**Enhanced resting-state functional connectivity between memory-task activation peaks is associated with memory impairment in MCI.**

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**Background:** Resting-state functional MRI is altered in Alzheimer’s disease (AD) and amnestic mild cognitive impairment (aMCI) but the correlates of episodic memory function are debated. Task-related fMRI studies have revealed a set of brain regions typically activated during episodic memory and may thus inform the search for correlates of episodic memory during resting state fMRI. Here, we aimed to assess whether resting-state activity in core brain regions for episodic memory defined by task fMRI is altered in AD and predicts memory performance in aMCI.

**Methods:** Twenty-three cognitively healthy elderly controls (HC) with normal biomarker levels of amyloid-beta, 76 aMCI subjects, and 19 AD dementia patients. Eighteen peak coordinates of brain activation during successful memory retrieval were selected from a previous meta-analysis of task-related fMRI. Using resting state fMRI scans, we placed spherical regions of interest (ROI) at each of the 18 coordinates to compute ROI-to-ROI functional connectivity. Differences in ROI-to-ROI functional connectivity between AD dementia and HC were determined, cross-validated in aMCI and tested as a predictor of memory impairment in regression analyses.

**Results:** Patients with AD dementia showed higher levels of functional connectivity between ROIs within the parahippocampus, parietal cortex and the lateral prefrontal cortex compared to HC (FDR - corrected \( P<0.05 \)). Cross-validation in MCI confirmed abnormally increased functional connectivity for each of these connections. The increase in functional connectivity between the parahippocampus and middle frontal gyrus was associated with reduced episodic memory performance in aMCI \( (\beta=-0.37; \text{95\% CI, -0.72 to -0.03, } P=0.036) \), independent of global amyloid-beta PET binding and APOE ε4-carrier status.

**Conclusions:** Increased functional connectivity between the parahippocampus and the middle frontal gyrus is predictive of impaired episodic memory in aMCI and may reflect overcompensation within the episodic-memory related functional neural network.
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