

Hippocampal maturity promotes memory distinctiveness in childhood and adolescence

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Adaptive learning systems need to meet two complementary and partially conflicting goals: detecting regularities in the world versus remembering specific events. The hippocampus (HC) keeps a fine balance between computations that extract commonalities of incoming information (i.e., pattern completion) and computations that enable encoding of highly similar events into unique representations (i.e., pattern separation). Histological evidence from young rhesus monkeys suggests that HC development is characterized by the differential development of intrahippocampal subfields and associated networks. However, due to challenges in the in vivo investigation of such developmental organization, the ontogenetic timing of HC subfield maturation remains controversial. Delineating its course is important, as it directly influences the fine balance between pattern separation and pattern completion operations and, thus, developmental changes in learning and memory. Here, we relate in vivo, high-resolution structural magnetic resonance imaging data of HC subfields to behavioral memory performance in children aged 6–14 y and in young adults. We identify a multivariate profile of age-related differences in intrahippocampal structures and show that HC maturity as captured by this pattern is associated with age differences in the differential encoding of unique memory representations.

hippocampal subfields | episodic memory | specificity | pattern separation | child development

Many years ago, the Swiss developmentalist Jean Piaget noted an imbalance between assimilation and accommodation during early and middle childhood in the sense that children tend to extract schematic knowledge at the expense of learning and recollecting specific events (1, 2). This imbalance has resurfaced in computational models of memory (3), and later as the imbalance between pattern completion and pattern separation, processes linked to computational properties of subfields within the hippocampus (HC) (4–6). Understanding the developmental organization of HC subfields is therefore crucial to understand how associated changes in HC-subfield computations drive concomitant changes in learning and memory.

An important step toward unraveling controversies about human hippocampal maturation (7, 8) is to acknowledge that the HC is not a homogeneous structure, but rather is composed of cytoarchitectonically and functionally distinct subfields (9). The availability of high-resolution, in vivo magnetic resonance imaging (MRI) of the HC permits the study of specific contributions of different HC subfields in humans (10–12). Computational and rodent models of HC function and high-resolution MRI studies in humans have sought to establish the contributions of individual HC subfields to specific mnemonic functions. For example, the dentate gyrus (DG) has been closely linked to pattern separation (6). Developmental findings from animal models (13) and initial evidence from human studies (14) suggest that the DG matures later than other HC subfields. Likewise, memory functions associated with pattern separation, such as recollection (6), show a protracted course of development that extends well into middle childhood (15). Thus, the DG is a candidate region of interest (ROI)

for investigating developmental associations between HC and pattern separation.

However, a sole focus on DG is not warranted. Hippocampal subfields are intricately interconnected (13, 16), and their independent demarcation on MRI images remains imperfect (17). Moreover, extant high-resolution MRI studies in human samples are inconsistent in assigning specific HC computations to specific subfields. For instance, pattern separation has been linked not only to DG, but also to the adjacent area 3 of Cornu Ammonis (CA3; e.g., refs. 10 and 18), entorhinal cortex (EC; ref. 19) and in some cases, data have suggested links to the subiculum (Sub; ref. 14). Thus, it appears oversimplified to assign computations, such as pattern separation and completion, to specific parts of the HC in a one-to-one manner (6). Rather, the HC network may be relatively biased toward more pattern separation or more pattern completion, reflecting differential contributions of its constituent parts (6, 10). In a similar vein, based on domain-specific pattern separation signals within the human EC, Reagh and Yassa (19) suggested a conceptual model of interference resolution in the medial temporal lobe (MTL), whereby incremental decrease in representational overlap is reached by pattern separation in domain-specific, parallel pathways already upstream of DG, including EC.

In sum, there is a clear tension between the desire to link structure and function at the level of specific subfields to behavior and the presence of massive connections and interactions within the HC network. Moreover, existing animal and human data suggest that all HC subfields undergo maturational changes during early development (13, 14, 20), albeit along different trajectories. Both of these observations call for a multivariate approach to investigate HC

Significance

Children tend to extract schematic knowledge at the expense of learning and recollecting specific events. Our findings allow us to speculate that the heterogeneous development of subregions within the hippocampus—a brain region crucial for laying down novel memories—contributes to this developmental lag in memory. Specifically, we used in vivo high-resolution structural MRI and memory tests in a large sample of children aged 6–14 years and young adults to characterize hippocampal development. We show that hippocampal maturity as expressed in the multivariate pattern of age-related differences in hippocampal subregions is specifically related to the ability to lay down highly specific memories.

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most likely harm the fine balance between pattern separation and completion operations required for a flexible and adaptive memory system (6). Age-graded changes in the balance between pattern separation and completion are likely to result from a multivariate pattern of subfield changes. Therefore, we examined the age-graded link of HC-subfields maturity to different memory processes from a multivariate perspective. Using partial least squares correlation analysis (PLSC), we extracted a single composite score that captures individual differences in the structural maturity of HC subfields. For simplicity, we refer to this score as “HC-maturity score” (*Methods*). Our PLSC analysis identified a single reliable latent variable (LV; $P = 0.038$) that optimally represents the association between participants’ age and ROI volumes ($r = 0.29$). Bootstrap ratios (BSR) indicated an age-associated increase of DG-CA3 (BSR = 2.3) volume, and a decrease of EC volume (BSR = -1.98) as the two stable components of the LV expressing the largest amount of information common to both age and the multivariate pattern of ROI volumes (Fig. 2).

Several previous reports (8, 30, 31) have suggested that the HC and associated memory functions reach maturity by middle childhood. In contrast, other studies have provided evidence for prolonged maturation of HC-dependent memory process until adolescence (7). In our view, these apparent contradictions can be overcome by acknowledging the heterogeneous course of HC maturation (e.g., refs. 13, 14, and 32). In particular, in light of the subfields’ different maturational trajectories, HC subfield data can yield a more fine-grained picture of age-graded volumetric differences than total HC volume can. With a whole HC analysis run on standard resolution MRI data, subtle maturational effects detectable by high-resolution MRI derived subfield data may go unnoticed. To check this claim empirically, we ran two additional analyses. First, to mimic whole HC analyses, we aggregated DG-CA3, CA1-2, Sub volumes, and computed an analogous PLSC with age, whole HC, and EC. In contrast to the original analysis based on subfield volumes, the analysis with age, whole HC, and EC failed to extract a significant and generalizable latent variable ($P = 0.17$). Second, a voxel-based morphometry (VBM) analysis revealed widespread age-related differences in gray matter volume (GM) over the cortex, but not in the MTL (see Fig. S2 for results and description of the VBM methods). In sum, previous research may have failed to find age-related differences in HC during middle childhood because their total HC target measure collapsed regions with heterogeneous maturational trajectories and/or did not include EC.

Multidimensional Structural Maturity of the Hippocampal Formation Is Associated with Memory Processes Enabling the Unique Encoding of Similar Representations. Next, we assessed the association between individuals’ HC-maturity scores and memory performance. Memory development across childhood is characterized by an overall improvement of mnemonic functions (21, 24). Nevertheless, the developmental timing and interdependence of different mnemonic operations remains controversial (33–36), especially in relation to their dependence on HC maturity (7 vs. 8). Therefore, in the present study, we comprehensively assessed memory processes potentially associated with HC maturity: pattern separation/completion, source memory, item, and associative memory.

A mnemonic similarity task adapted from (10, 37) was used to behaviorally assess pattern separation versus pattern completion bias (Fig. 3A and *SI Methods*). From this task, we computed a pattern separation/completion bias index that expresses the degree to which mnemonic similarity judgments are biased toward pattern separation (or against pattern completion) (10, 37). Several studies have corroborated the suggestion that this index is a reasonable estimate of the relative strength of HC pattern separation (37–39). Using two alternating contexts during learning blocks of the same task, we also assessed source memory. A second task adapted from

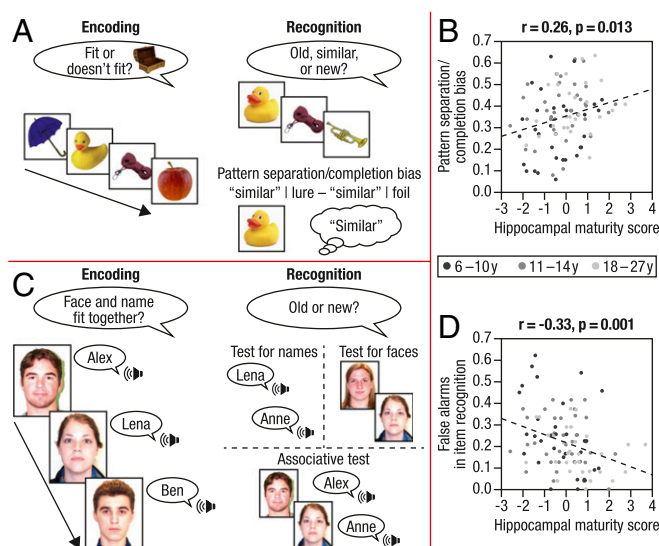


Fig. 3. Multidimensional structural maturity of the hippocampus is associated with memory processes enabling the unique encoding of similar representations. (A) Mnemonic similarity task used to assess pattern separation/completion bias. After incidentally encoding pictures of everyday objects, in a recognition task, participants saw the same target pictures intermixed with highly similar lures and novel foils. Their task was to identify image types by responding “old,” “similar,” or “new.” Pattern separation/completion bias was calculated by subtracting the proportion of similar responses to foils from the proportion of similar responses to lures. The resulting score weighs the tendency to encode two highly similar inputs into separate mnemonic representations against the tendency to assimilate the incoming information to already existing mnemonic representations. Trials that were responded either similar or old were followed by a source memory decision trial (not depicted; see *SI Methods* for details of material, design, and procedure). (B) Increasing HC maturity is associated with a shift in bias toward pattern separation. (C) The faces-and-names task used to assess item and associative memory. After incidentally encoding face-name pairs, participants performed an old/new recognition task composed of three tests administered in a counterbalanced order. Performance on the two item tests was merged to provide one item memory score. Hits and false alarms were calculated for both item and associative memory (see *SI Methods* for details). (D) Increasing HC maturity is related to a decrease in false item recognition. (B and D) Dashed lines represent least-square lines. Different shades of gray represent different age segments to illustrate that the HC maturity-behavior associations hold across age.

Naveh-Benjamin et al. (40) was used to assess item and associative memory (Fig. 3C and *SI Methods*).

To assess the dependence of each memory process on hippocampal maturity, we ran bivariate correlation analyses between the PLSC-derived HC maturity scores and the behavioral indicators. As predicted, the pattern separation/completion bias score correlated positively with the HC maturity score ($r = 0.26$, $P = 0.013$), revealing a moderate shift toward pattern separation with increasing HC maturity (Fig. 3B). In addition, false recognition of item memories (*Methods* and Fig. 3C) showed a significant negative association (Fig. 3D), $r = -0.33$, $P < 0.001$, with HC maturity. No other memory measure revealed significant associations with HC-maturity scores (Table S1). Importantly, the strength of correlations between HC maturity and pattern separation/completion and between HC maturity and false recognition of item memories were significantly stronger than the nonsignificant correlations between HC maturity and the other memory measures [indicated by a significant contrast among correlated correlation coefficients (41), $z = 2.67$, $P = 0.004$].

Both mnemonic similarity judgments and the rejection of foils in a recognition memory task involving highly similar items crucially depend on the orthogonalization of overlapping feature sets in representational space. Therefore, our results suggest that the multidimensional maturity of structures in the HC is specifically related to processes that enable the construction of unique

brain anatomy can serve as a summary description of biological maturity (45). The dimensionality reduction associated with these methods helps to test and refine theories of age-graded changes in brain-behavior relations.

The present study has several limitations, which can guide future research in the field. Given that development is a process unfolding in ontogenetic time, repeated within-subjects assessments are needed to directly capture longitudinal relationships between neural and behavioral variables of interest (46). For this reason, we refrained from using hierarchical linear regression models with age as independent variable, memory processes as dependent variables, and HC subfields as mediator variables. It has been shown analytically that these methods may fail to detect longitudinal mediation when it is present (false negatives) and detect mediation when it is absent (false positives) (47; see also ref. 48). A second limitation is related to the bias score used in this study, which pits pattern separation against pattern completion. Future studies need to obtain measures that separately index age differences in the efficiency of pattern separation and pattern completion mechanisms. The restriction of our analyses to HC body is a third limitation. Previous studies found both structural and functional age-related differences in source memory contributions of the HC head and tail, but not the body (27, 28). Investigating subfield contributions along the full anatomical extent of HC could therefore refine our understanding of how HC subfield and memory development are related (see ref. 29; however, this study also highlights the controversies regarding methods for identifying HC subfield in the head and tail, see ref. 49). Fourth, recent fMRI findings suggest that pattern separation may not be restricted to the HC (50, 51). In the present study, we selected a task that aims at studying age differences in pattern separation performed by the HC, but one that is not well-suited for examining pattern separation, and age differences therein, in other brain areas, such as visual cortex. Future studies need to address the maturational course of pattern separation in other brain areas and their contributions to behavioral development. Last, we devised this study to test the suggestion that HC and related mnemonic functions may develop beyond the onset of middle childhood, but had no a priori reason to postulate that this development may continue beyond middle childhood. Therefore, we did not include individuals aged 15–18 y in the present sample. Also, we did not include children below 6 y of age, reflecting practical limitations when conducting MRI studies with young children. Our results should encourage future research to explore HC subfields and related mnemonic development in a more extended age range.

We found that age-related shifts from pattern completion toward pattern separation are associated with maturational changes in HC subfields. If corroborated by longitudinal evidence from tasks directly measuring some form of knowledge extraction from invariances (i.e., category learning), this result has fundamental implications for theories of episodic memory development: It leads us to speculate that the extraction of invariance across a range of different experiences may precede the encoding, consolidation, and retrieval of detail for reasons that are rooted, at least in part, in the uneven maturational course of substructures within the HC. Returning to Piaget (1, 2), we conclude that this *décalage*, or developmental lag may be developmentally advantageous, as it helps children to recognize regularities, form stable representations of recurring episodes, predict the structure of future events, and build semantic knowledge.

Methods

Participants. Seventy children (35 girls; age range: 6–14 y; $M = 9.80$, $SD = 2.39$ y), and 33 young adults (18 women; age range: 18–27 y; $M = 23.21$, $SD = 2.5$ y) participated in the study. Participants provided written informed consent, also signed by the primary caregiver for all children. Participants were right-handed

and had no history of neurological or psychiatric disorders. They completed the study in two sessions lasting 2 h each and were paid 40 €. Behavioral data were not available for one child and one young adult because of technical issues. The Ethics Committee of the German Psychological Society (Deutsche Gesellschaft für Psychologie) approved the study.

Delineating ROIs in the MTL. Four ROIs were manually demarcated bilaterally (Fig. 1A) by two expert tracers on coronal slices of the high-resolution structural MR volume (voxel size: $0.4 \text{ mm} \times 0.4 \text{ mm} \times 2 \text{ mm}$). The segmentation protocol included three ROIs (Sub, CA1-2, and DG-CA3) segmented along the full range of the HC body, excluding head and tail, and the EC segmented in six slices anterior to the HC body. Bilateral ROIs were collapsed across hemisphere and adjusted for intracranial volume (ICV) for all following analyses (*SI Methods*).

Assessing the Multivariate Relationship Between ROI Volumes and Age Using PLSC. We chose to use PLSC (52, 53) to assess HC maturation on conceptual and methodological grounds. First, deciphering the role of various subregions in memory has proven difficult because the HC forms a hard-wired interconnected processing circuit of interdependent nodes. Second, from a developmental perspective, chronological age is only a proximate index of any assumed “latent maturational process.” Therefore, capturing a maturational process by sampling from participants of different ages is an oversimplified process. By extracting a latent HC subfield profile that maximally shares common variance with age, we aimed at increasing precision for sampling from a latent maturational process. Third, while univariate analyses can capture age-related differences in subregions separately, they ignore intercorrelated patterns of developmental processes affecting the different subparts in a concerted fashion.

Here, PLSC starts by calculating a between-subject correlation matrix (CORR) between (i) an n -element vector containing AGE (in month) and (ii) a $n \times 4$ -matrix of volumetric measures for each HC ROI. CORR is then decomposed by using singular value decomposition (SVD). $\text{SVD}_{\text{CORR}}(\text{AGE}, \text{ROI}) = \text{USV}^T$. This decomposition produces a left singular vector of AGE weights (U), a right singular vector of ROI weights (V), and a diagonal matrix of singular values (S). A single estimable latent variable (LV) results that optimally (in a least-squares sense) represents the associations between AGE and ROI volumes. This LV contains a profile depicting the ROIs that show the strongest relation to AGE. Significance of the detected association was assessed by using 5,000 permutation tests of the singular value corresponding to the LV. A subsequent bootstrapping procedure revealed the robustness of within-LV ROI weights across 5,000 bootstrapped resamples of the data. By dividing each ROI's weight (from V) by its bootstrapped SE, we obtained BSRs as normalized estimates of robustness (Fig. 2B). BSRs are comparable to conventional z values, where a value larger/smaller than ± 1.96 is treated as reliably robust. We also obtained a summary measure of each participant's robust expression of the estimated LV's profile, a within-person HC-maturity score, by multiplying the model-based vector of ROI weights (V) by each subject's vector of ROI volume estimates (Q), producing a single within-subject value, the HC-maturity score = VQ (Figs. 2C and 3B and D).

A comparable procedure was used to derive “frontal maturity score” for control analyses. Instead of volumetric measures of HC subfields, we used VBM derived gray matter volume (GM) estimates in six frontal ROIs of the Ipb40 Atlas (54). Results of this analysis are presented in Fig. 4. Whole-brain PLSC analyses, probing the associations between GM and age are reported in Fig. S1.

Voxel-Based Morphometry. We used the standard preprocessing pipeline of the CAT12 toolbox (dbm.neuro.uni-jena.de/cat) run in SPM12 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm) (version 6906) to obtain voxelwise and ROI specific GM estimates (see Fig. S2 for details). For ROI analyses (Fig. 4), GM estimates were collapsed across hemispheres, and ICV corrected using the same approach as for our HC analysis (*SI Methods*).

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