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NEUROIMAGING

Change in functional connectivity strength during rest and encoding is differentially related to Alzheimer's pathology and memory depending on *APOE* genotype

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Abstract

Background: The medial temporal lobe (MTL) and posteromedial cortex (PMC) are essential for episodic memory and affected early by Alzheimer's pathology, particularly in *APOE4* carriers. Functional connectivity (FC) changes within and between MTL and PMC could be detrimental or beneficial for cognition. However, the relation of those changes to Alzheimer's pathology and memory performance is unclear and most studies assess FC only during rest. We hypothesized that increasing FC strength would be associated with higher pathology burden, especially in *APOE4* carriers.

Method: In this preregistered study, we analysed longitudinal 3-Tesla fMRI over up to 4 years and cross-sectional amyloid-beta and tau PET (PREVENT-AD cohort; details in Figure 1). We assessed changes in resting-state FC (RSFC) and task-FC during intentional object-location encoding within ($\Delta FC_{PMC,}$ ΔFC_{MTL}) and between MTL and PMC ($\Delta FC_{MTL\text{-}PMC}$). The sample included 152 cognitively unimpaired older adults (63±5years, 102 female, 59 *APOE4*). We investigated associations between ΔFC strength with i) pathology burden and ii) change in delayed memory (RBANS composite score and fMRI-task object recognition), and interactions with *APOE* genotype. We used multiple regression and linear mixed models including *APOE*, age, sex and education.

Result: We found ΔFC by APOE interactions predicting pathology. Specifically, declining $RSFC_{PMC}$ ($p = 0.038$; Figure 2a) was related to more global amyloid in *APOE4* carriers only. In contrast, increasing encoding-FC_{MTL} was related to more entorhinal tau in *APOE4* carriers only ($p = 0.032$, Figure 2b). Regarding cognition, regardless of *APOE* status, increasing encoding-FC_{PMC} was related to decreasing RBANS ($p = 0.018$)

performance and object recognition ($p = 0.001$). Finally, increasing $RSFC_{MTL\text{-}PMC}$ was related to increasing RBANS performance ($p = 0.032$; Figure 3a), but increasing encoding-$FC_{MTL\text{-}PMC}$ was related to decreasing object recognition ($p = 0.014$; Figure 3b).

Conclusion: Our study shows *APOE*-dependent and region-specific associations of ΔFC strength within and between episodic memory areas with pathology burden and memory performance. Notably, associations differed between RSFC and task-FC. In *APOE4* carriers, longitudinally increasing FC or "hyperconnectivity" within MTL during encoding was related to tau in line with our hypothesis. However, in PMC, longitudinally decreasing FC during rest was related to more amyloid, indicating a disconnection in PMC regions. Our study highlights that pathology-related network changes manifest differentially during rest and task (memory encoding).

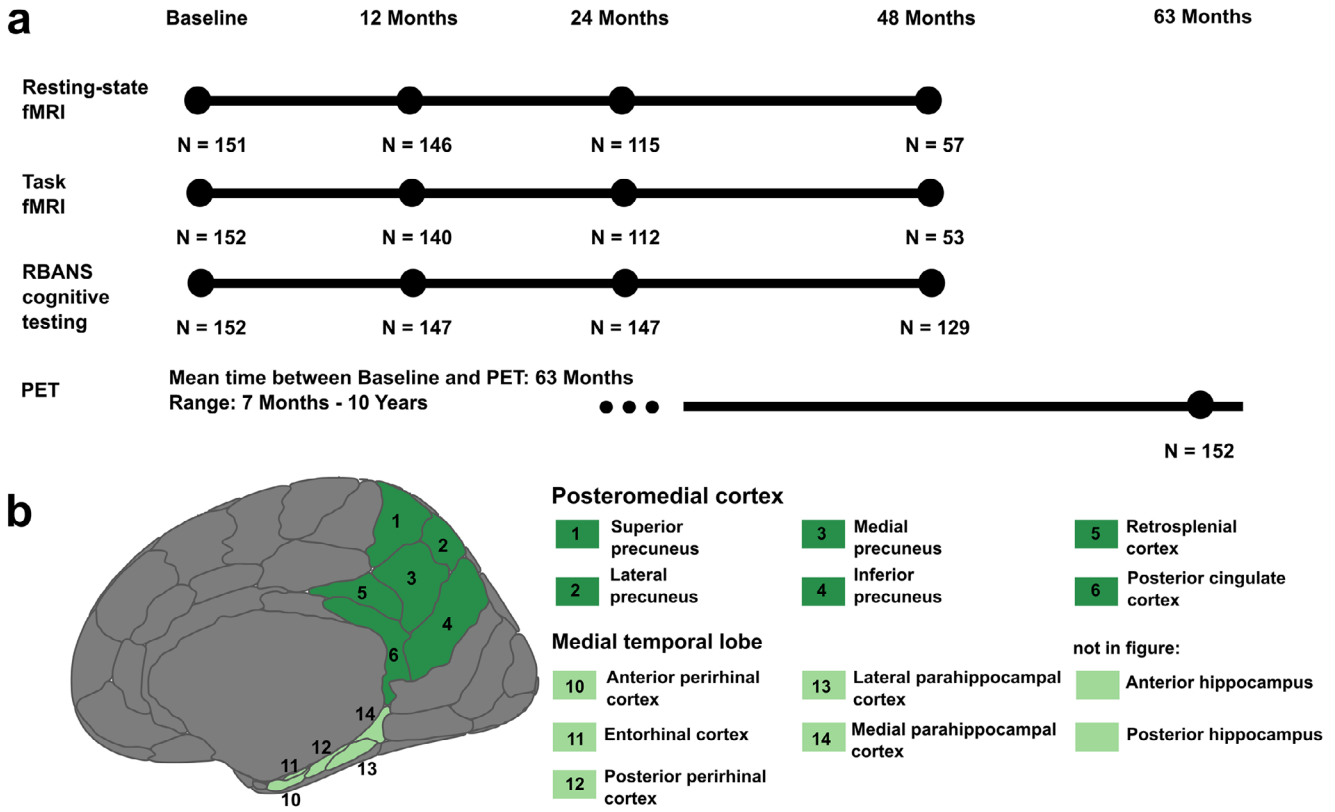

Figure 1. Study design and a priori defined regions of interest (ROIs) in cognitively normal older adults. a) Each participant underwent at least one baseline resting-state and task fMRI session and between 1 and 4 yearly follow-up fMRI examinations, with the last scan taking place 4 years (48 months) after baseline. Similarly, neuropsychological RBANS assessments were conducted at baseline and at yearly follow-up examinations. Participants also underwent PET scanning to quantify amyloid using ^{18}F-NAV4694 and tau using ^{18}F-flortaucipir. This took place between 7 months and 10 years after the baseline session. Whole-brain amyloid and entorhinal tau was assessed. Numbers (N) of data for each session and modality describe the cohort after exclusions due to MRI quality control. The study was preregistered under https://doi.org/10.17605/OSF.IO/NFRB5. **b)** The posteromedial cortex (PMC) ROI (dark green) comprised the retrosplenial cortex, posterior cingulate cortex, and four subregions of the precuneus. The medial temporal lobe (MTL) ROI (light green) comprises the anterior and posterior perirhinal cortex, entorhinal cortex, lateral and medial parahippocampal cortex, and anterior and posterior hippocampus. Regions were defined using the Brainnetome atlas. The CONN toolbox was used for preprocessing fMRI data and creation of first-level functional connectivity matrices. Mean functional connectivity was calculated for all regions within the MTL ROI, all regions within the PMC ROI, and between MTL and PMC regions separately for resting-state and encoding fMRI sessions. R was used for regression and linear mixed models. fMRI = Functional Magnetic Resonance Imaging, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, ROI = Region of Interest, PET = Positron Emission Tomography.

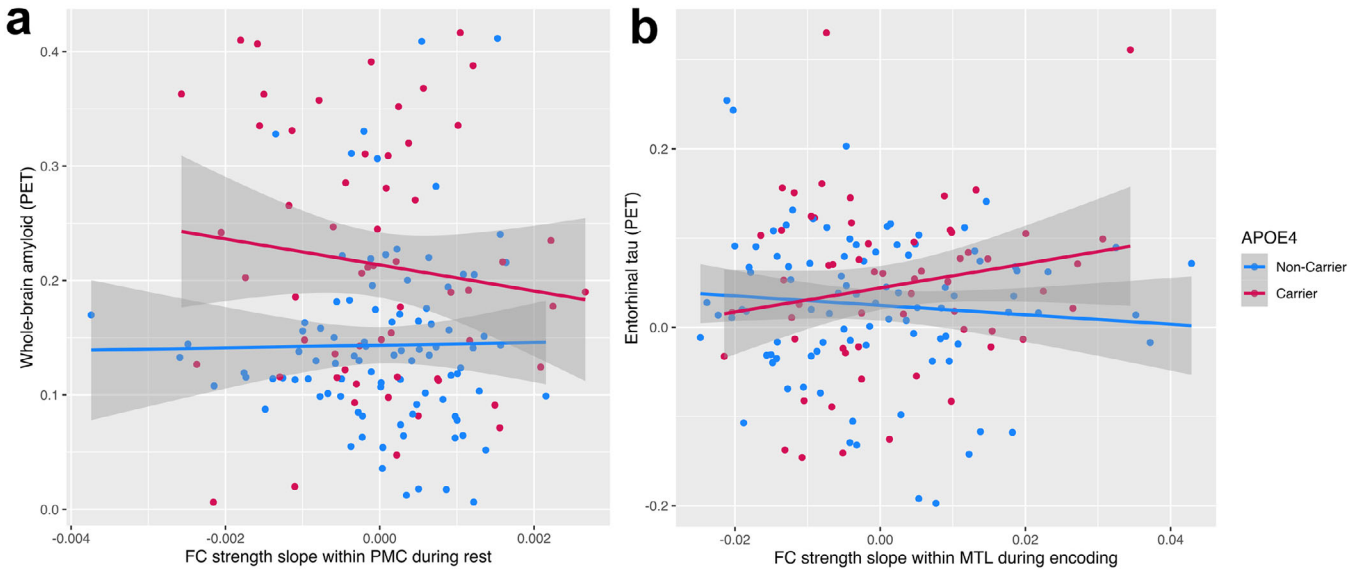

Figure 2. Functional connectivity (FC) strength during rest and encoding over time and the relationship with Alzheimer's pathology measured via PET imaging. a) The mean resting-state FC (RSFC) strength within posteromedial cortex (PMC), meaning the mean FC strength between PMC subregions, decreased over time (p=0.004). There was no difference in RSFC over time due to *APOE* genotype (p=0.639). Longitudinal $RSFC_{PMC}$ was differentially related to later whole-brain amyloid depending on *APOE* (p=0.038), with *APOE4* carriers showing more later amyloid with declining $RSFC_{PMC}$ (p=0.054) but not *APOE4* non-carriers (p=0.944). Further, declining $RSFC_{MTL}$ was related to more later amyloid regardless of *APOE* genotype (p=0.049). Amyloid was box-cox transformed. There were no associations of encoding-FC and later amyloid (all p>0.05). **b)** The mean FC strength during intentional encoding within medial temporal lobe (MTL), meaning the mean FC strength between MTL subregions, did not decrease significantly over time (p=0.232). There was no difference in encoding-FC over time due to *APOE* genotype (p=0.500). Longitudinal encoding-FC_{MTL} was differentially related to later entorhinal tau depending on *APOE* (p=0.049), with *APOE4* carriers showing more later tau with increasing encoding-FC_{MTL} (p=0.032) but not *APOE4* non-carriers (p=0.654). Tau was box-cox transformed. There were no associations of RSFC and later tau (all p>0.05). PET = Positron Emission Tomography.

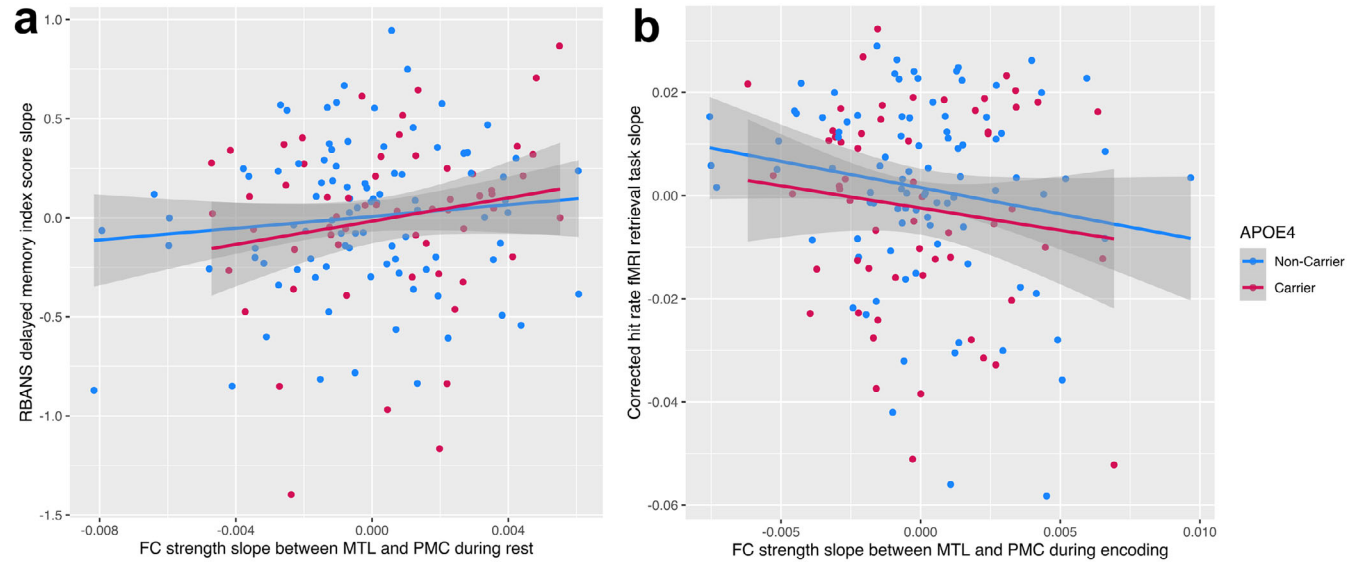

Figure 3. Episodic memory performance over time and the relationship with functional connectivity (FC) strength over time during rest and encoding. a) Recall performance measured via the RBANS delayed memory index score improved over time (p<0.001). Increasing resting-state FC between MTL and PMC ($RSFC_{MTL\text{-}PMC}$) was related to an increasing RBANS delayed memory index score (p=0.032). The slope of cognitive performance was used for visualization. **b)** Recognition performance measured via the corrected hit rate of the fMRI retrieval task of the items encoded during fMRI declined over time (p=0.023). Increasing encoding-$FC_{MTL\text{-}PMC}$ was related to decreasing encoding-task recognition performance (p=0.014). The slope of cognitive performance was used for visualization. There were no associations of RSFC and corrected hit rate (all p>0.05). RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.