**Supplementary**

***Supplementary table 1: MRI acquisition parameters***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** |  | **T1-MPRAGE** | | | **EPI - resting-state fMRI** | | | |
|  | Field strength | TR/TE (ms) | Flip Angle | Resolution (mm) | TR/TE (ms) | Flip Angle | Resolution (mm) | Volumes |
| DIAN | 3T | 2300/2.95 | 9° | 1.1 x 1.1 x 1.2 | 2230/30 | 80° | 3.3 x 3.3 x 3.3 | 140 |
| DELCODE | 3T | 2500/4.33 | 7° | 1 x 1 x 1 | 2580/30 | 80° | 3.5 x 3.5 x 3.5 | 180 |
| FACEHBI | 1.5T | 2200/2.66 | 8° | 1 x 1 x 1 | 4000/50 | 90° | 3.5 x 3.5 x 3.5 | 160 |

***Supplementary table 2: Robust linear mixed effects models for the interation EYO x Hipp-R to mediofrontal connectivity on Cognition in DIAN-MC and DELCODE***

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | LM delayed recall | | | MMSE |  |  |
|  | Model terms | B/SE | T | p | B/SE | T | p |
| DIAN-MC  Model 1a | Hipp-R FC x EYO | 0.144/0.071 | 2.031 | 0.045 | 0.234/0.061 | 3.881 | <0.001 |
| Hipp-R FC | 0.118/0.072 | 1.637 | 0.105 | 0.172/0.063 | 2.721 | 0.008 |
| EYO | -0.427/0.083 | -5.158 | <0.001 | -0.435/0.072 | -6.015 | <0.001 |
| Model 2a | Hipp-L FC x EYO | 0.160/0.077 | 2.067 | 0.041 | 0.177/0.068 | 2.624 | 0.009 |
|  | Hipp-L FC | 0.051/0.073 | 0.705 | 0.482 | 0.081/0.066 | 1.239 | 0.218 |
|  | EYO | -0.439/0.081 | -5.403 | <0.001 | -0.457/0.076 | -6.028 | <0.001 |
| DELCODE  Model 1b | Hipp-R FC x CSF A42/40 | -0.031/0.080 | -0.385 | 0.701 | -0.222/0.080 | -2.744 | 0.007 |
| Hipp-R FC | 0.134/0.083 | 1.618 | 0.096 | 0.209/0.081 | 2.577 | 0.011 |
| CSF A42/40 | 0.309/0.084 | 3.667 | <0.001 | 0.350/0.084 | 4.187 | <0.001 |
| Model 2b | Hipp-L FC x CSF A42/40 | 0.002/.078 | 0.024 | 0.981 | -0.205/0.079 | -2.588 | 0.011 |
|  | Hipp-L FC | 0.171/0.080 | 2.129 | 0.036 | 0.229/0.082 | 2.804 | 0.006 |
|  | CSF A42/40 | 0.281/0.083 | 3.387 | <0.001 | 0.335/0.084 | 3.973 | <0.001 |
| FACEHBI  Model 1c | Hipp-L FC x Global Amyloid SUVR |  |  |  | 0.037/0.143 | 0.256 | 0.798 |
| Hipp-L FC |  |  |  | 0.135/0.093 | 1.450 | 0.149 |
| Global Amyloid SUVR |  |  |  | -0.100/0.098 | -1.099 | 0.315 |
| Model 2c | Hipp-R FC x Global Amyloid SUVR |  |  |  | -0.019/0.124 | -0.155 | 0.877 |
|  | Hipp-R FC |  |  |  | 0.143/0.092 | 1.566 | 0.120 |
|  | Global Amyloid SUVR |  |  |  | -0.065/0.090 | -0.719 | 0.473 |

a=Model controlled for gender, education, family affiliation, hippocampus volume (fixed effects) and site (random effect);

b=Model controlled for gender, education, diagnosis, hippocampus volume, ApoE (fixed effects) and site (random effect)

c=Model controlled for gender, education, diagnosis, hippocampus volume, ApoE (fixed effects)

**Methods**

***Preprocessing of MRI data***

Prior to any analyses, functional and structural MRI images were visually inspected for artifacts. High-resolution T1-MPRAGE images were segmented into different tissue types using the SPM12 new segment approach. Using high-dimensional diffeomorphic registration algorithms implemented in DARTEL1 of SPM12 (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom: [www.fil.ion.ucl.ac.uk/spm)](http://www.fil.ion.ucl.ac.uk/spm)), a group specific template was built up in iterative steps of normalizing and averaging the scans, as previously described.2-4 The DARTEL template was then registered via affine registration to the MNI template and the transformation matrices of the high-dimensional normalization and the affine registration were combined to register each subject’s grey matter segment into MNI space. We applied Jacobian modulation to preserve local grey matter concentrations during spatial normalization. For functional MRI preprocessing, each individuals’ EPI image was slice-time corrected, realigned to the first volume and subsequently registered to the T1-MPRAGE image in native-space. In order to high dimensionally normalize the registered EPI images to MNI space, we applied the non-linear spatial transformation parameters that were estimated during spatial normalization of the T1-MPRAGE images in the previous step. The spatially normalized images were spatially smoothed, using an 8mm FWHM Gaussian kernel. For denoising of the spatially normalized and smoothed EPI images, we 1) removed the linear trend, 2) applied band-pass filtering using a frequency band of 0.01-0.08 Hz and 3) regressed out the 6 motion parameters estimated during realignment as well as the average BOLD signal of the white matter and cerebrospinal fluid compartment. To further minimize the impact of head motion on any connectivity analyses, we performed motion scrubbing following an established protocol5 that we applied previously in DIAN and DELCODE.4 In brief, we assessed the frame-wise displacement between any adjacent volumes where we censored volumes that exhibited a frame-wise displacement > 0.5mm as well as 1 preceding and 2 subsequent volumes. To avoid including subjects with excessive head motion, the current study included only subjects for which less than 30% of the resting-state data had to be censored. Due to the unavailability of field-maps in DIAN and FACEHBI, we did not apply distortion correction but used the SPM unwarping function in order to keep the processing pipeline consistent across studies. Applying field-map correction to the DELCODE sample, where field-maps were available, yielded consistent results with the analyses reported in this manuscript.

***Connectivity assessment***

For seed-based Hipp-connectivity, the seed ROI consisted of the right (Hipp-R) and left (Hipp-L) hemispheric anatomical ROIs included in the automatic anatomic labeling atlas,6 in line with previous approaches.7,8 For the canonical resting-state networks, we adopted pre-established 8mm spherical ROIs centered within the left inferior temporal cortex (MNI: x=-52, y=-66, z=-4) for the dorsal attention network (DAN), the posterior cingulate cortex for the default mode network (DMN, MNI: x=0, y=-51, z=29), the dorsomedial-frontal cortex for the control network ( CON, MNI: x=1, y=30, z=44), and the left insula for the salience network (SAL, MNI: x=-42, y=6, z=4). MNI-coordinates for theses canonical resting-state networks were adopted from previous work in AD.9 Prior to connectivity assessment, all seed ROIs were additionally masked with a group specific grey matter mask to ensure that only voxels with a high likelihood (i.e. >50%) of belonging to the grey matter were included in the analysis. Higher grey matter probability thresholds (i.e. >70%, > 80%), did not alter the result pattern of the current study. For each ROI, we extracted the mean time-series from the preprocessed and grey-matter masked resting-state fMRI data and assessed the Fisher-z transformed Pearson-moment correlations between the seed-ROI time course and each remaining voxel of the grey-matter, yielding a 3D connectivity map for each ROI per subject.

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