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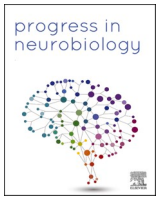

Original research article

# Hippocampal anterior- posterior shift in childhood and adolescence

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ABSTRACT

Hippocampal-cortical networks play an important role in neurocognitive development. Applying the method of Connectivity-Based Parcellation (CBP) on hippocampal-cortical structural covariance (SC) networks computed from T1-weighted magnetic resonance images, we examined how the hippocampus differentiates into subregions during childhood and adolescence (N = 1105, 6–18 years). In late childhood, the hippocampus mainly differentiated along the anterior-posterior axis similar to previous reported functional differentiation patterns of the hippocampus. In contrast, in adolescence a differentiation along the medial-lateral axis was evident, reminiscent of the cytoarchitectonic division into cornu ammonis and subiculum. Further meta-analytical characterization of hippocampal subregions in terms of related structural co-maturation networks, behavioural and gene profiling suggested that the hippocampal head is related to higher order functions (e.g. language, theory of mind, autobiographical memory) in late childhood morphologically co-varying with almost the whole brain. In early adolescence but not in childhood, posterior subicular SC networks were associated with action-oriented and reward systems. The findings point to late childhood as an important developmental period for hippocampal head morphology and to early adolescence as a crucial period for hippocampal integration into action- and reward-oriented cognition. The latter may constitute a developmental feature that conveys increased propensity for addictive disorders.

## 1. Introduction

The hippocampal formation (HF) plays a crucial role in cognitive and emotional development, including episodic memory, executive function, decision-making and emotion regulation in children and adolescents (Barch et al., 2019; Keresztes et al., 2017; Lee et al., 2014; Riggins et al., 2018; Tamnes et al., 2018). Childhood is marked by increased cortical grey matter volume (Gilmore et al., 2012; Mills et al., 2016) and by the segregation of functional and structural covariance networks (Woodburn et al., 2021; Zielinski et al., 2010). In addition, there is a shift from local to global connectivity patterns in children, that becomes functionally relevant with higher age enhancing modular specialization (Grayson and Fair, 2017). Further refinement of structural and functional networks continues during late childhood and adolescence to further support complex cognitive abilities (Khundrakpam et al., 2013; Solé-Padullés et al., 2016).

The HF is a heterogenous brain region showing subregional differentiation along the medial-lateral and longitudinal axis dividing it into subfields and subregions characterized by distinct gene transcription profiles, cytoarchitecture, connectivity and integration into behavioral systems (Amunts et al., 2005; Moser and Moser, 1998; Poppenk et al., 2013; Sekeres et al., 2018; Strange et al., 2014; Vogel et al., 2020).

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Hippocampal subregions and subfields were additionally suggested to follow different trajectories throughout development (Canada et al., 2020; Langnes et al., 2020). These hippocampal regional differences could be expected to go hand in hand with other brain regions' developmental trajectories (Douaud et al., 2014; Walhovd et al., 2014). Such a question can be investigated by examining hippocampal-whole brain structural covariance networks.

Neurobiologically, structural covariance is assumed to capture co-maturation and co-plasticity processes (Alexander-Bloch et al., 2013) relating to transcriptomic gene expression, and axonal connectivity (Romero-Garcia et al., 2018; Yee et al., 2018). Furthermore, functional and structural covariance networks share some topology resulting in a moderate to high convergence ranging from 30% to 58% (Goodkind et al., 2015; Paquola et al., 2018; Reid et al., 2016; Reid et al., 2017; Seeley et al., 2009; Shah et al., 2018; Sui et al., 2014). Hence, structural covariance, to some extend also reflects functional coupling between brain regions (Zielinski et al., 2010), and is thus suited to study hippocampal coordinated maturation and (functional) co-plasticity patterns representing to some extent inherited and environmental developmental processes.

A particularly important question in this regard, and given the intrinsic heterogeneity of the hippocampal formation, is subregional differences in the pattern of whole-brain co-variation profiles in childhood and adolescence. Investigating the whole HF in a data-driven approach is essential in this context since subregional differences can be expected to follow either microstructural properties (typically differentiating hippocampal subfields) or large-scale functional systems (typically differentiating anterior and posterior subregions). Furthermore, while hippocampal cortical and subcortical networks play an important role in neurocognitive development (Alexander et al., 1990; Murty et al., 2016; Shah et al., 2012), they remain poorly understood, especially in critical transitional phases.

Previous investigations of hippocampal structural covariance patterns in healthy adult populations have revealed a strong segregation between the head and body-tail regions, with a further cornu ammonis (CA) vs. subiculum-like differentiation within the body-tail region (Ge et al., 2019; Plachti et al., 2019; Plachti et al., 2020). Notably, this pattern was observed across distinct adults age groups derived from different study cohorts, including young, middle-age and older adults and appeared to follow structural connections between the HF and the neocortex/subcortical regions. However, the question remains open if regional HF structural covariance patterns are already established in early development or are evident only in older age groups during adolescence or adulthood.

To address this question, we examined structural covariance of the HF across different age groups including late childhood (6–10 years), early (11–14 years) and middle (15–18 years) adolescence derived from three openly available datasets. Furthermore, we did not a priori favor any existing hippocampal subdivision pattern (e.g. subfields or subregions) over another, but instead took the whole HF into consideration. The first objective of this study was hence to identify in a data-driven way the differentiation pattern in grey matter volume within the HF based on its whole brain co-maturation profiles. To do so, we used a clustering approach (Eickhoff et al., 2015; Eickhoff et al., 2018) on the multivariate profiles of hippocampal whole-brain structural covariance patterns. Our second aim was to reveal structural covariance networks of identified HF subregions, and to characterize these morphological networks with regards to behavioral systems revealed by meta-activation maps, as well as with regards to gene profiles, in line with the assumption that structural covariance is related to transcriptomic gene expression and/or functional coupling supporting behavioral systems. Here, we used brain activation maps from the NeuroSynth database storing thousands of activation studies published in the last decade and gene expression data obtained from the Allen Human Brain Atlas.

## 2. Methods

### 2.1. Datasets, and age-phenotypical groups

We used three different datasets: Enhanced Nathan Kline Institute-Rockland Sample (eNKI) (http://fcon_1000.projects.nitrc.org/indi/enhanced/), Child Mind Institute Healthy Brain Network (CMI-HBN) http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/About.html (Alexander et al., 2017) and Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2014) https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html.
From these datasets, we created three age cohorts corresponding to late childhood (age: 6–10 years, n = 316), early adolescence (age: 11–14 years, n = 328), and middle adolescence (age: 15–18 years, n = 361). The analyses of these data were approved by the ethical committee of the Heinrich Heine University Düsseldorf. (Table 1).

### 2.2. MRI preprocessing and structural covariance computation

In the present study we used T1-weighted anatomical MRI scans of the whole brain assessed with different scanning parameters (Supplementary Table 1), but all acquired on 3 T Scanners. Brain images were preprocessed with SPM12 and the voxel-based processing pipeline implemented in the CAT12 (version 12.5) toolbox, running in Matlab R2016a. We spatially normalized images using the DARTEL algorithm to the ICBM-152 template applying both affine and non-linear transformations. Subsequent preprocessing steps included: bias-field correction, segmentation into gray, white matter, and cerebrospinal fluid tissues, modulation for non-linear transformations only and finally smoothing with an isotropic Gaussian kernel (full-width-half-maximum = 8). Quality of non-smoothed images was ensured by the integrated Quality assurance (QA) check implemented in CAT12. First, we performed the covariance analysis implemented in CAT12 correlating grey matter images of the samples to detect outliers. Images being identified above two standard deviations were visually inspected and excluded from further analyses if displaying low quality. In addition, we evaluated images on a rating scale summarizing image quality based on image parameters (e.g. noise contrast ratio) showing good quality of images (Supplementary Fig. 1). To ensure stability, we created bootstrap samples, which corresponded to the size of the respective dataset (e.g. n = 100 => 100 bootstrap samples) and were subsequently used to calculate the respective structural covariance matrices. To compute structural covariance, grey matter probabilities of hippocampal voxels were correlated with whole brain grey matter probabilities using Pearson's correlation within each age-specific dataset-sample (i.e. eNKI 6–10 years old). Correlation values were afterwards z-transformed.

### 2.3. Volume of Interest

Hippocampal volume of interest (VOI) was created using the macroanatomical Harvard-Oxford atlas and cytoarchitectonic maps of the SPM Anatomy Toolbox atlas. For the sake of consistency and comparability, the same VOI as in previous publications was used (Plachti et al., 2019; Plachti et al., 2020).

### 2.4. Parcellation

Differentiation patterns within the HF were identified by applying an

**Table 1**
Demographics of samples.

| | N | Mean age (*M, SD, age range*) | Sex (males)% |
|---|---|---|---|
| Late childhood | 316 | 6–10 years (9.23, 1.16, 6 –10.9) | 52.5 |
| Early adolescence | 328 | 11–14 years (13.00, 1.20, 11 – 14.9) | 49.6 |
| Middle adolescence | 361 | 15–18 years (16.85, 1.17, 15 – 18.9) | 49.8 |

unsupervised clustering algorithm (k-means++ in Matlab), which was previously extensively used in the field of brain parcellation (Arslan et al., 2018; Barnett et al., 2019; Chang et al., 2012; Deen et al., 2010; Kahnt et al., 2012; Kelly et al., 2012; Kim et al., 2010; Thirion et al., 2014; Zhang et al., 2011). K-means was applied on the previously computed individual structural covariance patterns within each age-specific dataset-sample (i.e. eNKI 6–10 years old) representing the correlation of each hippocampal voxel to all grey matter voxels in the brain excluding the HF itself. Based on the similarity, or better to say dissimilarity, of structural covariance profiles across HF voxels, voxels were grouped either in the same or in a different cluster dividing the HF into 2–7 subregions (cluster solutions). For each cluster solution, we used 255 iterations and 500 repetitions. In order to identify which differentiation pattern fits the data in an optimal way, we applied three different criteria: stability of differentiation pattern assessed with split-half cross-validation, similarity between hippocampal voxels and its own cluster assessed with the silhouette criterion, and consistency of differentiation patterns across age groups. All three evaluation strategies will be presented in the following paragraphs.

### 2.5. Optimal hippocampal differentiation pattern: stability

To assess stability of differentiation patterns, we first divided each parcellation of each dataset-sample into halves 10,000 times (splits) and compared the halves using the adjusted Rand Index (aRI) to estimate how convergent the two halves were. High stability is expected if both halves are highly convergent to each other as reflected by a high aRI value. The aRI is a measure for consistency between two partitions ranging from $-1$ to $+1$ being adjusted for chance. Scores of 0 aRI indicate that the partitions are independent from each other, hence random, whereas a score of 1 indicates that the partitions are identical. Negative scores indicate that the differentiation patterns are less than expected from a random partition meaning that two partitions might be complementary. In the next step, we quantified statistically with an ANOVA, which partition ranging from 2 s to 7 subregions represents the most stable differentiation pattern.

### 2.6. Optimal hippocampal differentiation pattern: consistency

In addition to the stability criterion, we also tested for consistency of HF differentiation patterns. Doing so, we followed two different approaches, namely consistency of individual hippocampal voxels with regards to the subregion it was assigned to, and consistency of whole differentiation patterns across dataset-age samples.

For the first case, we used the silhouette score to assess how well the separation of hippocampal voxels was performed across cluster solutions. Silhouette scores can range from $-1$ to $+1$, with higher scores indicating for each hippocampal voxel that the voxel matched well to its own subregion/cluster (i.e. cohesion) but poorly with a neighboring subregion (i.e. separation). Silhouette plots were used to visualize the degree of coherence for each HF voxel.

For the second case, we compared all differentiation patterns obtained from the dataset-age samples with each other as well as to the young-adults differentiation pattern previously obtained from our work (Plachti et al., 2020), using the aRI. This procedure ensured to evaluate which differentiation pattern captured more likely intrinsic properties of hippocampal structural covariance, which are genuine and therefore reoccurring across different groups mirroring high similarity of differentiation patterns across dataset-age samples.

### 2.7. Age-specific differentiation patterns across datasets

Hippocampal parcellation was performed within the three age groups (6–10, 11–14, and 15–18 years of age) separately for each dataset sample (e.g. PNC 6–10 years; PNC 11–14 years, eNKI 6–10 years etc.). Data was not merged at the step of clustering. This was done to diminish the influence of dataset specific structured noise on parcellations and to maximize our ability to identify differentiation patterns reflecting developmental neurobiological mechanisms during late childhood and adolescence. Therefore, we first applied the clustering approach described above on structural covariance patterns of hippocampal voxels for each individual age-related dataset sample (e.g. PNC 6–10 years, eNKI 6–10 years). After clustering HF voxels for each age group and dataset, age group specific HF differentiation patterns were merged across datasets (e.g. pooling CMI-HBN 6–10 years, eNKI 6–10 years and PNC 6–10 years) by concatenating the dataset-age specific solution matrices. Subsequently, we applied bootstrapping (10,000 resampling) on the concatenated and 'merged' solution matrices to enhance further stability of differentiation patterns. This procedure provided robust age group specific HF differentiation patterns.

### 2.8. Underlying structural covariance networks

To reveal whole-brain structural covariance patterns for each of the identified HF subregions, we performed a general linear model (GLM) implemented in SPM at the voxel level. As the age samples from the different datasets had to be pooled together for this analysis, we preliminary harmonized grey matter probabilities across datasets applying the ComBat algorithm (Fortin et al., 2018; Fortin et al., 2017). Using GLM, we tested the linear relationship between each grey matter voxel in the brain with the averaged grey matter probabilities of hippocampal subregions of the age-specific hippocampal model identified in the previous step.

We used t-contrasts, comparing the association pattern of one subregion against the other subregions within the HF in order to estimate the unique structural covariance network of each specific hippocampal subregion. Associated structural covariance networks remained unthresholded ($T >= 1$, $P < 0.001$) since the clustering approach was performed on a full pattern of covariation without any restrictions. However, we also report results at the corrected level for multiple comparisons using the family wise error (FWE) rate ($T > 4.48$, $P < 0.05$) (Supplementary Figure 7).

### 2.9. Subregions' covariance networks and behavioral associations

After having identified the associated structural covariance networks underlying hippocampal differentiation patterns in each age cohort, we characterized those networks with regards to behavioral functions using NeuroSynth database (https://neurosynth.org/). We used the cognitive decoding tool containing more than 1300 terms, which were obtained from published functional activation studies (Yarkoni et al., 2011). Our primarily aim was not to give a detailed behavioral description of structural covariance networks but to get a broad overview of the behavioral concepts most associated with these networks (Hansen et al., 2021).

NeuroSynth provides for specific behavioral concepts such as 'memory' a meta-analytical map containing the most frequent associated voxels across activation studies, representing how often voxel coordinates and specific (behavioral) terms have been published together. Therefore, we compared the obtained unthresholded structural covariance patterns with the maps archived in NeuroSynth using Pearson's correlation. We included only correlations above $r >= 0.1$ and excluded non-behavior related terms (e.g. 'hippocampus', 'temporal', 'dementia') and summarized terms related to one category into a summary term (e.i. 'emotion' included 'affect', 'happy', 'fear'). Depending on the spatial extent of the structural covariance networks, the number of behavioral terms may differ from network to network. Notably, behavioral descriptions were interpreted qualitatively and not quantitively.

### 2.10. Gene fingerprints of structural covariance networks

In addition to the behavioral characterization of associated

structural covariance networks, we also characterized those structural networks with regards to their genetic profile. To do so, we used the gene decoding tool implemented in NeuroSynth and NeuroVault (Gorgolewski et al., 2015), which is based on the Allen Human Brain Atlas (http://human.brain-map.org/) microarray dataset containing human genes. Identically to the behavioral characterization, we used the unthresholded statistical maps obtained, which were hence compared with gene expression patterns (Gorgolewski et al., 2014). Concretely, Neurovault uses mixed-effect models to estimate associations between our statistical covariance map and the ~ 40,000 genes obtained from six donated brains of the Allen Brain Institute, revealing genes that are associated with our map. In the present study, we filtered only genes related to five different categories of interest, namely, brain, hormones, neurons, synapses and hippocampus. We only reported the max. 10 genes, which were positively correlated with our map, FDR $P < 0.05$ corrected and explained more than 5% of the variance. On the axis of the resulting spiderplots, we show how much variance (%) was explained.

## 3. Results

### 3.1. Optimal division patterns in childhood and adolescence

#### 3.1.1. Stability of hippocampal differentiation patterns

Optimal hippocampal differentiation patterns dividing the HF into two to seven subregions were identified by stability measures across 10 000 splits (cross-validation) estimated with the aRI. We performed a 6 (differentiation patterns: from 2 to 7) x 3 (age group: late childhood, early and adolescence) ANOVA with the aRI as dependent variable. Our results showed that main and the interaction effects were significant for the left HF: differentiation patterns $F(5,419982) = 16226.12$, $P < 0.001$, age group $F(2,419982) = 14504.15$, $P < 0.001$, differentiation pattern x age group $F(10,419982) = 1712.32$, $P < 0.001$. All six differentiation patterns showed high stability dividing the HF into 2 subregions ($M = 0.96$), 3 ($M = 0.95$), 4 ($M = 0.92$), 5 ($M = 0.91$), 6 ($M = 0.91$) and 7 ($M = 0.92$), with all comparisons being significant ($P < 0.001$) as revealed by post-hoc analyses correcting for multiple comparisons according to Tukey-Kramer. However, especially the simpler parcellation patterns dividing the HF into two, three and four subregions, seemed to be more stable compared to higher parcellation schemas (Fig. 1a). In addition, stability of differentiation patterns was dependent on age group as summarized in Fig. 1a. Results for right HF are shown in Supplementary Fig. 3.

Thus, our first exploration of stability of hippocampal differentiation patterns suggested that simpler patterns of two, three and four subregions represented hippocampal-cortical covariation patterns in an optimal way, with patterns of two and three subregions showing the most stable divisions. Based on this initial examination of the data, we then focused on subdivision models of two, three, and four subregions as representing reliable models across age groups, and we then examined further criteria to identify the optimal partition model among those levels.

#### 3.1.2. Consistency within hippocampal differentiation patterns

After examining the stability of age-specific hippocampal partitions, we further evaluated their consistency. To do so, we used the silhouette criterion summarizing how similar hippocampal voxels were to their own assigned subregion compared to a neighboring subregion. Statistical differences were evaluated with a 6 (differentiation pattern: 2–7) x 3 (age group: late childhood, early adolescence, middle adolescence) ANOVA using the silhouette measure as the dependent variable. All main and interaction effects were significant: differentiation pattern $F(5,14940) = 376.68$, $P < 0.001$, age group $F(2,14940) = 32.34$, $P < 0.001$ and the interaction between differentiation pattern x age group $F(10,14940) = 10.93$, $P < 0.001$ (Fig. 1b). Post-hoc comparisons corrected for multiple comparisons (Tukey-Kramer) revealed that all differentiation patterns differed significantly from each other ($P < 0.001$) besides three comparisons: differentiation pattern of 4 subregions compared to 5, 4 compared to 6, and 5 compared to 6 ($P > 0.1$). Results for the right HF are summarized in Supplementary Results 3. Overall, the similarity measure confirmed again that differentiation patterns of two and three subregions capture optimally structural covariance patterns within the HS.

#### 3.1.3. Consistency of differentiation patterns across age groups

To further support our decision that robust and highly consistent differentiation patterns of two and three subregions were driven by intrinsic properties of structural covariance patterns rather than by possible dataset specific (e.g. noise) properties, we tested the consistency of differentiation patterns across dataset-age groups, again measured with the aRI (Fig. 1c). The generally high aRI across the separate dataset-age groups for the differentiation pattern of two subregions suggested a global and robust differentiation independent of dataset or age group. The differentiation pattern of three subregions also displayed a stable pattern of high similarity across datasets and age groups but with some exceptions (e.g. CMI HBN 6–10 years, PNC 6–10 years, eNKI 15–18 years) probably capturing different age-related stages of hippocampal structural covariation.

Overall patterns of consistency of these hippocampal patterns seemed to follow a transition from childhood to adolescence. Thus, our examination of hippocampal consistency across dataset-age groups suggested to focus on hippocampal pattern of three subregions, since this pattern was most stable and consistent, but also most likely the one representing optimally age-related differences of hippocampal structural covariance. Hippocampal consistency measures for higher levels of differentiation (5–7 subregions) are summarized in Supplementary Fig. 2.

Overall, our data-driven examination of hippocampal differentiation patterns suggested that parcellating the HF into three subregions results in stable and highly consistent separation of voxels within the HF. On top, this pattern of differentiation was also consistent across age-specific samples and in line with the pattern previously evidenced in young adults (Plachti et al., 2019; Plachti et al., 2020). All further analyses were hence based on a three-subregion differentiation pattern for all age cohorts.

### 3.2. Age related hippocampal differentiation patterns

To obtain general, robust and age specific hippocampal differentiation patterns, we merged the previously identified dataset specific age group solutions across datasets to generate a consensus partition model of three subregions for each of the three age groups: late childhood, early adolescence, and middle adolescence. To do so, we merged the 3-clusters assignments matrices while applying bootstrapping to further enhance stability of the differentiation patterns for each age group separately.

The resulting age specific hippocampal patterns for all three age groups emphasized a division along the anterior-posterior and medial-lateral dimension, dividing the HF into an anterior (head), posterior lateral (body-tail CA) and posterior medial (body-tail subiculum) subregion. Strikingly, this pattern was mainly evident in early and middle adolescence groups, while in late childhood (Fig. 1D), subregions were mainly differentiated along the anterior-posterior dimension with an anterior (head), middle (body) and posterior (tail) subregions. Of note, in the late childhood group, the posterior (green) subregion appeared to extend into the anterior-lateral direction approaching the hippocampal head. Furthermore, the differentiation pattern of early and middle adolescence resembled the hippocampal division previously observed in young adults (Ge et al., 2019; Plachti et al., 2020). In order to quantify these differences and resemblances, we used the aRI index and compared the age specific hippocampus-models with each other and to the young adults' hippocampal pattern (20–35 years and 35–55 years old obtained from (Plachti et al., 2020)) at different levels of

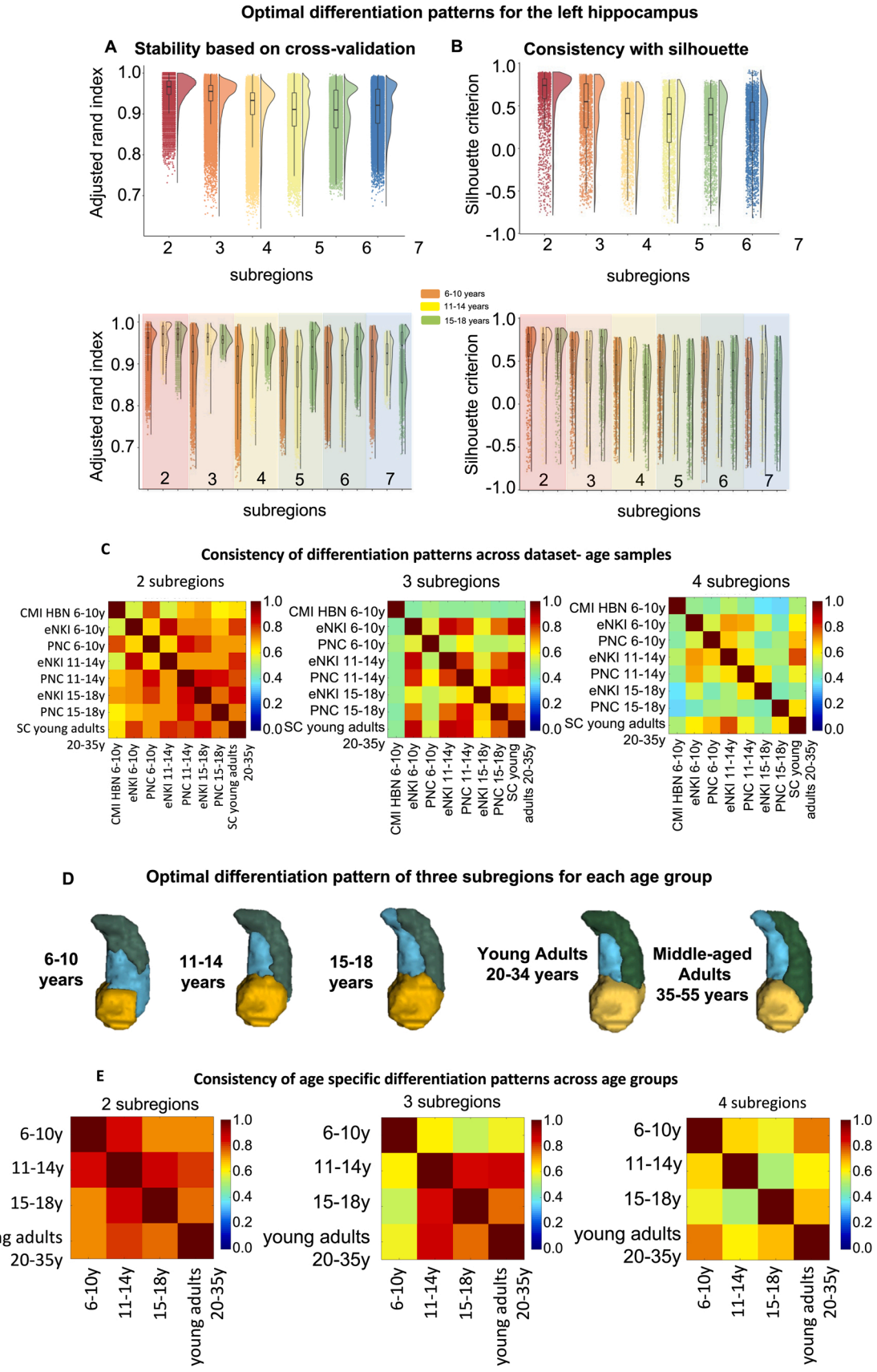


**Fig. 1.** Stability and consistency of differentiation patterns measured with the aRI or the silhouette scores (A, B). Basic divisions of 2 and 3 subregions were more stable and consistent within hippocampal voxels and across age groups. A division into 3 subregions appeared optimal to study age related differences since it was a robust and consistent subdivision, which in addition captured age related differences across groups (C, D, E). Adults' hippocampal differentiation patterns in (D) were previously obtained in a former study (Plachti et al., 2020).

differentiation (Fig. 1E). As expected, the highest similarity was observed for pattern of 3 subregions for the early and middle adolescence groups and both groups were more similar to young adults. The comparison between late childhood and early adolescence also displayed high convergence in hippocampal patterns of 3 subregions (~ 0.6 aRI) indicating high relatedness. High similarity was found between all age groups for the division level of 2 subregions, again highlighting that a head vs. body-tail subregion is a constant feature of hippocampal differentiation across all age groups. Findings for the right HF are represented in the Supplementary Fig. 3.

### 3.3. Whole brain structural covariance patterns of each subregion

After delineating robust partitions of the HF based on the individual voxels' structural covariance profiles, we examined the underlying structural covariance networks that guided the differentiation among hippocampal voxels in each age group. For each age group, the associated structural covariance networks for the left hippocampal differentiation pattern are summarized in Fig. 2, and in the Supplementary Fig. 6 for the right HF and for both hippocampi after FWE correction.

In late childhood, the head (yellow) subregion co-varied with almost the whole grey matter volume of the brain, with an emphasis on fronto-temporal brain regions including middle, superior frontal, orbital cortex, and (para)cingulate gyrus, temporal pole, middle temporal and inferior temporal gyrus. However, covariation was also observed with the insular cortex, thalamus, caudate, angular gyrus, lateral occipital cortex, and (pre)cuneous cortex.

In early adolescence the whole brain structural covariance network of the hippocampal head subregion was less in spatial extent but kept its core associations especially with frontal regions such as frontal pole, frontal orbital cortex, subcallosal cortex, inferior frontal gyrus, frontal medial cortex, precentral gyrus, paracingulate gyrus, but also with insular cortex, temporal pole, temporal fusiform cortex, central opercular cortex, precuneous cortex, intracalcarine cortex and amygdala. In middle adolescence, this network was again smaller in spatial extent and included amygdala, temporal fusiform cortex, inferior temporal gyrus, temporal pole, insular cortex, cingulate gyrus, lateral occipital cortex, intracalcarine cortex, central opercular cortex, superior frontal gyrus and precentral gyrus.

In late childhood, the structural covariance network of the tail (green) hippocampal subregion was dominated by associations with posterior brain regions such as posterior cingulate gyrus, precuneous cortex, cuneal cortex, supracalcarine and intracalcarine cortex, lingual gyrus, occipital fusiform gyrus, occipital pole, but also showed associations with frontal and subcortical brain regions including the putamen, thalamus, insular cortex, middle frontal gyrus, frontal pole, frontal orbital cortex and inferior frontal gyrus. This pattern of structural covariance was also evident, although smaller in spatial extent, in early adolescence and covered posterior regions of the lingual gyrus, precuneous cortex, cuneal cortex, lateral occipital cortex, occipital pole, intracalcarine cortex and the posterior division of the inferior temporal gyrus. However, some frontal brain regions were also associated with the hippocampal tail subregions including the frontal pole, inferior frontal gyrus (pars opercularis, pars triangularis), frontal orbital cortex, frontal operculum cortex. In middle adolescence, however, except for the frontal pole, frontal associations were not observed, and the structural covariance network included intracalcarine cortex, occipital pole, caudate, parahippocampal gyrus, and cingulate gyrus (posterior

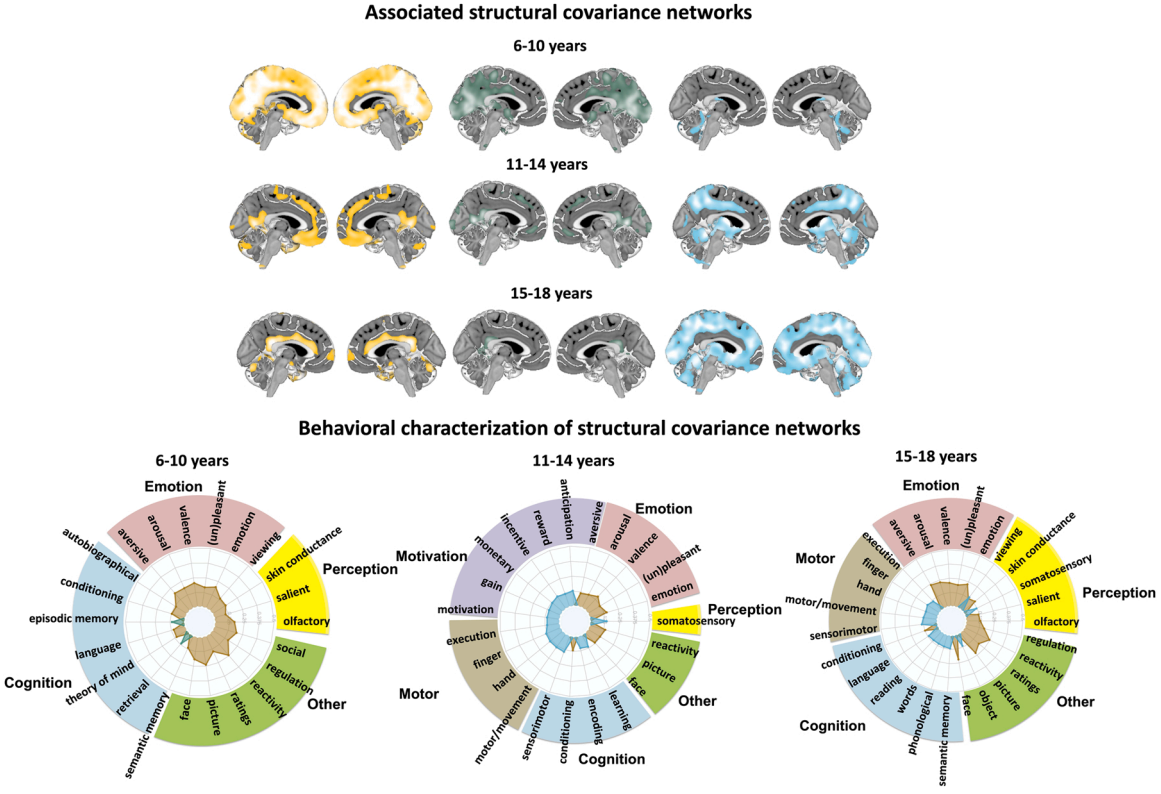


**Fig. 2.** Structural covariance networks of left hippocampal subregions and their behavioral characterization. Hippocampal subregions' associated unthresholded structural covariance networks (T > =1) are displayed for each of the investigated age group in the upper panel of the figure, whereas behavioral characterization of the structural covariance networks, performed with Neurosynth (r > =0.1), are summarized in the lower panel of the figure. In late childhood, anterior hippocampal subregions covaried with almost the whole brain, whereas posterior subregions' structural covariance networks spatially expanded in middle adolescence. This pattern of results was also visible in networks' behavioral associations. In late childhood, anterior hippocampus seems to covary with brain regions, involved in higher cognitive function including language, theory of mind, but also emotion and perception. In early adolescence, medial body-tail (blue) hippocampal subregion was linked to motivational and motor systems.

division).

Underlying structural covariance network of the body (blue) hippocampal subregion in late childhood revealed associations with the cerebellum IX, I-IV, Crus I and II, precentral and postcentral gyrus, paracingulate gyrus and superior temporal gyrus (posterior division). In early adolescence the spatial extent of the whole brain structural covariance network of the medial body-tail (blue) subregion was greatly enlarged and showed a scattered association pattern with the putamen, caudate, thalamus, accumbens, lingual gyrus, cerebellum V, I-IV, VI, Crus I, inferior temporal gyrus, middle temporal gyrus (temporooccipital and posterior parts), lateral occipital cortex, parietal operculum cortex, supramarginal gyrus, precentral and postcentral gyrus, cingulate gyrus, precuneous cortex and middle and superior frontal gyrus. In the group of middle adolescence, the associated structural covariance network of the medial body-tail (blue) subregion remained but additionally included frontal associations such as with frontal orbital cortex, subcallosal cortex, frontal pole, paracingulate gyrus and middle frontal gyrus.

In sum, our results suggested that the anterior (yellow) subregion is generally associated with frontal brain regions, although in late childhood it covaried with almost the whole brain. In contrast, the medial body-tail (blue) subregion was primarily associated with subcortical and motor-related brain regions, whereas the body-tail (green) subregion covaried with posterior brain regions connecting the occipital with parietal and subcortical brain regions (especially in late childhood).

### 3.4. Behavioral characterization of structural covariance networks

To better understand how the structural covariance networks relate to behavioral systems, we performed behavioral decoding of each identified whole-brain structural covariance pattern using NeuroSynth. Results for the right HF are presented in the Supplementary Figure 6.

In late childhood, the structural covariance pattern of the head (yellow) subregion was particularly spatially expanded and was accordingly associated with a variety of behavioral terms such as perception (viewing, olfactory), emotion ((un)pleasant, valence) and cognition (memory, theory of mind) (Fig. 2). The behavioral characterization of the hippocampal head subregion's networks did not differ across the age groups although the patterns differed from each other in spatial extent. In contrast, the structural covariance network of the lateral body-tail (green) subregion was mainly related to episodic memory and retrieval in late childhood.

The most important difference in behavioral characterization was found for the early adolescence group, whose structural covariance network of the medial body-tail (blue) subregion expanded in size and in behavioral terms as well. Accordingly, the structural covariance network was linked to terms pertaining to the motivation system (e.g., reward, incentive) and motor related behavioral terms (e.g. execution, movement), which was not evident for late childhood. In the group of middle adolescence, the medial body-tail (blue) subregion's network was also associated with motor related behavioral terms but not with motivation, while associations with terms pertaining to cognitive function such as language and reading were found again. Finally, the behavioral concepts associated with the network of the lateral body-tail (green) subregion remained elusive across age groups, suggesting a physiological network rather than a specific behavioral system.

### 3.5. Gene expression profiles of structural covariance networks

As structural covariance networks reflect not only functional interaction for behavioral functions, but also transcriptomic gene expression, we here also further characterized the underlying structural networks with regards to genes profiles. As summarized in Fig. 3, by using the Allen Human Brain Atlas microarray dataset, each hippocampal subregion's covariation networks showed a unique gene profile.

The network of the head subregion (yellow) was likely associated with processes responsible for maintaining automatic physiological responses (e.g., *NTRS1*~ blood pressure and sugar, body temperature, *NPY*~ pain perception, *MCHR2* and *THRA* ~ thyroid and melanin hormone), supporting its behavioral profile of the head subregion associated with emotions (e.g., arousal, aversive), perception (e.g. salient) and reactivity and regulation processes (Fig. 2). The gene profile of the

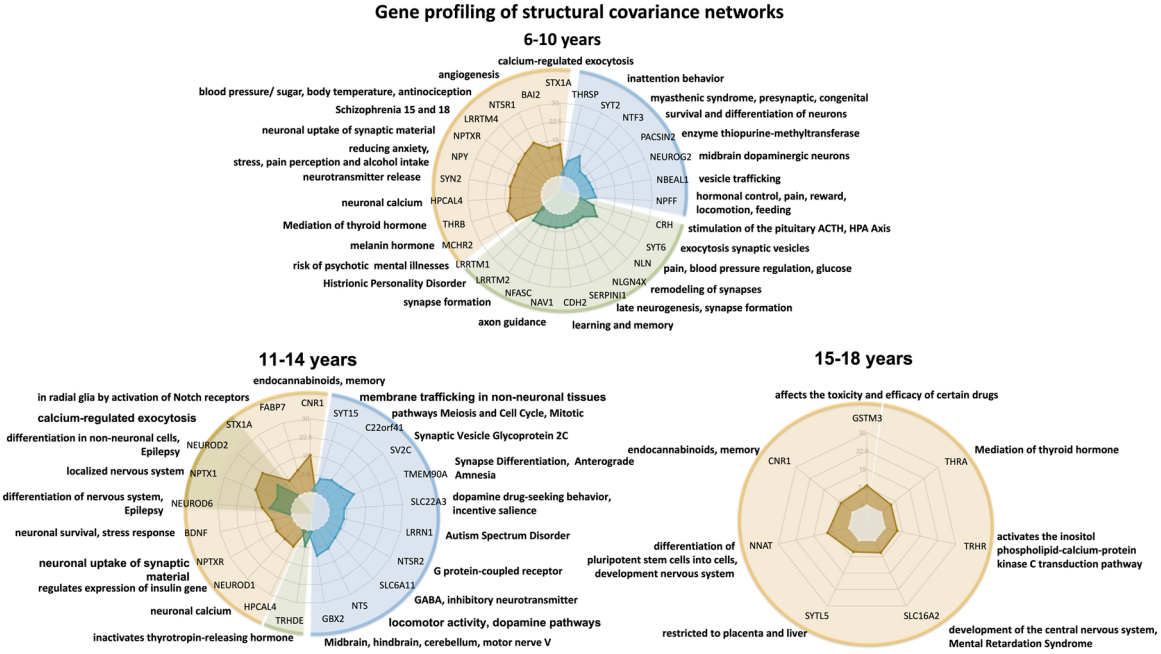


**Fig. 3.** Gene mapping of structural covariance networks associated with the left hippocampal differentiation pattern. Gene profiling of the unthresholded structural covariance networks was performed with Neurosynth and NeuroVault based on the Allen Human Brain Atlas. A maximum of 10 genes, which were positively correlated with the networks, FDR $P < 0.05$ corrected and explained more than 5% of the variance, were reported. In early adolescence structural covariance network of the medial body-tail (blue) hippocampal subregion was also genetically linked to motivation and reward systems. In late childhood, hippocampal tail (green) subregion is probably related to axonal and synaptic formation.

lateral body-tail subregion's (green) network appeared to be involved among others in the endocrine stress reaction (e.g., *CRH*~ HPA axis, *NLN*~ pain, blood pressure, reproduction, glucose metabolism), but also in memory and learning processes especially in terms of synapse formation, guidance and neurogenesis (e.g., *LRRTM2*, *NFASC*, *NAV1*, *SERPINI1*, *NLGN4X*). However, the lateral body-tail (green) subregion's network was relatively less characterized in terms of common human behavior functions, which again may suggest an involvement in physiological rather than observable behavioral processes. Finally, the gene profile of the structural covariance network of the medial body-tail subregion (blue) seemed to be related to an action-oriented and partly motivational network as represented by the associated genes (e.g., *THRSP*~ attention, *NEUROG2* and *NTS* ~ dopaminergic pathway, *NPFF*~ reward, pain and *SLC22A3* ~ incentive). This gene profile is particularly consistent with the behavioral characterization of early adolescence with a behavior related to 'motivation', 'reward', 'incentive', and 'gain'. The gene profiles for the right HF are depicted in Supplementary Figure 10.

## 4. Discussion

In the present study, we explored hippocampal differentiation patterns based on whole-brain structural covariance patterns in children and adolescents. Our findings showed that the HF is optimally and robustly differentiated into three stable subregions across childhood and adolescence. Overall, across all age groups, the hippocampal head emerged as a distinct subregion with a specific structural covariance's profile. However, the further medial-lateral subdivision of the body-tail corresponding to hippocampal subfields was only expressed in early adolescence. The latter finding suggests that the typical CA-subiculum differentiation previously reported in adults and previously evidenced using structural covariance (Ge et al., 2019; Plachti et al., 2019; Plachti et al., 2020) seemed to appear at the stage of adolescence.

Further differences between age groups were also observed when examining the structural covariance networks of each identified hippocampal subregion within each age group. Strikingly, the hippocampal head with its extended structural covariance network (including frontal, parietal and temporal brain regions) appeared to hold a core role in brain structural development in late childhood. The behavioral characterization of this brain spatial pattern revealed associations with a wide range of behavioral terms pertaining to emotions, perception, and higher order cognition, a pattern of associations which was furthermore supported by its gene mapping profile including *NTSR1* (e.g., blood pressure and sugar, body temperature), *NPY* (pain perception), *MCHR2* and *THRB* (e.g. thyroid and melanin hormone). Altogether these results further reinforce the hypothesis according to which the hippocampal head is involved in a self-oriented behavioral system (Plachti et al., 2019; Zheng et al., 2021) of reactivity and regulation. Importantly, the current study emphasized that this involvement is already apparent in late childhood.

In late childhood, the differentiation pattern of the HF was evident mainly along the anterior-posterior dimension, dividing it into an anterior (head), middle (body) and posterior (tail) subregion. When examining the underlying structural covariance networks three observations were noteworthy. First, both the hippocampal anterior head (yellow) and posterior tail (green), covaried with parietal and occipital cortex in late childhood, but not in adolescents. This finding may imply that structural covariance networks are not yet well separated in childhood, but only start to differentiate with age in line with the segregation of hippocampal resting-state functional connectivity (Blankenship et al., 2017). Functional connectivity investigation have indeed revealed that the connectivity patterns of the anterior HF to posterior brain regions, such as sensorimotor and visual cortices, diminish in adulthood (Tang et al., 2020). Further complementing these findings, our study suggests that functional interaction of the hippocampal head with posterior regions could already decrease (in line with anterior-posterior functional segregation) at the stage of adolescence.

Secondly, the structural covariance network of the anterior hippocampal subregion revealed a morphological co-variation pattern with almost the whole brain, but especially with temporal, (medial) frontal and subcortical brain regions. This highly extended network of the anterior HF contrasted with the limited covariance patterns of body and tail hippocampal subregions, emphasizing that the anterior but not the posterior HF is coupled with almost the whole-brain due to co-maturation, co-development or co-plasticity in late childhood, highlighting its crucial role in development. This observation may be related to the earlier evolvement of the anterior HF compared to posterior HF, as reported in a longitudinal sample of 4–8-year-old (Canada et al., 2021) and in 6–10 year old children and assessed with shape analysis (Lin et al., 2013). Though specific investigations would be needed to identify the neurobiological factors playing a role in the brain morphological covariance of the hippocampal head in childhood, the neuron production in the dentate gyrus (Lavenex and Banta Lavenex, 2013) a hypothesis. It indeed represents the origin of neurogenesis in the anterior HF (Li et al., 2013), hence possibly boosting co-development.

Thirdly, the behavioral profiling of anterior hippocampal subregion's structural covariance network indicated an involvement in several behavioral systems, based on the associated meta-analytical maps, such as perception (e.g., olfactory), emotions, and higher-order cognition (e.g., language, theory of mind, semantic and autobiographical memory) in line with the broad spatial extent of structural covariance. In agreement with our structural covariance's findings, a recent study has highlighted that the grey matter volume of the anterior, but not the posterior HF, relates to memory and language abilities in early childhood and importantly, was correlated with environmental factors (Decker et al., 2020). Along the same line, volumetric growth of the anterior, but not posterior HF was identified to be relevant for item-item memory improvements in middle childhood and adolescence (Lee et al., 2020). This again confirms our own observation that the anterior HF co-develops with almost the whole brain and therefore is involved in many behavioral systems in the first periods of life, including multiple functional domains such as language, memory, emotion and perception.

These considerations lead us to speculate that late childhood is a time window of high plasticity and vulnerability for the anterior HF, which again may have crucial implications and consequences for adolescence, a time, where psychiatric mood disorders emerge (Paus et al., 2008). Critical life periods were already identified in comparative studies in rodents, monkeys and birds. Functional deficits such as spatial learning are impossible to rehabilitate if adverse environmental factors occur (Lavenex and Banta Lavenex, 2013). This is likely comparable to the reported effects of a deprived environment on anterior HF development and cognitive abilities during childhood identified by Decker et al. (2020).

In late childhood the posterior tail subregion showed an expansion into the anterior-lateral direction, pointing to the evolvement of a pattern along the medial-lateral dimension as evidenced in healthy adults (Plachti et al., 2020). This could again suggest that late childhood is a transitional phase and that the organization of the HF, although still showing mainly an anterior-posterior differentiation, is already on the way to adopting the medial-lateral differentiation of adolescents. Indeed, previous reports showed that the posterior HF comes into the front during late childhood and adolescence by increasing in volume with age (Lee et al., 2020; Lynch et al., 2019), while the anterior HF decreased with age in a sample of 4–25 years old participants (Gogtay et al., 2006). Considering the underlying structural covariance network of the posterior tail (green) subregion, we observed an expansion primarily to posterior brain regions, with the gene mapping profiling suggesting an involvement in synaptic formation, axon guidance, late neurogenesis, remodeling of synapses and the exocytosis of synaptic vesicles (e.g., *NFASC, NAV1, SERPINI1, NLGN4X* and *SYT6*). Thus, axonal and synaptic connections of the posterior HF to important mnemonic circuits (via the fornix) may appear in late childhood,

explaining its increase in volume around the age of 8 and 12 years (Supplementary Figure 5) and its involvement in episodic memory and retrieval, and the association with the *CDH2* gene (learning and memory). Based on the gene mapping results we assumed that processes related to synaptic stabilization first suggested by (Changeux and Danchin, 1976) and myelination (Arnold and Trojanowski, 1996; Benes, 1989) are especially evident in late childhood and continue to refine during early and middle adolescence. Hence, the emergence of the medial-lateral differentiation in the posterior body-tail HF may represent on the one hand the cytoarchitectonic differentiation into subiculum and CA (Amunts et al., 2005), and, in a similar vein, co-evolving pattern with white matter connections (Maller et al., 2019), since macro-structural grey and microstructural white matter tend to covary in a coordinated manner during development (Moura et al., 2017). Therefore, we argue that the period of late childhood and early adolescence is a pivotal transition phase for structural covariance networks (Vijayakumar et al., 2021) of the posterior HF. In this period of time major connections between the HF and posterior brain regions (Meissner et al., 2021), as well as to subcortical and limbic regions via fornix and superior corona radiata (Benear et al., 2020; Jacobus et al., 2013) are strengthened, probably through processes of increased synaptogenesis as suggested by our gene profiling, as well as myelination and co-maturation patterns as reported in the literature.

It is widely accepted that adolescence is a developmental transition period to adulthood, which is marked by higher vulnerability to addictive behavior such as nicotine, alcohol, and drugs (Geier, 2013; R. R. R. Andrew Chambers et al., 2003), but is also characterized by an increase in risky behavior (Blakemore and Robbins, 2012). This disposition was explained by changes in reward behavior and in neural motivation circuitry (Doremus-Fitzwater and Spear, 2016; Telzer, 2016), resulting in the inability to control impulses, postpone gratification and maintain goal-directed behavior (Geier, 2013).

Interestingly, our findings on structural covariance in this age range could be relevant to this context, as the hippocampal medial body-tail (blue) comparable to the subiculum showed spatial covariance patterns with motor- and reward related brain regions. Associations were found between hippocampal medial body-tail and nucleus accumbens, the basal ganglia, ventral striatum, and cerebellum, which is related to learning of motoric output and sensory expectations (Schultz, 2016; Shadmehr et al., 2010; van Duijvenvoorde et al., 2016; Wolpert et al., 2011). The HF was already identified in previous studies as one of the regions belonging to the ventral striatum network associated with reward behavior (Haber and Knutson, 2010) and decision making (Ernst et al., 2005). The structural covariance network of the medial body-tail (blue) HF was related to 'reward', 'incentive', 'gain', 'monetary' but also to 'movement', 'finger', 'execution', indicating an involvement in a reward-oriented action system. This profile was further supported by gene mapping highlighting the involvement of *SLC22A3* and *NTS*. These genes are indeed assumed to be part of the dopamine pathways, locomotor activity and drug-seeking behavior (https://www.genecards.org/). It has been suggested that adolescents have a higher sensitivity for reward (Galvan et al., 2006) shown in fMRI studies with higher activity of reward circuitry to monetary reward (Ernst et al., 2005) and in reinforcement learning (Davidow et al., 2016). Hippocampo-cortical connectivity may play a role in the development of these reward-oriented behavior as, increased functional connectivity between the HF and ventral striatum predicting substance abuse has been shown in adolescents (Huntley et al., 2020).

Our finding of the medial body-tail (blue) HF interacting with reward and motivational networks especially in early adolescence is also in accordance with previous longitudinal findings of reward sensitivity increase between the period of early (9–12 years) to late (13–17 years) adolescence (Urošević et al., 2012). However, only recently a longitudinal study pointed to the earlier maturation of functional connectivity between posterior HF and prefrontal brain regions influencing planning and problem-solving behavior (Calabro et al., 2020). The hippocampal-prefrontal connectivity was furthermore modulated by dopaminergic circuits suggesting an increased involvement of the dopaminergic system mediating goal-oriented behavior in early and middle adolescence (Calabro et al., 2020), supporting our observation of the hippocampal medial body-tail playing a major role during adolescence, and its involvement in reward and motor behavior probably modulated by dopaminergic and GABA circuits.

Overall, our findings highly support the assumption that adolescence is a crucial period of life, probably susceptible to the emergence of substance abuse disorders (Paus et al., 2008) which might partly be related to the co-maturation and co-plasticity of the posterior HF, with limbic and frontal cortices. Higher sensitivity towards reward in adolescence may also promote goal-directed behavior in education, sports and other beneficial domains promoting and enhancing health (Telzer, 2016).

## 5. Limitations and perspectives

The analyses of the study were conducted in a cross-sectional study design. Thus, we can only interpret our HF parcellations as inter-individual age-related differences rather than intra-individual age-related changes of hippocampal differentiation patterns. With the perspective of acquisition of longitudinal neuroimaging data in developmental cohorts, future studies could evaluate age-related changes in hippocampal large-scale integration and how these changes relate to the development of behavioral functions.

Another limitation of the present study is the use of standard maps derived from adult data to characterize the structural covariance networks. For inferences about behavioral systems to which the networks pertain we used the Neurosynth database. NeuroSynth pooled the results of thousands of activation studies reported in the literature and the vast majority of these studies have been performed in adult samples. For inference about gene expression patterns to which our structural covariance maps relate, we used the Allen Human Brain Atlas. This atlas is based on gene expression data obtained from six adult brain donors. Although these resources provide robust spatial patterns of behavioral systems and gene expression in adults, they neglect potential age-related differences. Therefore, our characterizations were based on the assumption that in its core, neither spatial distribution of behavioral domains nor spatial distribution of gene expressions are inherently different between children, adolescents and adults. However, we are fully aware that these may differ in some cases between the age-groups (Ofen et al., 2012; Sterner et al., 2012). To the best of our knowledge, however, such robust activations and gene expression maps are currently lacking for developmental populations. Therefore, future studies are needed to more precisely disentangle how hippocampal structural maturation during the pivotal phases of life, childhood and adolescence relate to changes in functional networks associated to behavioral function and to gene expression.

## Code availability

Any custom code used to compute the parcellation based on structural covariance networks method detailed in this paper will be made available upon request.

## Authorship contributions

AP, RL, SE and SG contributed to the study design. AP, FH and SM contributed to the data processing. AP ran the data analyses. SM provided support in data analyses. AP and SG wrote the first draft. All authors contributed to the manuscript edition and revisions.

## Competing interest

HRS has received honoraria as speaker from Sanofi Genzyme,

Denmark, Lundbeck AS, Denmark, and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora, Denmark, and Lundbeck AS, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. HRS has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark.

## Data Availability

Datasets are openly available at http://fcon_1000.projects.nitrc.org/indi/enhanced/access.html, http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/About.html, and https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2023.102447.

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