Heritability of hippocampal microstructural and functional organization

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Introduction

Hippocampus is a highly complex region participating in a wide range of cognitive functions. This diverse set of functions is enabled by its unique structure (Insausti et al., 2017) and connectivity with the neocortex (Paquola et al. 2020).

Here, we studied the genetic control over hippocampal subfield functional organization and microstructure using a twin-design. We characterized the functional features by the connectivity gradients and microstructural features by the T1w/T2w intensity maps, and their covariation with the cortex. Then, we computed the effects of familial relatedness on both feature axes.

Methods

Resting-state (rs) fMRI time series and T1w/T2w intensity maps were selected from Human Connectome Project S900 release (Van Essen et al. 2013). Data was composed of monozygotic and dizygotic twins, siblings and unrelated individuals.

Hippocampal subfields subiculum (SUB), CA1-3 (CA), and CA4-DG (DG) were automatically delineated using the SurfPatch algorithm (Figure 1A) (Caldairou et al. 2016).

rs-fMRI time series were resampled to FreeSurfer (v5.3.0) cortical surfaces and to the Glasser Atlas (Glasser et al. 2016) of 360 parcellations.

Quality assessment resulted in 709 subjects to be included (395 women, mean ± SD age = 28.7 ± 3.7 y).

Hippocampal functional organization was characterized by implementing the diffusion embedding on hippocampal-cortical functional connectivity (FC) (Figure 1A) (Vos de Wael et al. 2020). This method revealed the FC gradients (Figure 1C) (Vos de Wael et al. 2018).

Next, heritability of hippocampal-functional FC and T1w/T2w intensity maps were assessed (Figure 2).

We computed the hippocampal-cortical structural covariance (SC) of T1w/T2w maps to uncover the microstructural similarity between subfields and cortex (Figure 3A). Further, the genetic correlation of the SC was obtained to underline the pleiotropy between hippocampal and cortical microstructure.

Heritability and genetic correlation analysis were all conducted with the Sequential Oligogenic Linkage Analysis Routines (SOLAR, v8.5.1) (Almasy and Blangero 1998).

Last, to explore whether microstructural and functional features drive an organizational axis together, we obtained the *fused* gradients using FC and SC simultaneously (Figure 4A).

Results

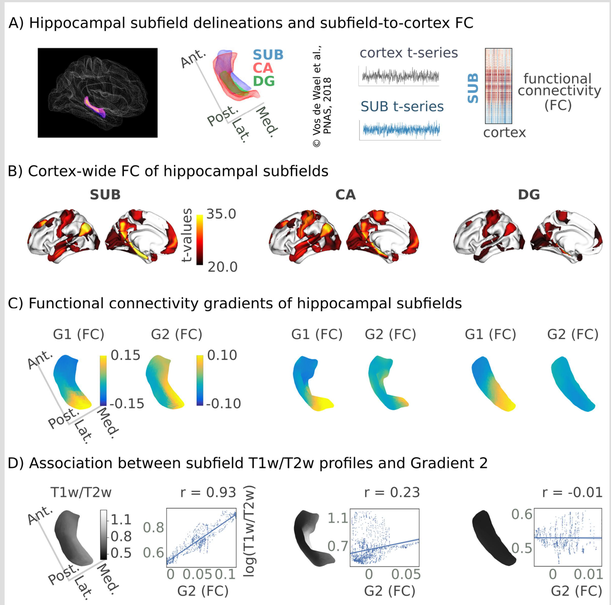

Figure 1. A. Hippocampal surfaces subiculum (SUB, blue), CA1-3 (CA, red), and CA4-DG (DG, green) were delineated using SurfPatch (Caldairou et al. 2016). A group average functional connectivity (FC) was computed for each subfield. B. Cortex wide FC was thresholded at t>20 to represent the highest connections. C. Gradient 1 (G1 (FC)) depicts an anterior-to-posterior connectivity axis, whereas Gradient 2 (G2 (FC)) a medial-to-lateral axis. D. T1w/T2w profile correlates strongly with G2 (FC) for SUB (r=0.93), however, not for the CA (r=0.23) and DG (r=-0.01).

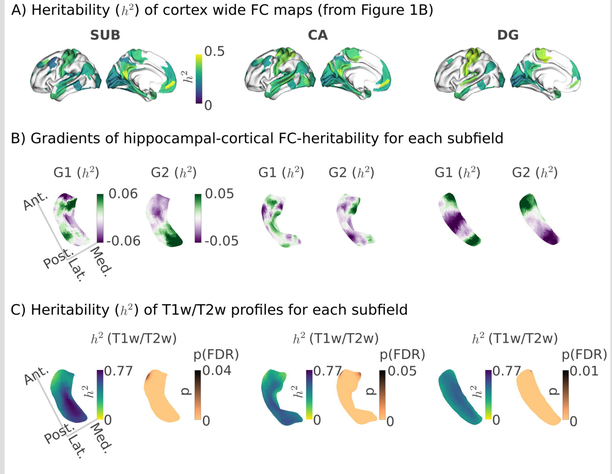

Figure 2. A. Hippocampal-cortical FC is the highest heritable in ventromedial, posterior cingulate, and precuneus regions for SUB (left), followed by a similar pattern for CA (middle), and is the highest in somatomotor cortex for DG (right). B. The first two gradients of heritability (G1 (h^2) and G2 (h^2)) represent the continuous transitions of FC-h^2 maps. G2 (h^2) depicts an anterior-posterior separation for SUB and DG. C. h^2 scores reached up to 0.77 along the subfields (viridis colormap) and p-values were significant for most of the subfield vertices after FDR correction (copper colormap).

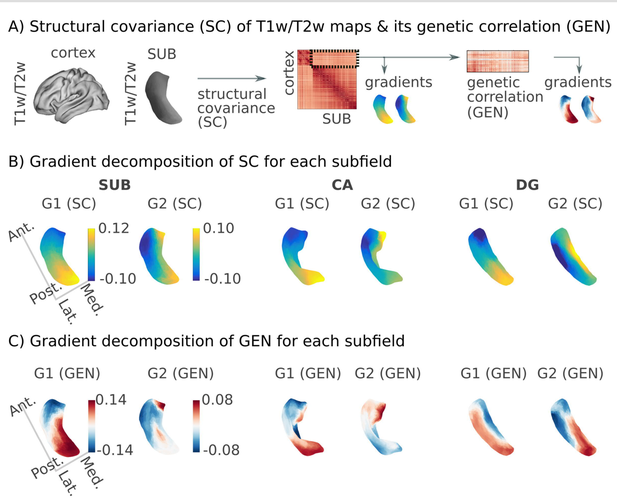

Figure 3. A. Structural covariance (SC) and its genetic correlation (GEN). B. G1 (SC) depicts an anterior-posterior axis, whereas G2 (SC) a medial-to-lateral axis. C. G1 (GEN) indicates an anterior-to-posterior separation along SUB and CA, whereas it becomes more posterolateral-to-anteromedial along DG. G2 (GEN) displays also an anterior-to-posterior axis along CA and DG. D. Anterior portions of subfields (blue) share more microstructural similarity with the anterior cortex and posterior portions (yellow) with the posterior cortex for SUB and CA. E. Anterior portions of subfields (dark blue) share more genetic similarity with the anterior cortex for SUB and DG, whereas it spreads throughout the cortex for CA. Posterior portions of subfields (red) share more genetic similarity with somatomotor, auditory and visual areas for SUB and with angular gyrus for DG.

Conclusion

We replicated the anterior-posterior (A-P) and medial-lateral (M-L) functional configuration of hippocampal subfields in 709 subjects (Vos de Wael et al. 2018) (Figure 1C). We additionally showed that the microstructural covariance reveals also an A-P and a M-L axes (Figure 3B). Overall, the A-P axis was even preserved along the fused gradients, that were based on FC and SC together (Figure 4A).

T1w/T2w maps, that are interpreted as a marker for the microstructure (Glasser and Van Essen 2011), were strongly heritable along all the subfields, whereas the heritability of hippocampal-cortical FC was moderate (Figure 2).

Individual variation in hippocampal microstructural and functional organization is under genetic control and point to a differentiable organization across subfields (Figures 2, 3C, 3D).

Anterior hippocampal portions were coupled more strongly to DMN and SM networks, whereas posterior portions to FPN and DAN (Figure 4B, 4C). Coherency in the A-P axis was topographically similar to the whole-brain multiple demand axis, which separates higher order functional modalities (Figure 4E).

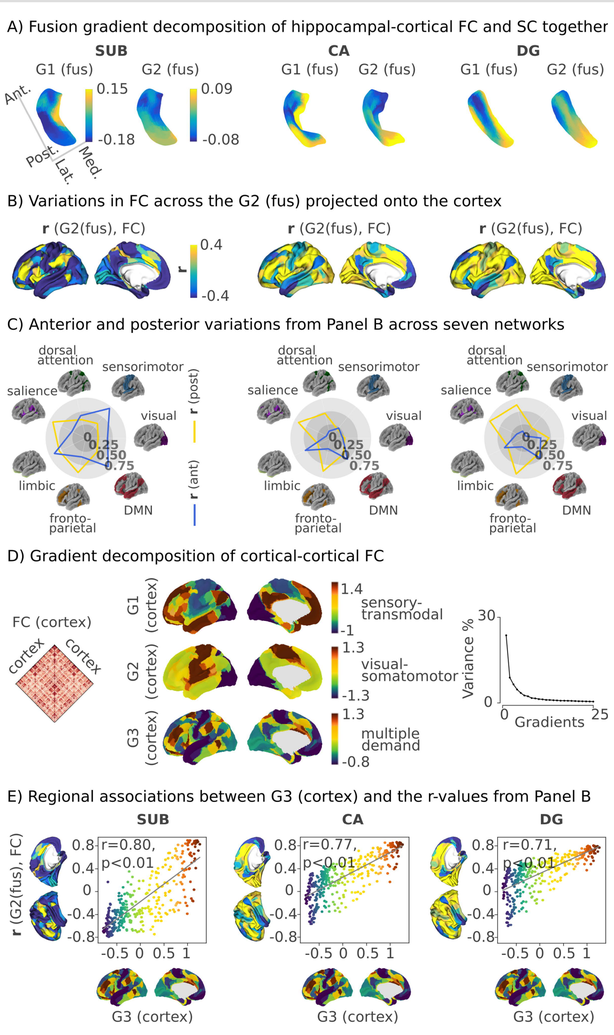

Figure 4. A. First fusion gradient G1 (fus) depicts a ventral-dorsal axis, whereas the second fusion gradient G2 (fus) an anterior-posterior axis. B. Anterior portions of subfields (blue) are functionally coupled with somatosensory, DMN and limbic areas, whereas posterior portions (yellow) with fronto-parietal and salience domains. C. Post-hoc analyses for Panel B findings using seven networks (Yeo et al. 2011). D. First three gradients of whole-brain FC. E. Anterior-posterior hippocampal axis projected onto the cortex (r (G2(fus), FC)) aligns with the multiple demand axis (G3 (cortex)) (SUB: r=0.80, CA: r=0.77, DG: r=0.71).

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