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NEUROIMAGING

Connectome-based predictions of cognition and sex differences in midlife individuals at risk for Alzheimer's Disease

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Abstract

Background: Females generally show better memory performance, particularly in episodic memory, than males across the lifespan [1-3]. However, two-thirds of Alzheimer's disease (AD) cases occur in females, who experience more rapid cognitive decline and brain atrophy in the presence of AD-related neuropathology [4]. The functional brain architecture underlying episodic and relational memory in middle-aged individuals—and whether this differs by sex—remains poorly understood. This study aimed to identify the functional brain architecture associated with episodic and relational memory using a data-driven approach, focusing on sex differences.

Method: Resting-state functional MRI data and neuropsychological assessments were obtained from 488 cognitively healthy individuals (316 F/172 M), aged 40-59 years, from the PREVENT-Dementia study. Connectome-based predictive modeling (CPM) was used to identify functional brain networks related to episodic and relational memory across the entire cohort, within female-only and male-only subgroups. Model generalizability was evaluated using data from the Cambridge Center for Ageing and Neuroscience (Cam-CAN) dataset.

Result: CPM identified both positive and negative networks significantly associated with episodic and relational memory in the entire cohort (positive: r = 0.16, $p < 0.001$; negative: r = 0.10, $p = 0.017$; Figure 1A). These networks were particularly characterized by within-network and between-network connections involving default mode and cingulo-opercular networks in the positive network (Figure 2A). Sex-stratified analyses revealed distinct model performance: both positive and negative networks predicted episodic and relational memory in the female-only group (positive: r = 0.18, $p_{\text{-corrected}} = 0.002$; negative: $r = 0.11$, $p_{\text{-corrected}} = 0.048$; Figure 1B), whereas only the negative network predicted episodic and relational memory in the male-only group (positive: r = 0.01, $p_{\text{-corrected}} = 0.836$; negative: r = 0.16, $p_{\text{-corrected}} = 0.048$; Figure 1C)

after Bonferroni correction. These results didn't generalize to the external Cam-CAN dataset.

Conclusion: We identified brain networks underlying episodic and relational memory in middle-aged individuals, revealing sex-specific differences. These findings suggest potential sex-specific mechanisms in memory-related brain networks during midlife, which may contribute to differing trajectories of cognitive decline in aging and Alzheimer's disease. However, the lack of generalizability to an external dataset underscores the need for further validation in diverse populations.

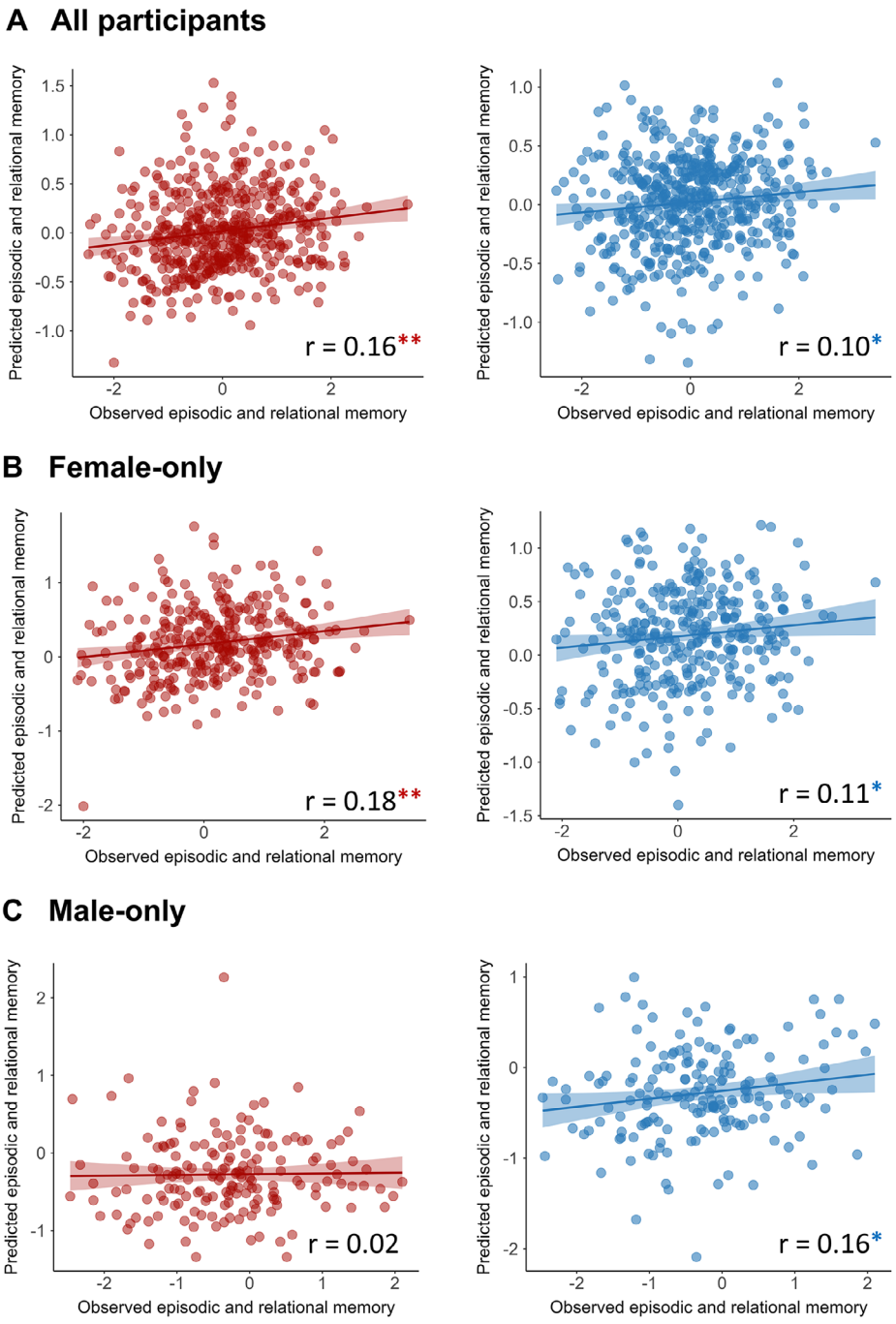

Figure 1. The predictive performances of CPM models. Correlation between observed and predicted episodic and relational memory in positive and negative networks for (A) all participants, (B) female-only group, and (C) male-only group. Red and blue lines/scatters represent positive and negative networks respectively. * = $p < 0.05$, ** = $p < 0.005$.

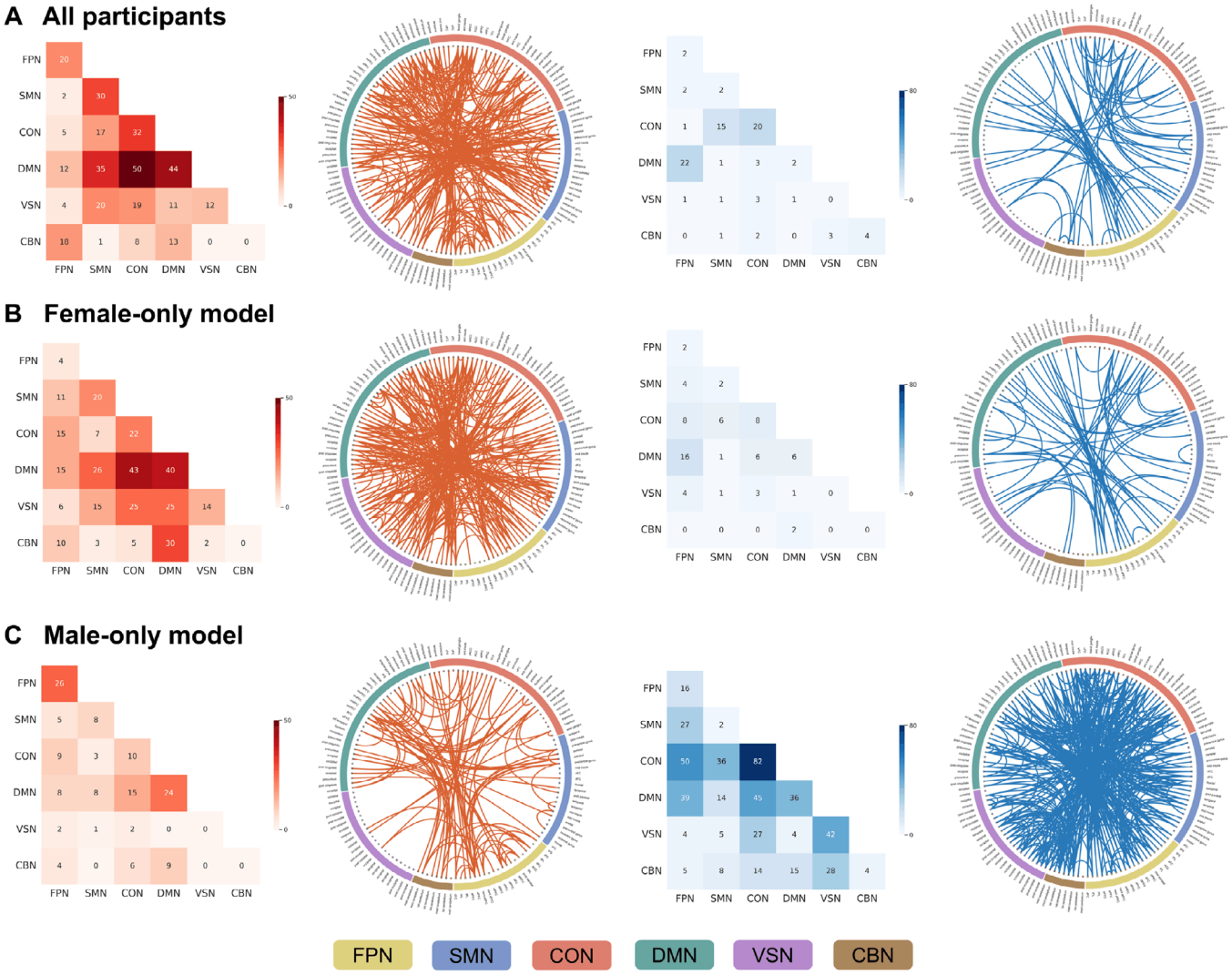

Figure 2. Connectome of positive and negative networks of episodic and relational memory. Connectivity matrices and circular plots of positive and negative networks of episodic and relational memory for (A) all participants, (B) female-only group, and (C) male-only group. Red and blue matrices/spheres represent positive and negative networks respectively. Abbreviation: FPN, frontoparietal network; SMN, sensorimotor network; CON, cingulo-opercular network; DMN, default mode network; VSN, visual network; CBN, cerebellum network.