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NEUROIMAGING

Episodic memory network connectivity with aging and Alzheimer's disease pathology in cognitively unimpaired older adults

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Abstract

Background: Regions of the medial temporal lobe and posteromedial cortex are crucial for episodic memory and are among the first to be affected by Alzheimer´s disease (AD) pathology. Hyperconnectivity in association with amyloid and tau pathology has been found in preclinical stages of AD, and may be compensatory or detrimental to memory function. Aiming to identify distinct connections displaying aberrant resting-state functional connectivity (rsFC), we hypothesized lower rsFC with higher age in non-pathological aging, and higher rsFC with higher pathology burden, especially in *APOE4* carriers.

Method: In this preregistered study, we analysed cross-sectional resting-state fMRI data and blood- and PET-markers of amyloid, tau and *APOE* status from an observational aging cohort (SFB1436). RsFC strength was examined between predefined ROIs. The sample included 187 cognitively unimpaired older adults (71±7years, 92 female, 44 *APOE4* carrier). We investigated associations between rsFC, AD pathology burden, and CAG (cognitive age gap) and potential *APOE* interactions. Multiple regression models and a moderation analysis with rsFC strength were used. An A-T- subcohort was formed to investigate the effect of age on rsFC and to differentiate it from the effect of pathology.

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Result: We found a significant association between higher blood-based pathology and low rsFC in the right posterior hippocampus to bilateral subgenual medial prefrontal cortex (mPFC). No significant association was observed between rsFC and tau-PET burden, APOE4 status or age (within A-T-subcohort). Additionally, there was no significant effect of pathology on CAG. Furthermore, we found no evidence of rsFC moderating the relationship between pathology and CAG.

Conclusion: Our results do not support the initial hypothesis, which predicted hyperconnectivity in distinct brain regions with high pathology. This could be due to relatively low overall pathology burden, consistent with an early preclinical stage of potential disease progression. This interpretation is further supported by the absence of significant associations between pathology or rsFC strength and memory performance. We identified lower rsFC strength in two distinct connections with higher blood-based pathology. These alterations were not observed in the A-T-subcohort, suggesting it to be an early marker differentiating pathological from healthy aging.

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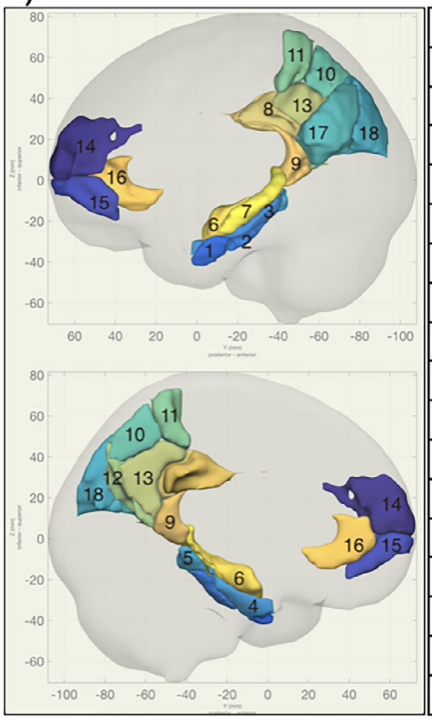
a)

	N (f/m)	Ø Age	Ø Edu Yrs	ApoE e4 carriers	Ø AT_Term	Ø MetaROI DVR	Ø CAG
Whole Sample	187 (92/95)	71±7	15±2	44	1.53±1.32	0.92±0.06	-0.08±4.1
Blood Sample	187 (92/95)	71±7	15±2	44	1.53±1.32	0.92±0.06	-0.08±4.1
Tau PET Sample	117 (51/66)	71±7	15±2	30	1.52±1.21	0.92±0.06	0.02±4.05
A-T- Subcohort (AT_Term ≤ 1.97)	156 (76/80)	70±6	15±2	29	1.08±0.3	0.9±0.06	-0.3±4.03

b)



1	Anterior Perirhinal Cortex (PRC)	PhG_L(R)_6_1
2	Posterior Perirhinal Cortex (PRC)	PhG_L(R)_6_2
3	Lateral Posterior Parahippocampal Cortex (PHC)	PhG_L(R)_6_3
4	Entorhinal Cortex (EC)	PhG_L(R)_6_4
5	Medial Posterior Parahippocampal Cortex (PHC)	PhG_L(R)_6_6
6	Anterior Hippocampus (aHC)	Hipp_L(R)_2_1
7	Posterior Hippocampus (pHC)	Hipp_L(R)_2_2
8	Posterior Cingulate Cortex (PCC)	CG_L(R)_7_1
9	Retrosplenial Cortex (RSC)	CG_L(R)_7_4
10	Lateral Precuneus (PCun)	PCun_L(R)_4_1
11	Superior Precuneus (PCun)	PCun_L(R)_4_2
12	Inferior Precuneus (PCun)	PCun_L(R)_4_3
13	Medial Precuneus (PCun)	PCun_L(R)_4_4
14	Superior Medial Prefrontal Cortex (mPFC)	SFG_L(R)_7_7
15	Inferior Medial Prefrontal Cortex (mPFC)	OrG_L(R)_6_1
16	Subgenual Medial Prefrontal Cortex (mPFC)	CG_L(R)_7_7
17	Anterior Angular Gyrus (AG)	IPL_L(R)_6_5
18	Posterior Angular Gyrus (AG)	IPL_L(R)_6_1

Figure 1. Study design and a priori defined ROIs a) All participants were healthy, cognitively unimpaired and ≥60 years old. Each participant had one baseline resting-state fMRI scan and *APOE* status available. For blood amyloid and tau burden, the 1/Abeta1-42/1-40 *pTau217 (AT_Term) was used. Brain tau pathology (MetaROI DVR) was assessed using 60-minute dynamic PET imaging with the radiotracer [18F]PI-2620. To assess memory function, we used a cognitive age gap (CAG) measure. Numbers (N) describe the samples after exclusions due to MRI quality control. A blood based pathology and a Tau PET sample were formed that included all the participants that had blood based pathology or tau PET status available, respectively. A non-pathological (A-T-) cohort was formed by excluding all participants with AT_Term>1.97. The cut-off point was determined using Gaussian mixture modelling. **b)** 18 ROIs were selected based on their involvement in episodic memory function. Both hemispheres were included, resulting in a total of 36 ROIs. The regions were defined using the Brainnetome atlas.
fMRI = Functional Magnetic Resonance Imaging, PET = Positron Emission Tomography, ROI = Region of Interest.

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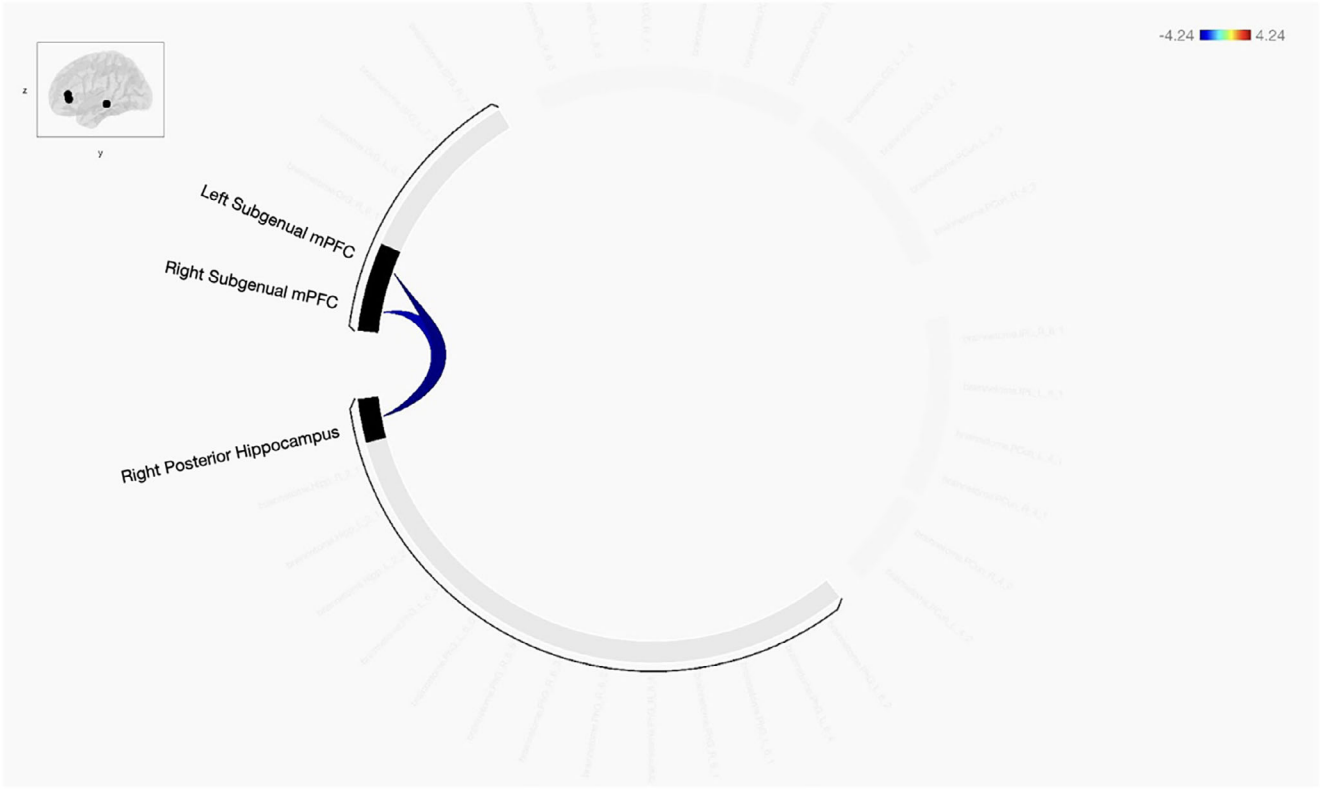

Figure 2. Functional connectivity strength in relation to Alzheimer's pathology burden in cognitively unimpaired older adults. Analysis of functional data was carried out with the Matlab toolboxes SPM and Conn. We observed reduced rsFC strength between the right posterior Hippocampus and bilateral subgenual mPFC. The model included the effect of AT_Term on rsFC, and *APOE* status, age and sex as covariates. Network based statistics were used with a connection threshold of p<0.001 and a cluster threshold of p<0.05 and a two-sided test.
Connection brainnetome.Hipp_R_2_2 -brainnetome.CG_L_7_7 T(182) = -4.24, p-unc: 0.000035
Connection brainnetome.Hipp_R_2_2 -brainnetome.CG_R_7_7 T(182) = -3.78 p-unc: 0.000216
rsFC = resting-state functional connectivity, mPFC = medial prefrontal cortex

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