < AD

Table 1 Demographic and clinical characteristics of participants

^aANOVA for continuous variables [$F(2, 117)$] and chi-square test [$\chi^2(2)$] or Fisher's exact test for categorical variables, as appropriate. ^bPairwise group comparisons were performed with Tukey's honestly significant difference (HSD) test for continuous variables. For APOE $\epsilon 4$ carriers and amyloid PET positivity, post-hoc pairwise Fisher's exact tests with Holm correction were conducted. AD = Alzheimer's disease; APOE = apolipoprotein E; CERAD-TS = Consortium to Establish a Registry for Alzheimer's Disease – Total Score; CN = cognitively normal; GDS = Global Deterioration Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PET = positron emission tomography, SD = standard deviation; y = years.

Functional connectivity	Disease stage $\times$ CR $\times$ FC		CR $\times$ FC					
	F(2, 117) ^a	P	CN		MCI		AD	
			β^b	P	β^b	P	β^b	P
VAN $\leftrightarrow$ SMN	3.75	0.027	-0.33 ^{c,d}	0.008	0.20 ^c	0.147	0.00 ^e	0.977
VAN $\leftrightarrow$ Rt SN	3.85	0.024	-0.19 ^c	0.102	0.31 ^{c,d}	0.022	0.01 ^d	0.918
VAN $\leftrightarrow$ AN	3.99	0.021	0.04 ^c	0.607	-0.28 ^{c,d}	0.032	0.16 ^d	0.132
Lt. ECN $\leftrightarrow$ Rt ECN	3.85	0.024	-0.07	0.568	-0.19 ^d	0.148	0.22 ^d	0.031

Table 2 Cognitive reserve (CR) as a stage-dependent moderator of the relationship between functional connectivity (FC) and cognitive performance (CERAD-TS)

^aThe overall three-way interaction (disease stage $\times$ CR $\times$ FC) was tested by comparing a full model (including all lower-order terms and the three-way interaction) with a reduced model (excluding the three-way interaction) using ANOVA. All models were adjusted for covariates (age, sex and APOE $\epsilon 4$ carrier status). ^b β values represent unstandardized regression coefficients for the CR (years of education) $\times$ FC interaction term within each diagnostic group (disease stage). Bold indicates significant interaction effects within each group at $P < 0.05$. Superscript letters denote significant pairwise differences in the interaction effects: ^cCN vs. MCI, $P < 0.05$; ^dMCI vs. AD, $P < 0.05$; ^eCN vs. AD, $P < 0.05$. AD = Alzheimer's disease; AN = auditory network; CERAD-TS = Consortium to Establish a Registry for Alzheimer's Disease – Total Score; CN = cognitively normal; CR = cognitive reserve; ECN = executive control network; FC = functional connectivity; Lt = left; MCI = mild cognitive impairment; Rt = right; SMN = sensorimotor network; SN = salience network; VAN = ventral attention network.