Changes in anterior and posterior hippocampus differentially predict item-space, item-time, and item-item memory improvement

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ARTICLE INFO

ABSTRACT

Relational memory improves during middle childhood and adolescence, yet the neural correlates underlying those improvements are debated. Although memory for spatial, temporal, and other associative relations requires the hippocampus, it is not established whether within-individual changes in hippocampal structure contribute to memory improvements from middle childhood into adolescence. Here, we investigated how structural changes in hippocampal head, body, and tail subregions predict improvements in the capacity to remember item-space, item-time, and item-item relations. Memory for each relation and volumes of hippocampal subregions were assessed longitudinally in 171 participants across 3 time points (M_{age} at T1 = 9.45 years; M_{age} at T2 = 10.86 years, M_{age} at T3 = 12.12 years; comprising 393 behavioral assessments and 362 structural scans). Among older children, volumetric growth in: (a) head and body predicted improvements in item-time memory, (b) head predicted improvements in item-item memory; and (c) right tail predicted improvements in item-space memory. The present research establishes that changes in hippocampal structure are related to improvements in relational memory, and that sub-regional changes in hippocampal volume differentially predict changes in different aspects of relational memory. These findings underscore a division of labor along the anterior-posterior axis of the hippocampus during child development.

1. Introduction

Over the last decade, a growing body of research has begun to characterize the neural mechanisms underlying the development of memory during childhood (Ofen et al., 2007; Ghetti and Lee, 2011; DeMaster and Ghetti, 2012; Güler and Thomas, 2013; Schlichting et al., 2017). The hippocampus is a brain structure critical to the capacity to remember the past in detail (Tulving and Markowitsch, 1998; Burgess et al., 2002), yet a long held, if inadequately tested assumption, is that the hippocampus does not contribute to memory improvements in middle childhood. This assumption is based primarily on evidence

showing limited difference in overall hippocampal structure with age (Giedd et al., 1996), standing in contrast to the robust differences observed in infancy (Insausti, 2010). However cross-sectional evidence reporting associations between age-related differences in hippocampal structure and age-related improvements in memory in middle childhood challenge this assumption (DeMaster et al., 2014; Lee et al., 2014; Daugherty et al., 2016; Riggins et al., 2018). Yet, without longitudinal evidence, a direct link between changes in hippocampal structure to changes in memory cannot be established. The present longitudinal study establishes this link within the transition from childhood into adolescence, a period of marked improvements in the ability to

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remember specific details about our pasts (Ghetti and Lee, 2011).

This ability depends on mechanisms that bind features of experiences into integrated memory representations (Eichenbaum and Cohen, 2001); these features include where an event happened (item-space) (Ekstrom et al., 2011), when it happened (item-time) (Eichenbaum, 2013), and with what other events it co-occurred (item-item) (Giovanello et al., 2004). The hippocampus is critical for learning and recalling these arbitrary memory relations (Konkel et al., 2008; Ranganath, 2010). Although there is substantial evidence that the hippocampus is necessary to learn all forms of arbitrary relations (e.g., Konkel et al., 2008), it is also increasingly clear that that there is some degree of segregation within the hippocampus (Poppenk and Moscovitch, 2011), such that item-item relations may be supported by more anterior regions (Giovanello et al., 2009), whereas item-space relations may be supported more strongly by right-lateralized posterior hippocampal regions (Persson et al., 2018).

This functional segregation aligns well with two lines of evidence suggesting a co-occurrence of distinct structural changes in the anterior and posterior hippocampus and behavioral changes in relational memory. First, age-related differences between memory for spatial, temporal and associative information have been documented in cross-sectional studies against a backdrop of general memory improvement during childhood (Ghetti and Lee, 2011; Picard et al., 2012; Guillery-Girard et al., 2013; Lee et al., 2014). This body of research indicates that memory for spatial relations may be more robust at a younger age compared to memory for temporal relations (Picard et al., 2012; Guillery-Girard et al., 2013; Lee et al., 2016) and item-item associative relations (Lee et al., 2016). Second, initial cross-sectional findings point to heterogeneous development of the hippocampus during middle childhood in subregions along the anterior-posterior axis which exhibited distinct relations with memory (DeMaster et al., 2014; Lee et al., 2017; Schlichting et al., 2017; Riggins et al., 2018; DeMaster et al., 2013). Specifically, these studies suggested that while hippocampal body may exhibit age-related increases in volume after middle childhood, hippocampal head may exhibit age-related increases in volume up to middle childhood and declines afterwards. Pointing to a functional dissociation, superior relational memory performance was observed in young adults with smaller hippocampal head volumes and in children with larger hippocampal tails (DeMaster et al., 2014; Lee et al., 2017; Schlichting et al., 2017) This initial evidence suggests functional dissociations along the hippocampal axis during child development, but longitudinal data would provide the best evidence for distinct relations between hippocampal sub-regions and relational memory improvements over time.

The central hypothesis guiding the present research is that changes in hippocampal structure will predict developmental improvements in relational memory during middle childhood. We further predicted that relational memory will develop differentially as a function of type of relation, with the ability to remember item-space relations developing earlier than the other relations. We also predicted distinct developmental trajectories of hippocampal volume as a function of subregion, with the hippocampal head decreasing and the hippocampal body increasing in volume at least prior to age 10 (Lee et al., 2014). Finally, we hypothesized that volumetric changes in hippocampal subregions would predict behavioral changes differently as a function of type of relation. For example, changes in more posterior subregions (i.e., tail) were expected to relate to the development of memory for item-space relations (Poppenk and Moscovitch, 2011).

2. Materials and methods

2.1. Participants

Our sample included 171 participants at T1 (84 females; 143 behavioral assessments; 155 structural scans; $M_{age} = 9.45$ years, $SD_{age} = 1.09$, 7.1–12.0 years), 140 participants at T2 (66 females; 136 behavioral assessments, 118 structural scans; $M_{age} = 10.86$ years, $SD_{age} = 1.22$, 8.2–13.86 years), and 119 participants at T3 (52 females; 114 behavioral assessments, 88 structural scans; $M_{age} = 12.12$ years, $SD_{age} = 1.31$, 9.0–15.16 years). Item-space, item-time, and item-item memory at T1 did not significantly differ between those who returned at T2 compared to those who did not ($\chi^2 = 2.61$, $df = 3$, $p = .46$ uncorrected), or between participants who returned for T3 and those who did not ($\chi^2 = 1.31$, $df = 3$, $p = .73$ uncorrected). Head, body, and tail volumes did not differ at T1 in those who returned at T2 than those who did not (χ^2s ≤ 1.17, dfs $= 2$, $ps \geq 0.56$ uncorrected), or between participants who returned for T3 and those who did not (χ^2s ≤ 2.13, dfs $= 2$, $ps \geq .34$ uncorrected). Children were ineligible if parents reported a learning disability, neurological or psychological diagnosis requiring medication at the time of enrollment. Children were compensated for their participation. This research was conducted with the approval of the Institutional Review Board at the University of California, Davis.

Behavioral and imaging data were collected over two visits. The Triplet Binding Task (TBT) was administered on the first visit. Magnetic Resonance Imaging (MRI) occurred approximately one week after the behavioral assessment.

2.2. Triplet binding task

The TBT is a memory task that assesses item-time, item-space, and item-item relational memory and item-recognition memory using (Konkel et al., 2008; Lee et al., 2016). To counter fatigue, the TBT was administered over two separate sessions on the same day. In each session, each memory type was assessed in blocks to minimize increased task-switching costs in younger children. Blocks were counterbalanced across participants. Within each assessment block, 5 encoding-retrieval phases were administered. TBT stimuli included color images of novel and obscure real-world objects unlikely to be familiar to participants; these stimuli limit the utility of semantic-based organizational memory strategies known to underlie some developmental improvements in memory (Bjorklund et al., 2009).

2.2.1. Encoding phase

Prior to each testing block, participants were instructed and tested on their understanding of the task, the relation to be encoded, and the triplet trial structure using practice encoding and retrieval phases. The encoding phase format was identical for item-time, item-space, item-item, and item-recognition encoding conditions. Each encoding phase comprised three trials. In each trial, three novel objects (i.e. triplet) were sequentially presented for one second to three set locations on a computer screen, one object per location (see Fig. 1B Top). Each of the three spatial positions (top-left, bottom, and top right of screen) was clearly separated in space. A one second inter-trial fixation was then presented before proceeding to the next of the three encoding trials. To aid learning, the encoding phase was repeated a second time.

2.2.2. Retrieval phase

Retrieval immediately followed each encoding phase. Each retrieval phase, depending on the testing block, assessed memory for item-space, item-time, or item-item relations, or item recognition memory (Fig. 1B Bottom). The retrieval phase comprised three target and/or 8lure probes. Overall, 15 targets and 15 lures were probed in each retrieval condition.

2.2.2.1. Item-space. In each item-space test probe, three objects from the same encoding trial appeared together on the screen. Participants decided whether all objects appeared at their original positions or not. In target trials all objects maintain their original positions, while in lure trials the spatial positions of two objects are exchanged All probe items were shown simultaneously and belonged to the same encoding triplet, thus neither temporal nor item-relational retrieval cues were provided.
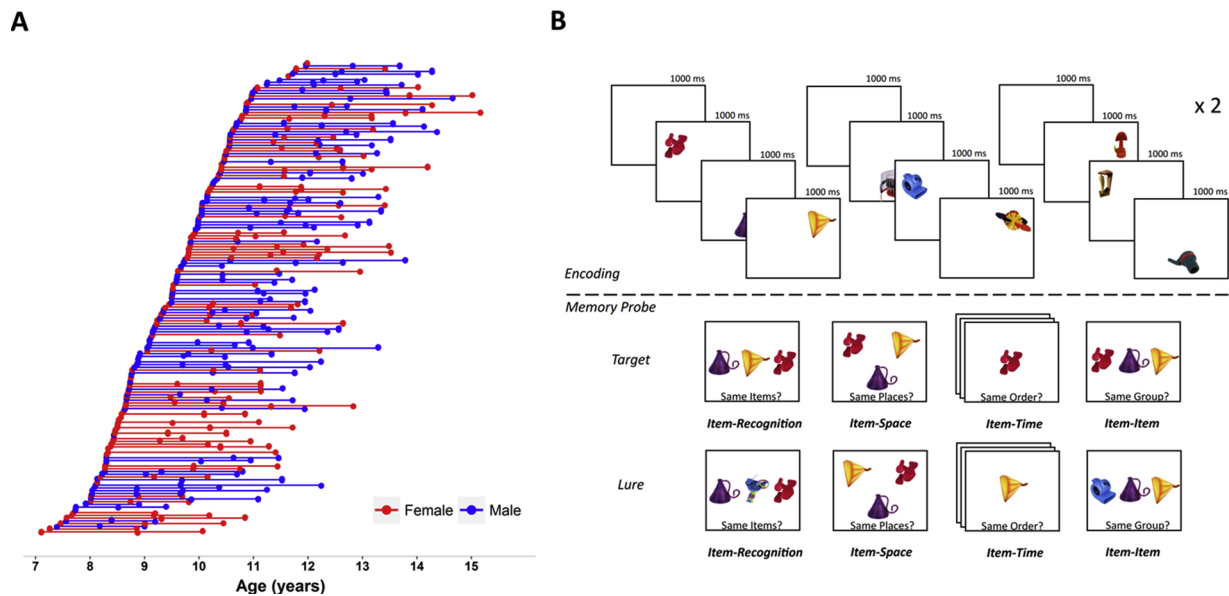
Fig. 1. A. Longitudinal cohort of 172 children providing MRI structural images and relational memory assessments on up to three occasions (362 longitudinal scans, 393 longitudinal behavioral assessments). **B.** Triplet Binding Task (TBT). Encoding: Item-Recognition, Item-Space, Item-Time, and Item-Item relation conditions shared identical encoding procedures. Within each encoding trial, three items were shown sequentially to one of three possible spatial positions (top-left, bottom, or top-right), together forming a triplet. Children were informed which memory relation should be attended prior to the start of each condition block. Memory probe: Target and lure test trials for item-recognition, item-space, item-time, and item-item relation conditions are shown, from left to right, respectively. For item-recognition and item-item memory probes, items were shown simultaneously, randomly assigned to one of three positions in a line across the middle of screen, thus neither spatial nor temporal retrieval cues were available to support memory retrieval. For item-space memory probes, items from the same encoding triplet were shown simultaneously, thus neither temporal nor item-relational retrieval cues were provided. Likewise, for item-time memory probes, item sequences were shown at the center of the screen and all items belonged to the same encoding triplet, thus neither spatial nor item-relational retrieval cues were provided.

2.2.2.2. Item-time. In each item-time retrieval phase, three objects from the same encoding trial were sequentially presented to the center of the screen. No object appeared at their original spatial position. Participants decided whether the sequence of objects in the probe appeared in their original order or not. In target trials all objects maintain their original order, while in lure trials the ordinal position of two objects are switched. For item-time memory probes, item sequences were shown at the center of the screen and all items belonged to the same encoding triplet, thus neither spatial nor item-relational retrieval cues were provided.

2.2.2.3. Item-item. In each item-item test probe, three objects appeared on the screen at three horizontal positions. No object appeared at their original spatial position. Participants decided whether all objects had appeared together in the same trial (i.e. triplet) or not. In target trials all objects came from the same encoding trial, while in lure trials one object was exchanged with an object from another trial from the same encoding phase. For item-item memory probes, items were shown simultaneously at randomly assigned positions in a line across the middle of screen, thus neither spatial nor temporal retrieval cues were provided to support item-item retrieval.

2.2.2.4. Item recognition. In each item-recognition test probe, three objects appeared together on the screen at three horizontal positions. No object appeared at their original spatial position. Participants decided whether all objects had previously been studied. In target trials all objects were studied, while in lure trials two of the three objects were new. Items were shown simultaneously at randomly assigned positions in a line across the middle of screen, thus neither spatial nor temporal retrieval cues were provided to support item-recognition memory.

2.3. Structural magnetic resonant imaging

Magnetic Resonance Imaging (MRI) was acquired at the University of

California, Davis Imaging Research Center in a 3 T Siemens Tim Trio scanner with a 32-channel head coil. Two 7½-minute T1-weighted MPRAGE images were acquired (TE: 3.2 ms; TR: 2500 ms; in-plane resolution: 640×256 matrix, 0.35 mm x 0.70 mm; slice resolution: 640, 0.35 mm). Each participant's two structural images were co-registered, averaged, and oriented so that the coronal plane was perpendicular to the long axis of the hippocampus. Each image was cropped into left and right hippocampal regions, after which retrospective bias correction was performed.

2.3.1. Hippocampal segmentation

Hippocampal segmentation was performed using the Automatic Hippocampal Estimator using Atlas-based Delineation (AHEAD) software which implements a state-of-the-art multi-atlas joint label fusion approach to image segmentation (Wang and Yushkevich, 2013). Briefly, manually labeled atlases of left and right hippocampus are non-linearly registered to each participant's structural image using Advanced Normalization Tools. This produces candidate segmentations for each target's hippocampus from which a consensus segmentation is computed using joint label fusion, an advanced weighted voting procedure (Wang and Yushkevich, 2013). The multi-atlas of the hippocampus was produced by expert manual rater (JKL) in 14 children balanced for sex and age using an established protocol (Lee et al., 2015), a quantity of atlases sufficient to yield high accuracy segmentation (Asman and Landman, 2013). Each segmentation was manually reviewed for accuracy.

2.3.2. Delineation of hippocampal sub-regions

Head, body, and tail subregions were delineated by blinded rater PD and JKL under an established protocol (DeMaster et al., 2014). This segmentation had excellent inter-rater reliability (Head/Body Division: ICC = .98; Body/Tail Division: ICC = .99). Each subregion volume was adjusted by estimated intracranial volume (ICV) using the analysis of covariance approach (Raz et al., 2005). ICV estimates were obtained

using previously described procedures (Lee et al., 2014).

2.4. Analytical approach

All analyses used mixed random effect models capable of accounting for within-subject dependencies in the data (Hoffman, 2015). Since accelerated longitudinal designs enroll participants across a range of starting ages, the effects of age comprise both the within-individual effect of age change and the between-subject effect of cross-sectional differences in age. We therefore followed the approach in which the effects of age at each time point are separated into a within-subject time-varying covariate (i.e. change in age since T1) and a between-subject time-invariant covariate (i.e. starting age at T1) (Sliwinski et al., 2010; Hoffman, 2015). Given that at most only three measurement occasions were available, we did not estimate non-linear within-subject effects. However, we capitalize on the accelerated longitudinal design to test whether children of different starting ages have different within-subject trajectories. Time invariant covariates (e.g., starting age at T1) were centered at the mean of the measure at the T1. All mixed effect models included a random intercept and random slope for change in age since T1. Estimation of model parameters used restricted maximum likelihood (REML), while model comparisons used maximum likelihood (ML). Data were inspected for univariate and multivariate outliers using distribution-based outlier detection, data and Q-Q plots, Z-scoring, and Cook's distance. Mixed models were fitted and plotted using the lme4 (ver. 1.1), lmerTest (ver. 2.0) and effects (ver. 3.1) packages in R (ver. 3.3.1). Model comparisons were used to build up each model over baseline models, beginning with first-order effects and systematically testing inclusion of higher order interaction effects.

To evaluate and interpret interactions involving continuous variables (i.e., starting age at T1 and change in age since T1), associations were estimated at different values of these covariates by re-centering the covariate and re-estimating model parameters. Evaluating the effect of differing starting ages at Time 1, age at T1 was centered to either 8 and 11 years, respectively—round numbers that roughly represent the lower and higher ends of the Time 1 age range. For change in age since T1, models were evaluated at one and three years, representing shorter and longer delays, which are well represented in our data. For clarity, we reiterate that no age-groups were formed or analyzed; interpretations of interactions relied on estimating the model at different intercept values of continuous covariates.

2.4.1. Behavioral model

Memory scores were computed at each time point and relation as the difference between hit and false alarm rates. Models include the effects of starting age at T1, change in age, and memory relation, and control for effects of sex and item-recognition at T1. The full behavioral model is described in Table 1.

2.4.2. Hippocampal model

We tested for main and interactive effects of starting age at T1,

Table 1
Fixed and Random Effect Models.

Behavioral: Memory = Sex + Item-recognition$_{T1}$ + Age$_{T1}$ * ΔAge * Relation + (1 + ΔAge | Participant)
Hippocampal: Volume = Sex + Hemisphere + Age$_{T1}$ * ΔAge * Subregion + (1 + ΔAge | Participant)
Brain–Behavior: Memory = Sex + Item-recognition$_{T1}$ + Head$_{T1}$ + Body$_{T1}$ + Tail$_{T1}$ + Age$_{T1}$ * ΔAge * ΔHead + Age$_{T1}$ * ΔAge * ΔBody + Age$_{T1}$ * ΔAge * ΔTail + (1 + ΔAge | Participant)

Note: '*' denotes inclusion of main and interactive effects between operands. '(1 + Δ Age | Subject)' indicates a random intercept and slope model. Female gender, item-item relations, and hippocampal head served as reference categories. Brain-Behavior models examined each relation separately. T1 subscript denotes value at Time 1.

change in age, and hippocampal subregion, and control for effects of sex and hemisphere. The hippocampal model is described in Table 1. We also computed partial derivatives to derive the starting age at T1 in which the slope of change in age would be predicted to equal zero (i.e., the apex/base of the trajectories).

2.4.3. Brain-behavior model

Brain-behavior analyses examined item-time, item-space, and item-item memory separately. Each model simultaneously tested the effects of changes in hippocampal head, body, and tail on memory performance, while accounting for their volumes at T1. The brain-behavior model is described in Table 1. Model comparisons tested the effect of head, body, and tail changes together as a block, building up the model. We began by testing the change in model fit by simultaneously adding the three volume changes (as a block) over a baseline model, which included age at T1, change in age, item-recognition at T1. We then proceeded by testing the change in fit by adding the two-way interactions between changes in head, body, and tail volume and change in age since T1, as a block. Likewise, the two-way interactions with change in head, body, and tail volume and age at T1. Lastly, we tested the change in model fit by adding the three-way interactions between changes in head, body, and tail volumes with change in age and age at T1. Primary analyses summed volumes across hemispheres. Additional analyses considering left and right hippocampal structures separately were also conducted.

3. Results

3.1. Distinct developmental trajectories of relational memory

We first conducted the longitudinal analysis of relational memory (See Table 1). Overall, relational memory was greater in children who were older at T1 ($\chi2 = 17.8$, $df = 1$, $p < .0001$; $\beta = .18$, $b = .04$, t (170) = 4.4, $p < .0001$), capturing cross-sectional differences, and it increased more as more time passed, as indicated by a positive association with change in age ($\chi2 = 25.5$ $df = 1$, $p < .0001$; $\beta = .17$, b = .04, t (121) = 5.19, $p < .0001$). Improvements in relational memory over time were greater for children who were younger at T1 (age at T1 x change in age in years interaction; $\chi2 = 7.90$, $df = 1$, $p = .005$; $\beta = .18$, b = -.02, t (140) = -2.88, $p = .004$). We also found a significant effect of type of relation ($\chi2 = 368.5$, $df = 2$, $p < .0001$), such that the highest performance was observed for item-space memory (M=.45; SE= .01), which was greater than item-time (M=.36, SE=.01; t (864) = 7.1, $p < .0001$). Item-time was, in turn, greater than item-item memory (M=.17, SE .01; t (864) = 10.03, $p < .0001$). Consistent with our primary hypothesis, the magnitude of memory improvement over time depended on the type of relation, as indicated by a significant interaction between change in age and type of relation ($\chi2 = 6.21$ $df = 2$, $p = .04$) (Fig. 2). See Table 2 for parameter estimates for each type of relation separately. See Table S1 for parameter estimates testing the interaction with type of relation, and Fig. S1 for a plot of depicting how change in each task condition are inter-related. The positive association between change in age and change in memory was stronger for item-time and item-item than for item-space (item-space: $\beta = .09$, $b = .02$, t (374) = 2.17, $p = .03$; item-time relative to item-space, $\beta = .08$, $b = .03$, t (867) = 2.18, $p = .03$; item-item relative to item-space, $\beta = .08$, $b = .03$, t (867) = 2.11, $p = .04$). Associations between change in age and performance did not differ between item-time and item-item relations ($p = 0.94$). Model parameters predicted that item-space memory plateaued around 10.4 years, item-time memory around 12.2 years of age, and item-item around 12.5 years. Thus, consistent with prior work, item-space memory matured earlier than both item-item and item-time relations.

Given overall performance differences between relational conditions, we conducted a follow-up analysis to examine how baseline performance at Time 1 in each task was related to developmental trajectories. Within each relational condition, we subtracted baseline
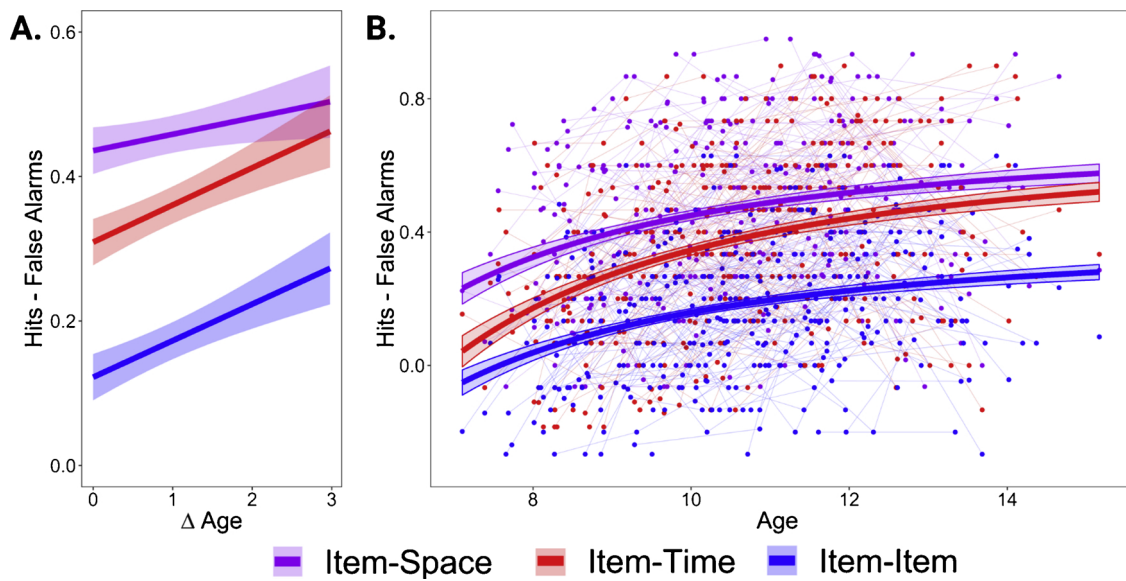
Fig. 2. Developmental changes in memory for item-space, item-time, and item-item relations. Error bands represent 95 % confidence intervals. **A.** Depicting the interaction between memory relation and within-subject changes in age since Time 1 (ΔAge) at the mean age of Time 1. **B.** A descriptive spaghetti plot of item-space, item-time, and item-item memory performance by years in age, best fit with inverse quadratic fractional polynomials. Note that the use of age conflates between-person cross-sectional differences with within-person changes, and thus these fit lines may not always reflect true average longitudinal change.

Table 2
Parameter Estimates for Item-Time, Item-Item and Item-Space Models.

Effect	Beta	b	SE	t	p
Item-Time					
(Intercept)	–	.323	.023	14.3	<.001
Item-Recognition	.310	.353	.066	5.39	<.001
Male	−.048	−.025	.029	−.861	.390
Start-Age	.213	.044	.013	3.29	.001
ΔAge	.212	.051	.011	4.61	<.001
Start-Age x ΔAge	−.125	−.019	.009	−2.05	.043
Item-Item					
(Intercept)	–	.133	.019	6.93	<.001
Item-Recognition	.162	.151	.053	2.87	.005
Male	−.033	−.014	.023	−.605	.546
Start-Age	.204	.035	.012	2.95	.004
ΔAge	.244	.048	.009	5.27	<.001
Start-Age x ΔAge	−.128	−.016	.008	−2.07	.041
Item-Space					
(Intercept)	–	.457	.023	20.2	<.001
Item-Recognition	.328	.357	.065	5.49	<.001
Male	−.076	−.038	.029	−1.31	.191
Start-Age	.180	.036	.014	2.66	.009
ΔAge	.083	.019	.011	1.73	.086
Start-Age x ΔAge	−.139	−.020	.009	−2.18	.031

Notes: Model Fits: Item-Time: $\chi2 = 68.7$, $df = 5$, $p < 1.85e\text{-}13$; Item-Space: $\chi2 = 48.2$, $df = 5$, $p = 3.3e\text{-}9$; Item-Item: $\chi2 = 48.0$, $df = 5$, $p = 3.6e\text{-}9$; Interactions with sex were not significant ($\chi2s \leq 4.66$, $dfs = 3$, $ps \geq .20$). Note: ΔAge is defined at time in years since Time 1. Item-recognition and Start-Age are centered at the mean at Time 1. Left hemisphere and female are reference categories.

from subsequent measurements, generating change scores as an outcome measure. We compared these change scores and included baseline performance in each condition as a covariate. These results replicated the primary behavioral findings, namely that developmental improvements significantly differed by type of relation ($\chi2 = 8.22$, $df = 3$, $p = .042$), such smaller increases over time were observed for item-space compared to item-item performance (b=-.023, SE=.01, t (994)=-2.18, $p = .029$). Moreover, baseline performance negatively predicted change in performance (b=-.10, SE=.02, t(975)=-8.421,

$p<2e\text{-}16$), consistent with the fact that children who have already achieved high performance levels at the beginning of the study do not have as much room to grow as those who have not; critically, however, these regressions were not significantly biased by relational condition ($\chi2 = 1.404$, $df = 2$, $p = .50$).

Finally, we examined developmental improvements in performance on the item-recognition condition. Item-recognition improved with starting age at T1 (b = .047, SE = .013, t(184.6) = 3.64, p = .0004) and with change in age (b = .021, SE = .010, t(167.1) = 2.22, p = .028), but did not observe a significant age at T1 by change interaction ($\chi2 = 1.95$, df = 1, p = 16). (See Table S3 for parameter estimates and Fig. S2 for a trajectory plot).

3.2. Distinct developmental trajectories of hippocampal subregions

We assessed developmental changes in hippocampal head, body, and tail (See Table 1). We found a significant interaction between change in age and hippocampal subregion ($\chi2 = 8.83$ $df = 2$, $p = .012$), which was further moderated by starting age at T1 ($\chi2 = 9.80$, $df = 3$, $p = .020$). As predicted, we found distinct within-subject trajectories for the three subregions (Fig. 3). See Table S3 for parameter estimates of this full model. For completion, we also estimated longitudinal models using total hippocampal volume, the results of which are reported in Table S4. Given the differences in volumetric change as a function of subregion, we examined the trajectory of each subregion separately.

3.2.1. Hippocampal head

As predicted, hippocampal head volumes declined over time, as indicated by the negative effect of change in age ($\chi2 = 5.63$, $df = 1$, $p = .02$; $b = -7.07$, $t(449) = -2.62$, $p = 9.2e\text{-}3$). This effect was moderated by starting age at T1 ($\chi2 = 4.65$, $df = 1$, $p = .03$; $\beta = -.06$, $b = -5.51$, $t(457) = -2.16$, $p = .03$), such that greater volumetric declines were observed in children who were older at T1. Associations with change in age did not significantly differ between hemispheres ($\chi2 = .60$, $df = 1$, $p = .44$) or sex ($\chi2 = 2.58$, $df = 1$, $p = .11$) (Table 3). A descriptive examination of the partial derivatives of model parameters suggests that peak volume of hippocampal head occurred at 8.17 years of age before declining during late childhood.
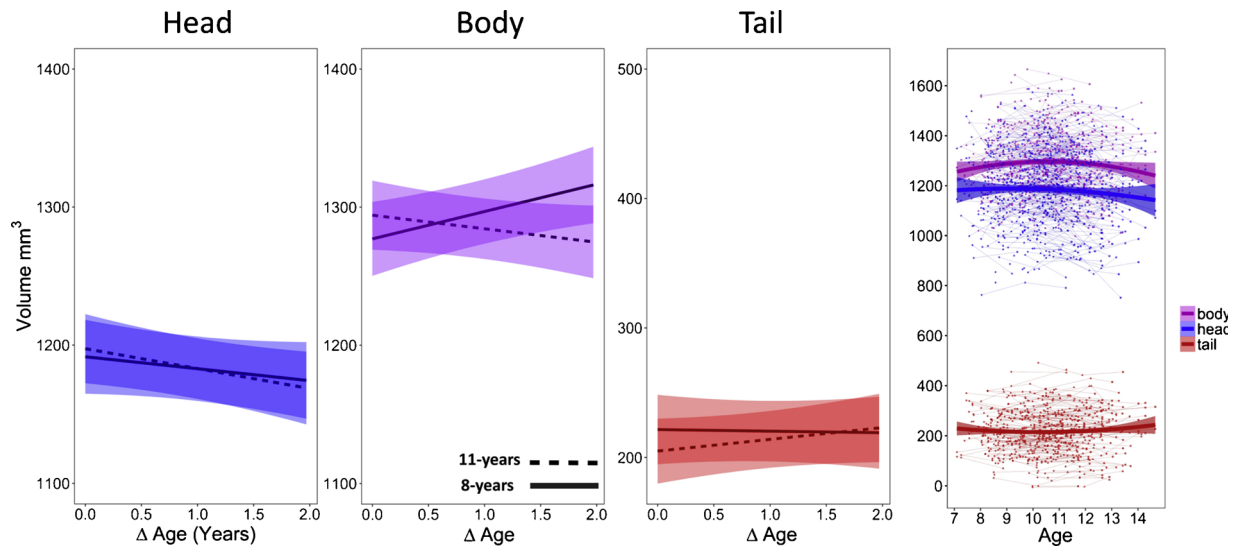
Fig. 3. Developmental changes in head, body, and tail ICV-corrected volume. Error bands represent 95 % confidence intervals. **A.** Depicting the three-way interaction between hippocampal sub-region, within-subject change in age since Time 1 (ΔAge), and cross-sectional differences in the starting age at Time 1. The relation between ΔAge and subregional volume was estimated at two different values of the starting age at Time 1 continuous covariate, computed by centering the covariate to 8 or 11 years, respectively, ages chosen as round numbers roughly representing the lower and higher ends of the Time 1 age range. Note that these analyses did not bin children into age groups but rather reflect the estimates of model at different values of a continuous covariate. **B.** Spaghetti plots of head, body, and tail ICV-corrected volume over time with quadratic lines fitted.

Table 3
Parameter Estimates for Models of Hippocampal Head, Body, and Tail Change.

Sub-Region	Effect	Beta	b	SE	t	p
Head	(Intercept)	–	1128	16.4	68.8	<.001
	Male	.030	11.7	22.3	.525	.600
	Hemisphere [Right]	.313	106	5.23	20.2	<.001
	Start-Age (Mean-Centered)	.011	3.02	10.2	.298	.770
	ΔAge	−.060	−7.07	2.70	−2.62	.009
	Start-Age x ΔAge	−.056	−5.51	2.56	−2.16	.033
Body	(Intercept)	–	1314	13.4	98.1	<.001
	Male	−.133	−26.1	18.1	−1.44	.150
	Hemisphere [Right]	−.104	−33.5	4.93	−6.80	<.001
	Start-Age (Mean-Centered)	.015	1.40	8.35	.167	.873
	ΔAge	.012	1.68	2.53	.661	.514
	Start-Age x ΔAge	−.061	−4.86	2.39	−2.03	.042
Tail	(Intercept)	–	208	9.38	22.1	<.001
	Male	.067	11.5	12.6	.912	.363
	Hemisphere [Right]	.024	4.10	2.92	1.40	.164
	Start-Age (Mean-Centered)	−.042	−3.30	5.86	−.564	.572
	ΔAge	.022	1.76	1.50	1.17	.240
	Start-Age x ΔAge	.010	.538	1.42	.377	.712

Model Fits: Hippocampal Head: χ2 = 312, *df* = 5, *p* < 2.2e-1; Hippocampal Body: χ2 = 51.4, *df* = 5, *p* = 7.2e-10; Hippocampal Tail: χ2 = 4.44, *df* = 5, *p* = 0.49. Note: ΔAge is defined as time in years since Time 1; Left hemisphere and female are reference categories; Volumes are in cubic mm.

3.2.2. Hippocampal body

As predicted, hippocampal body exhibited a non-linear trajectory. Change in age significantly interacted with age at T1 (χ2 = 4.10, *df* = 1, *p* = .04; β=-.06, b = -4.86, *t* (496) = -2.03, *p* = .04): The volume of the hippocampal body increased over time for younger children, but it declined for older children. Association with changes in age did not significantly differ by hemisphere (χ2 = .60, *df* = 1, *p* = .44) or sex (χ2 = 3.4e-3, *df* = 1, *p* = .95) (Table 3). A descriptive examination of the partial derivatives of model parameters suggests that peak volume of

hippocampal body occurred at 9.79 years before declining in late childhood.

3.2.3. Hippocampal tail

No significant developmental changes were observed for either left or right tail (Table 3).

3.3. Linking hippocampal and relational memory development

We examined whether and how volumetric changes along the anterior-posterior axis predicted the development of each type of memory relation (See Table 1). All models included volume at T1, changes in volume since T1, age at T1, and changes in age since T1, as well as their interactions. Volume and volume changes were in cubic millimeters for unstandardized betas. The primary longitudinal effects of interest were the two- and three-way interactions between age at T1, change in age, and change in volume. These interactions allow us to link developmental changes in volume to behavioral development, with the additional consideration that longitudinal relations may depend on the age at the start of the study. We started by examining item-time and item-item memory, because they showed the most robust behavioral change, and ended with item-space memory, which we established develops relatively earlier (see Methods for detailed description of the models). For these, left and right hippocampal volumes were summed because no hemispheric differences were observed.

3.3.1. Item-Time

Consistent with predictions, changes in hippocampal head, body, and tail predicted item-time memory. Specifically, we observed a significant three-way interaction between change in hippocampal subregion volumes, age at T1 and change in age (χ2 = 12.1, *df* = 3, *p* = .007) (See Table 4). Increase in head and body volumes, but not tail, significantly predicted greater memory performance after longer delays (e.g., a 3-year change is depicted in Fig. 4A), but not shorter delays (e.g., a 1-year change in age is depicted in Fig. S3A), indicating that several years were necessary for these brain-behavior relations to manifest. Furthermore, this result depended on age at T1. When the model was evaluated for children who were older at T1 (e.g., 11 years, as depicted in Fig. 4A), volumetric

Table 4
Hippocampal Volume Predicting the Development of Item-Time Memory.

Effect	Left and Right Hippocampal Sum				
	Beta	b	SE	t	p
(Intercept)	–	3.2e-1	2.5e-2	13	<.0001
Item-Recognition	0.28	3.2e-1	7.4e-2	4.4	<.0001
Sex [Male]	−0.053	−2.8e-2	3.2e-2	−0.86	0.39
Start-Volume Head	−0.049	−4.5e-5	5.6e-5	−0.79	0.43
Start-Volume Body	−0.065	−7.0e-5	6.6e-5	−1.1	0.29
Start-Volume Tail	0.062	9.8e-5	9.9e-5	0.99	0.32
Start-Age	0.25	5.8e-2	1.7e-2	3.4	0.001
ΔAge	0.26	6.2e-2	1.3e-2	4.7	<.0001
ΔHead	−0.063	−1.9e-4	4.1e-4	−0.47	0.64
ΔBody	−0.056	−1.6e-4	3.8e-4	−0.43	0.67
ΔTail	−0.2	−1.4e-3	9.5e-4	−1.5	0.14
Start-Age x ΔAge	−0.13	−2.1e-2	1.2e-2	−1.7	0.095
Start-Age x ΔHead	−0.26	−6.4e-4	3.2e-4	−2	0.048
Start-Age x ΔBody	−0.22	−6.3e-4	3.7e-4	−1.7	0.096
Start-Age x ΔTail	−0.037	−2.6e-4	1.0e-3	−0.25	0.8
ΔAge x ΔHead	0.072	1.1e-4	2.2e-4	0.5	0.62
ΔAge x ΔBody	0.14	2.0e-4	1.9e-4	1.1	0.29
ΔAge x ΔTail	0.11	4.0e-4	5.0e-4	0.8	0.42
Start-Age x ΔAge x ΔHead	0.33	4.1e-4	1.9e-4	2.2	0.027
Start-Age x ΔAge x ΔBody	0.29	4.2e-4	1.9e-4	2.2	0.032
Start-Age x ΔAge x ΔTail	0.12	4.2e-4	5.5e-4	0.77	0.44

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

increases in head and body volume predicted better item-time memory (Body: $\beta = .47$, $b = .001$, $SE = 4.9e-4$, $t = 2.59$, $p = .01$; Head: $\beta=.35$, $b = .001$, $SE = 5.1e-4$, $t = 1.87$, $p = .06$), but was not significant for children who were younger at T1 (e.g., 8 years, as depicted in Fig. 4A), despite the appearance of a negative relation ($ps \geq .17$). Change in the tail was not associated with item-time performance ($ps \geq .18$).

Thus, although the normative pattern of volumetric change in this sample was a linear decrease in the head, and a curvilinear in the body volume over time, protracted increases in head and body volume in older children predicted better item-time memory. Parameter estimates for models separating left and right hippocampal structures are also included in Table S5.

We replicated the preceding results with a post-hoc analysis that included change in item-item and item-space memory as time-varying covariates. Item-time memory was significantly related to increases in item-space memory ($\beta = .18$, $b = .21$, $SE = 0.066$, $t = 3.27$, $p = .001$), but not significantly to increases in item-item memory ($\beta=.05$, $b=.07$, $SE = .07$, $t = .95$, $p = .34$). Critically, we replicated the interaction between volumetric changes, change in age, and age at T1 ($\chi2 = 10.5$, $df = 3$, $p = .015$), that were similarly focused on changes in the head (interaction: $\beta=.33$, $b=4.2e-4$, $SE = 1.8e-4$, $t = 2.27$, $p = .024$) and body (interaction: $\beta=.28$, $b=4.0e-4$, $SE = 1.9e-4$, $t = 2.05$, $p = .041$).

3.3.2. Item-Item

Consistent with our prediction, changes in hippocampal structure predicted item-item memory. Specifically, we found a significant interaction between volumetric changes in head, body, and tail (as a block) and age at T1 ($\chi2 = 8.82$, $df = 3$, $p = .03$), but this interaction was not significantly moderated by changes in age ($\chi2 = 3.2$, $df = 3$, $p = .37$) (See Table 5). Examining the volumetric change and age at T1 interaction, we found that among children who were young at T1 (i.e., 8 years), increases in body volume predicted greater item-item memory ($\beta = .27$, $b = .0007$, $SE = 2.5e-4$, $t = 2.93$, $p = .004$). In contrast, among children who were older at T1 (i.e., 11 years), increases in head volume predicted better behavioral performance ($\beta=.24$, $b = .0006$, $SE = 2.3e-4$, $t = 2.38$, $p = .02$) (See Fig. 4B and Fig. S3B). Parameter estimates for models separating left and right hippocampal structures are also included in Table S6.

Overall, volumetric changes in hippocampal body appeared to differentially predict item-time and item-item memory. Consistent with

this, we found that the age at T1 by change in body

volume interaction was significantly different for item-time and item-item memory ($\chi2 = 8.92$, $df = 1$, $p = .003$). In younger children, the association between change in body and memory was more positive for item-item than item-time ($\beta=.32$, $b = 001$, $SE = 5.2e-4$, $t = 2.50$, $p = .014$), but in older children, there was a trend for a more negative relation for item-item than item-time memory ($\beta=-.28$, $b=-0.001$, $SE = 5.8e-4$, $t=-1.93$, $p = .055$). Overall results are consistent with the protracted behavioral trajectory of item-item memory and suggest a transition from body to head in supporting developmental improvements in item-item memory.

We replicated the preceding analysis in a post-hoc analysis that included change in item-time and item-space memory as time-varying covariates. Item-item memory was not significantly related to increases in item-time memory ($\beta = .08$, $b = .07$, $SE = .057$, $t = 1.27$, $p = .21$) or item-space memory ($\beta=.04$, $b=.04$, $SE = .06$, $t = .74$, $p = .45$). The interaction between volumetric changes and age at T1 ($\chi2 = 9.96$, $df = 3$, $p = .019$) was replicated as well, which revealed similar relations with changes in the head (interaction: $\beta=.12$, $b=2.5e-4$, $SE = 1.2e-4$, $t = 2.05$, $p = .042$) and the body (interaction: $\beta=-.16$, $b=-3.8e-4$, $SE = 1.4e-4$, $t=-2.69$, $p = .008$).

3.3.3. Item-space

No significant relations between changes in hippocampal structure and item-space memory were found when we used volume changes summed across hemispheres ($\chi2 s \leq 4.04$, $dfs = 3$, $ps \geq .26$) (See Table S7), nor did using overall hippocampal volume perform better than using subregions ($\chi2 = 3.84$, $df = 8$, $p = .87$).

Given the suggestion from the literature that associations between change in head, body, and tail volumes and spatial memory could be right-lateralized, we also tested our model in the right hippocampus. This analysis revealed a significant three-way interaction between changes in right hippocampus, changes in age, and starting age at T1 ($\chi2 = 10.6$, $df = 3$, $p = .01$) (See Table 6). Volumetric changes significantly more positively predicted memory performance with longer

delay (e.g. 3 years; Fig. 4C), but not significantly with shorter delays (e.g., 1 year; $ps > .098$; Fig. S3C). In other words, in younger children at T1, there was a trend for reduction of tail volume over time predicting better item-space memory ($\beta=-.32$, $b= -.004$, $SE = .002$, $t=-1.86$, $p = .07$), but in older children at T1, volumetric increases in the tail predicted better item-space memory ($\beta=.528$, $b=.006$, $SE = .003$, $t = 2.16$, $p = .03$). However, neither the body ($ps \geq .11$) nor the head ($ps \geq .21$) were significantly associated to item-space memory at those starting ages. Thus, although the hippocampal tail did not seem to show an average pattern of volumetric change based on previous analyses; the present results suggest that individual differences in tail development predict item-space memory performance.

Finally, we replicated the preceding results in a post-hoc analysis that included change in item-time and item-item memory as time-varying covariates. Item-space memory was significantly related to increases in item-time memory ($\beta = .20$, $b = .22$, $SE = 0.066$, $t = 3.40$, $p = .0008$), but not with item-item memory ($\beta=.02$, $b=.03$, $SE = .07$, $t = .38$, $p = .71$). Also, we replicated the relation with right tail with a model that included change in item-time and item-item memory as time-varying covariates, which revealed a similar significant three-way interaction between changes in right hippocampal tail, changes in age, and starting age at T1($\beta=.34$, $b=1.8e-3$, $SE = 8.8e-4$, $t=2.07$, $p = .040$).

4. Discussion

The ability to remember associations between events and their spatio-temporal context depends on hippocampal mechanisms, which bind contextual features into integrated event representations (Eichenbaum and Cohen, 2001). Here, we asked whether volumetric changes in hippocampal volume predict longitudinally improvements in relational memory, and whether those developmental associations differed
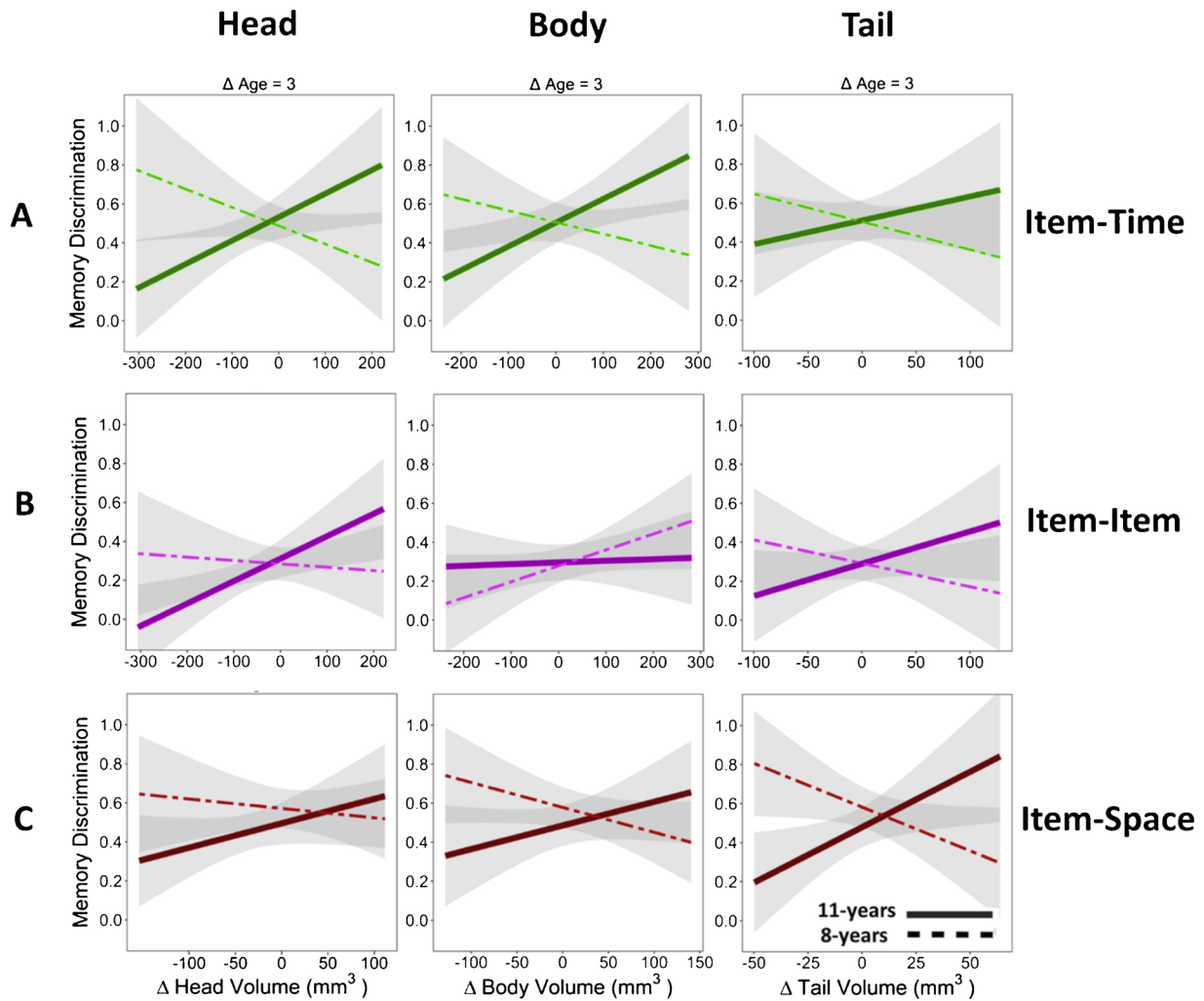
Fig. 4. Depicting interactions between change in ICV-corrected volume, starting age at Time 1 and change in age since Time 1 (evaluated at ΔAge = 3 years) for each memory relation. See Supplemental Fig. 1 for depiction of interaction evaluated at one year since Time 1; relations between volume changes and memory were stronger at longer delays. The association between ΔAge and each memory relation was estimated at two different values of the starting age at Time 1 continuous covariate by centering the covariate to 8 or 11 years, respectively. These ages roughly represent the lower and higher ends of the Time 1 age range. No age-groups were formed or analyzed; results represent the estimates of the model at different values of continuous covariates. Error bands represent 95 % confidence intervals. **A.** Item-Time. **B.** Item-Item. **C.** Item-Space.

depending on hippocampal subregion or type of memory relation.

This is the first report showing that longitudinal improvements in relational memory differed as a function of the type of memory relation, such that item-space memory developed more rapidly than item-time and item-item memory. In the largest longitudinal study of hippocampal subregions to date, this research showed that hippocampal head, body, and tail follow different developmental trajectories from childhood into adolescence. Linking structural and behavioral changes, we report for the first time that volumetric changes in hippocampal head, body, and tail differentially predicted longitudinal improvement in item-space, item-time, and item-item.

4.1. Developmental change in relational memory depends on the nature of the relation

In our initial cross-sectional analysis (Lee et al., 2016), item-space memory reached adults' levels of performance before item-time memory, which in turn preceded item-item memory. In the present research, we examined within-person change while accounting for cross-sectional differences and showed that item-space memory improves until around 10½, whereas item-time and item-item memory followed prolonged trajectories with improvements about 12 and 12½ years of age

respectively. This finding is additionally consistent with prior cross-sectional evidence that spatial memory develops earlier than temporal memory (Picard et al., 2012; Guillery-Girard et al., 2013; Lee et al., 2016). We cannot rule out the possibility that aspects of our tasks might differ across conditions for reasons other than the type of relation manipulated. For example, one could argue that failure to reject distractors may be influenced more strongly by proactive interference in the item-item relation because only in that condition encoding of members of previous triplets may directly impact performance on an ongoing trial. On the other hand, one could also argue that the use of the same three locations across all trials also may generate interference in the item-space condition. More generally, it is possible that differences in difficulty—particularly in the item-item condition—may be at least in part due to differences that transcend relational binding processes and have to do with the task design. We cannot totally exclude this possibility. However, analyses in which baseline performance was accounted for did not meaningfully alter the behavioral trajectories, suggesting that the trajectories were not a simple consequence on initial difficulty. Future research might alter encoding parameters (e.g., exposure time, clarity of event boundaries) to explore this issue more fully. Nevertheless, we argue that the use of novel stimuli and arbitrary associations with identical encoding procedures is an effective way to assess

Table 5

Hippocampal Volume Predicting the Development of Item-Item Memory.

Effect	Left and Right Hippocampal Sum				
	Beta	b	SE	t	p
(Intercept)	–	1.2e-1	2.2e-2	5.4	<.0001
Item-Recognition	0.16	1.5e-1	6.2e-2	2.5	0.013
Sex [Male]	−0.0048	−2.1e-3	2.7e-2	−0.077	0.94
Start-Volume Head	−0.013	−1.0e-5	4.7e-5	−0.21	0.83
Start-Volume Body	0.025	2.3e-5	5.6e-5	0.41	0.69
Start-Volume Tail	0.018	2.4e-5	8.2e-5	0.29	0.78
Start-Age	0.2	3.9e-2	1.5e-2	2.6	0.012
ΔAge	0.27	5.5e-2	1.1e-2	5	<.0001
ΔHead	−0.048	−1.2e-4	3.5e-4	−0.35	0.73
ΔBody	−0.00071	−1.7e-6	3.4e-4	−0.005	>0.99
ΔTail	−0.15	−8.7e-4	8.5e-4	−1	0.31
Start-Age x ΔAge	−0.081	−1.1e-2	1.0e-2	−1.1	0.29
Start-Age x ΔHead	0.12	2.5e-4	1.2e-4	2.1	0.039
Start-Age x ΔBody	−0.13	−3.0e-4	1.4e-4	−2.2	0.028
Start-Age x ΔTail	0.015	8.5e-5	3.3e-4	0.26	0.8
ΔAge x ΔHead	0.16	2.1e-4	1.8e-4	1.1	0.26
ΔAge x ΔBody	0.1	1.2e-4	1.6e-4	0.76	0.45
ΔAge x ΔTail	0.13	3.8e-4	4.3e-4	0.88	0.38

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

Table 6

Right Hippocampal Volume Predicting the Development of Item-Space Memory.

Effect	Right Hippocampus				
	Beta	b	SE	t	P
(Intercept)	–	4.6e-1	0.025	18	<.0001
Item-Recognition	0.31	3.5e-1	7.2e-2	4.8	<.0001
Sex [Male]	−0.083	−4.2e-2	3.2e-2	−1.3	0.19
Start-Volume Head	−0.027	−4.6e-5	1.0e-4	−0.45	0.66
Start-Volume Body	−0.042	−7.6e-5	1.1e-4	−0.68	0.5
Start-Volume Tail	0.039	1.1e-4	1.8e-4	0.61	0.54
Start-Age	0.28	6.3e-2	1.7e-2	3.8	0.0003
ΔAge	0.12	2.9e-2	1.3e-2	2.2	0.028
ΔHead	−0.086	−4.2e-4	6.5e-4	−0.65	0.52
ΔBody	−0.018	−8.3e-5	6.3e-4	−0.13	0.9
ΔTail	−0.14	−1.7e-3	1.7e-3	−0.99	0.32
Start-Age x ΔAge	−0.21	−3.4e-2	1.2e-2	−2.7	0.0077
Start-Age x ΔHead	−0.055	−2.3e-4	5.5e-4	−0.42	0.68
Start-Age x ΔBody	−0.11	−4.7e-4	5.8e-4	−0.81	0.42
Start-Age x ΔTail	−0.33	−4.0e-3	1.8e-3	−2.3	0.025
ΔAge x ΔHead	0.13	3.2e-4	3.6e-4	0.88	0.38
ΔAge x ΔBody	0.025	5.5e-5	3.2e-4	0.17	0.86
ΔAge x ΔTail	0.16	9.6e-4	9.2e-4	1	0.3
Start-Age x ΔAge x ΔHead	0.12	2.4e-4	3.1e-4	0.78	0.44
Start-Age x ΔAge x ΔBody	0.2	4.4e-4	3.2e-4	1.4	0.18
Start-Age x ΔAge x ΔTail	0.41	2.4e-3	9.6e-4	2.5	0.012

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

relational memory. The more rapid development of item-space memory compared to the other relations suggests that relational memory processes are not fully unitary.

Although item-time memory was generally better than item-item, their developmental trajectories were similar. This may have been due to the dependence of these tasks on shared hippocampal operations. For example, performance on both item-time and item-item memory may have benefitted from some form of temporal processing—the former from processing the precise temporal order of the images and the latter from processing which groups of items were presented together in the same temporal context (Davachi and DuBrow, 2015). On the other hand, there may also be differences in how the hippocampus supports item-time and item-item memory despite the apparent similarity in behavioral trajectory, which may help to explain why item-item is a more challenging task (Pathman and Ghetti, 2014, 2015). Disentangling these two possibilities was made possible by the longitudinal design

combining assessments of both brain and behavior and was addressed in the brain–behavior analyses. Overall, these behavioral findings provide the first longitudinal evidence of protracted and distinct developmental trajectories of different aspects of relational memory. The examination of these relations within participants and within the same task form, which constrain response demands, offers strong support for a functional distinction in relational memory.

4.2. Developmental change in hippocampal volumes varies along the anterior-posterior Axis

We provided new longitudinal evidence indicating that hippocampal head, body, and tail develop differentially from middle childhood into adolescence. Consistent with the findings of the seminal longitudinal study of 31 individuals that first examined morphometric development along the anterior–posterior axis (Gogtay et al., 2006), hippocampal head declined in volume from middle childhood to adolescence, while hippocampal body increased in volume until about 10 years of age and declined thereafter. Hippocampal tail volume was stable throughout middle childhood and adolescence, suggesting that its development occurred earliest, consistent with previous reports (Gogtay et al., 2006; DeMaster et al., 2014; Riggins et al., 2018).

Curvilinear trajectories in hippocampal development are frequently observed (Lee et al., 2014, 2017). Although not yet definitively linked, volumetric increases may reflect ongoing synaptogenesis and dendritic elaboration, while volumetric declines may reflect synaptic pruning (Stiles and Jernigan, 2010). It is not known why the body, unlike the head and the tail, continues to increase in volume into late childhood (i. e. 9–10 years of age). However, the body has been postulated to act as a bridge or integrator of anterior and posterior mechanisms (Bast et al., 2009). We can speculate that continued dendritic elaboration in the body, compared to head and tail, may be important for the body to complete the required connections with head and tail. Whatever the reason, the diverging developmental trajectories of head, body, and tail reported here provide a demonstration that the hippocampus is not a uniform structure and joins the growing body of evidence suggesting functional differences along the anterior–posterior hippocampal axis (Poppenk and Moscovitch, 2011).

4.3. Changes in hippocampal volume predict developmental improvements in relational memory

We found evidence that increases in hippocampal volumes over time predicted longitudinal improvements in relational memory. We note that these positive relations with behavior are observed even in the context of normative volumetric decreases (e.g., hippocampal head). Previous cross-sectional studies have reported negative associations between hippocampal head volume and behavior (DeMaster et al., 2014; Schlichting et al., 2017), suggesting the hypothesis that decreases of hippocampal head over time may promote behavioral improvements. Instead, even though we confirmed normative volumetric declines in this region during development, greater memory performance was observed among those with a relative *increase* in volume. These findings may shed light on underlying mechanisms. One possibility is that these positive associations may depend on ongoing synaptogenesis and dendritic elaboration within hippocampal circuitry (Huttenlocher and Dabholkar, 1997) and these processes may be particularly important for behavior, even when other mechanisms of structural change, such as pruning, may result in a net loss of volume. Relatedly, the relational memory tasks presented in DeMaster et al. (2014) and Schlichting et al. (2017) required participants to maintain associative memories over longer delays than required in the present study, potentially hinting at a tradeoff between the initial fidelity of relational encoding representation and the maintenance/integration of that representation over time (Morton et al., 2017). The possibility that hippocampal changes may differentially support memory encoding and retention cannot be directly

addressed in this study. Our findings overall support a nascent body of cross-sectional research obtained over the last decade linking the hippocampus to age-related differences in memory (DeMaster et al., 2014; Daugherty et al., 2016). These findings dispel a long-held, but not adequately tested assumption, that the hippocampus and the associative processes it supports do not contribute to developmental improvements in memory after early childhood (Ghetti and Lee, 2011).

We also assessed, for the first time, whether the longitudinal association between hippocampal structure and memory differed as a function of subregion and type of memory relation. These analyses revealed distinct associations, suggesting that processes supporting memory for item-space, item-time, and item-item relations are not uniform across the anterior-posterior axis of the structure. Bilateral increases in the volume of hippocampal head and body predicted larger improvement in item-time memory in older children. In contrast, increases in body volumes predicted item-item memory in younger children and increases in head volume predicted better item-item memory in older children, suggesting a developmental transition from body to head for this type of relation. Finally, the relation between volumetric changes and the development of item-space memory was right lateralized and restricted to the tail, increases in right hippocampal tail over time predicted greater item-space memory, particularly in older children.

Overall, these data suggest that protracted increase in sub-regional volumes are associated with behavioral improvement. It is somewhat surprising that we did not detect reliable relations between hippocampal growth and memory in younger children for item-time and item-space memory. It is possible that memory improvements in younger compared to older children reflect not only change in relational memory, but also increased consistency in children's engagement with the memory task, potentially obscuring relations between memory and volumetric change. However, contrary to this possibility, we found an association between increases in hippocampal body in younger children and item-item memory, the most difficult of the three relational tasks and, potentially, the most likely to produce less consistent data. Nevertheless, we cannot exclude the possibility that our *change in age* parameter captured more variance than our *change in volume parameter* because of additional processing demands in young children. Change in age was included to model time and to account for any source of development due to extra hippocampal processes, but shared variance with measures of hippocampal development cannot be excluded.

Our results are consistent with prior evidence that the hippocampus supports memory for item-space, item-time, and item-item relations (Konkel et al., 2008; Konkel and Cohen, 2009), but also indicate heterogeneity in how each subregion contributes to these memory relations. Memory for temporal order reliably recruits the hippocampus in functional neuroimaging studies (Eichenbaum, 2013); however, while we only observed relations with item-time memory for the hippocampal head and body, associations with hippocampal tail have also been reported (Roberts et al., 2018), suggesting that temporal memory may not be strongly localized to any anterior-posterior subregion. Memory for associations between items has been preferentially associated with hippocampal head and body (Giovanello et al., 2004, 2009), and our results are consistent with these findings. It is notable that although item-time and item-item memory within-person trajectories were similar behaviorally, their trajectories were supported by different hippocampal subregions, underscoring the advantage of a longitudinal design. Finally, spatial memory is frequently associated with posterior hippocampus (i.e. tail and body) (Persson et al., 2018). We found evidence consistent with this suggestion restricted to the right tail.

Many open questions remain about the processes that might underlie these different longitudinal structure-behavior relations. One possibility is that hippocampal head, body, and tail differ in terms of cell types and genetic expression (Cembrowski et al., 2016), synaptic plasticity (Babiec et al., 2017), and relative cytoarchitectural composition (i.e. dentate gyrus, CA 1,3)(Lee et al., 2014; Riggins et al., 2018). For example, there is some evidence for a division of time and space in some cytoarchitectural circuits (Eichenbaum, 2013). Another possibility is that each subregion supports the same set of operations via the tri-synaptic circuit, but on different types of information received through differential connections with extrahippocampal brain regions. More anterior subregions exhibit greater functional connectivity with perirhinal cortex, while more middle and posterior regions of the hippocampus exhibit greater functional connectivity with posterior parahippocampal cortex (Preston and Eichenbaum, 2013). The perirhinal cortex is widely recognized as a region supporting complex item representations, while posterior parahippocampal cortex may support spatial and non-spatial contextual associations (Ranganath, 2010). Relatedly, evidence from non-human primates may suggest that the tri-synaptic circuit is not fully mature until the end of childhood (Lavenex and Banta Lavenex, 2013), the development timing of which may differ along the anterior–posterior axis and in relation to their inputs from the medial temporal, as well as parietal and prefrontal regions. A third possibility is that the differences we observed reflect more general divisions of labor that transcend the type of relation examined (Poppenk and Moscovitch, 2011; Schlichting et al., 2017). Although we have no reason to suspect that our item-time and item-item tasks required more generalization processes (as suggested by being the only tasks associated with changes in hippocampal head), the current study cannot exclude this possibility directly. Future research is required to disentangle these possibilities.

The present research has several limitations. One potential limitation is that we did not differentiate between encoding and retrieval operations, and thus we cannot address hypotheses that anterior and posterior hippocampus preferentially support encoding and retrieval, respectively (Kim, 2015). However, it is not clear how differential support for encoding or retrieval operations could explain the structure-behavior relations we observed here, especially given identical encoding procedures, and minimization of retrieval demands using short-term memory delays. Another limitation is that this research did not disambiguate between egocentric and allocentric spatial representations; future research will need to examine whether each would follow different developmental trajectories or have different relations with hippocampal development. Another potential limitation is that we focused exclusively on the development of the hippocampus, while extra-hippocampal changes can additionally account for memory changes. However, the goal of this research was to examine relational memory processes in the hippocampus in a task that manipulated the type of relation. Moreover, our task used materials and procedures designed to ensure that differences in performance across relational conditions depended more strongly on hippocampally mediated associative processes (Konkel et al., 2008; Konkel and Cohen, 2009) than on pre-frontally mediated strategic or controlled processes (Ghetti and Angelini, 2008; Bjorklund et al., 2009; Shing et al., 2010). These procedures included identical encoding procedures across relational conditions, the use of novel objects, which could not easily be labeled, and arbitrary relations among them. As discussed earlier, retrieval demands were reduced by testing memory over short delays. Finally, this research did not address how cytoarchitectural subfields in the hippocampus (i.e. dentate gyrus, CA 1–3) may account for the relations with head, body, and tail development, which should be the subject of future research and analysis.

In conclusion, we present the first evidence to establish distinct links between subregional changes in hippocampal structure to the differential development of relational memory for associations between items and space, time, and other items. These results—beyond their implication to theories of memory development—begin to disentangle the contributions of the hippocampus to three critical dimensions of relational memory.

Declaration of Competing Interest

We have no conflicts of interest to report.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2019.100741.

References

Asman, A.J., Landman, B.A., 2013. Non-local statistical label fusion for multi-atlas segmentation. Med. Image Anal. 17, 194–208.

Babiec, W.E., Jami, S.A., Guglietta, R., Chen, P.B., O'Dell, T.J., 2017. Differential regulation of NMDA receptor-mediated transmission by SK channels underlies dorsal-ventral differences in dynamics of schaffer collateral synaptic function. J. Neurosci. 37, 1950–1964.

Bast, T., Wilson, I.A., Witter, M.P., Morris, R.G.M., 2009. From rapid place learning to behavioral performance: a key role for the intermediate hippocampus. PLoS Biol. 7, e1000089.

Bjorklund, D.F., Dukes, C., Brown, R.D., 2009. The development of memory strategies. The Development of Memory in Infancy and Childhood, 2nd Ed. Studies in Developmental Psychology. Psychology Press, New York, NY, US, pp. 145–175.

Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human Hippocampus and spatial and episodic memory. Neuron 35, 625–641.

Cembrowski, M.S., Bachman, J.L., Wang, L., Sugino, K., Shields, B.C., Spruston, N., 2016. Spatial Gene-Expression Gradients Underlie Prominent Heterogeneity of CA1 Pyramidal Neurons. Neuron 89, 351–368.

Daugherty, A.M., Bender, A.R., Raz, N., Ofen, N., 2016. Age differences in hippocampal subfield volumes from childhood to late adulthood. Hippocampus 26, 220–228.

Davachi, L., DuBrow, S., 2015. How the hippocampus preserves order: the role of prediction and context. Trends Cogn Sci (Regul Ed) 19, 92–99.

DeMaster, D., Pathman, T., Ghetti, S., 2013. Development of memory for spatial context: hippocampal and cortical contributions. Neuropsychologia 51, 2415–2426.

DeMaster, D., Pathman, T., Lee, J.K., Ghetti, S., 2014. Structural development of the hippocampus and episodic memory: developmental differences along the anterior/ posterior axis. Cereb. Cortex 24, 3036–3045.

DeMaster, D.M., Ghetti, S., 2012. Developmental differences in hippocampal and cortical contributions to episodic retrieval. Cortex.

Eichenbaum, H., 2013. Memory on time. Trends Cogn Sci (Regul Ed) 17, 81–88.

Eichenbaum, H., Cohen, N.J., 2001. From Conditioning to Conscious Recollection Memory Systems of the Brain. Oxford University Press.

Ekstrom, A.D., Copara, M.S., Isham, E.A., Wang, W., Yonelinas, A.P., 2011. Dissociable networks involved in spatial and temporal order source retrieval. NeuroImage 56, 1803–1813.

Ghetti, S., Angelini, L., 2008. The development of recollection and familiarity in childhood and adolescence: evidence from the dual-process signal detection model. Child Dev. 79, 339–358.

Ghetti, S., Lee, J., 2011. Children's episodic memory. Wiley Interdiscip. Rev. Cogn. Sci. 2, 365–373.

Giedd, J.N., Vaituzis, A.C., Hamburger, S.D., Lange, N., Rajapakse, J.C., Kaysen, D., Vauss, Y.C., Rapoport, J.L., 1996. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4-18 years. J. Comp. Neurol. 366, 223–230.

Giovanello, K.S., Schnyer, D., Verfaellie, M., 2009. Distinct hippocampal regions make unique contributions to relational memory. Hippocampus 19, 111–117.

Giovanello, K.S., Schnyer, D.M., Verfaellie, M., 2004. A critical role for the anterior hippocampus in relational memory: evidence from an fMRI study comparing associative and item recognition. Hippocampus 14, 5–8.

Gogtay, N., Nugent, T.F., Herman, D.H., Ordonez, A., Greenstein, D., Hayashi, K.M., Clasen, L., Toga, A.W., Giedd, J.N., Rapoport, J.L., Thompson, P.M., 2006. Dynamic mapping of normal human hippocampal development. Hippocampus 16, 664–672.

Guillery-Girard, B., Martins, S., Deshayes, S., Hertz-Pannier, L., Chiron, C., Jambaqué, I., Landeau, B., Clochon, P., Chételat, G., Eustache, F., 2013. Developmental trajectories of associative memory from childhood to adulthood: a behavioral and neuroimaging study. Front. Behav. Neurosci. 7, 126.

Güler, O.E., Thomas, K.M., 2013. Developmental differences in the neural correlates of relational encoding and recall in children: an event-related fMRI study. Dev. Cogn. Neurosci. 3, 106–116.

Hoffman, L., 2015. Longitudinal Analysis : Modeling Within-Person Fluctuation and Change. Routledge.

Huttenlocher, P.R., Dabholkar, A.S., 1997. Regional differences in synaptogenesis in human cerebral cortex. J. Comp. Neurol. 387, 167–178.

Insausti, R., 2010. Postnatal Development of the Human Hippocampal Formation. Springer.

Kim, H., 2015. Encoding and retrieval along the long axis of the hippocampus and their relationships with dorsal attention and default mode networks: the HERNET model. Hippocampus 25, 500–510.

Konkel, A., Cohen, N.J., 2009. Relational memory and the Hippocampus: representations and methods. Front. Neurosci. 3, 166–174.

Konkel, A., Warren, D.E., Duff, M.C., Tranel, D.N., Cohen, N.J., 2008. Hippocampal amnesia impairs all manner of relational memory. Front. Hum. Neurosci. 2, 15.

Lavenex, P., Banta Lavenex, P., 2013. Building hippocampal circuits to learn and remember: insights into the development of human memory. Behav. Brain Res. 254, 8–21.

Lee, J.K., Ekstrom, A.D., Ghetti, S., 2014. Volume of hippocampal subfields and episodic memory in childhood and adolescence. Neuroimage 94, 162–171.

Lee, J.K., Johnson, E.G., Ghetti, S., 2017. Hippocampal Development: Structure, Function and Implications. The Hippocampus from Cells to Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible Cognition. Springer International Publishing, Cham, Switzerland, pp. 141–166.

Lee, J.K., Nordahl, C.W., Amaral, D.G., Lee, A., Solomon, M., Ghetti, S., 2015. Assessing hippocampal development and language in early childhood: evidence from a new application of the Automatic Segmentation Adapter Tool. Hum. Brain Mapp. 36, 4483–4496.

Lee, J.K., Wendelken, C., Bunge, S.A., Ghetti, S., 2016. A time and place for everything: developmental differences in the building blocks of episodic memory. Child Dev. 87, 194–210.

Morton, N.W., Sherrill, K.R., Preston, A.R., 2017. Memory integration constructs maps of space, time, and concepts. Curr. Opin. Behav. Sci. 17, 161–168.

Ofen, N., Kao, Y.-C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., Gabrieli, J.D.E., 2007. Development of the declarative memory system in the human brain. Nature Neuroscience Vol 10 (9), 1198–1205.

Pathman, T., Ghetti, S., 2014. The eyes know time: a novel paradigm to reveal the development of temporal memory. Child Dev. 85, 792–807.

Pathman, T., Ghetti, S., 2015. Eye movements provide an index of veridical memory for temporal order. PLoS One 10.

Persson, J., Stening, E., Nordin, K., Söderlund, H., 2018. Predicting episodic and spatial memory performance from hippocampal resting-state functional connectivity: evidence for an anterior-posterior division of function. Hippocampus 28, 53–66.

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., Piolino, P., 2012. How do the different components of episodic memory develop? Role of executive functions and short-term feature-binding abilities. Child Dev. 83, 1037–1050.

Poppenk, J., Moscovitch, M., 2011. A hippocampal marker of recollection memory ability among healthy young adults: contributions of posterior and anterior segments. Neuron 72, 931–937.

Preston, A.R., Eichenbaum, H., 2013. Interplay of hippocampus and prefrontal cortex in memory. Curr. Biol. 23, R764–773.

Ranganath, C., 2010. Binding items and contexts: the cognitive neuroscience of episodic memory. Curr. Dir. Psychol. Sci. 19, 131–137.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.

Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., Hancock, G.R., 2018. Protracted hippocampal development is associated with age-related improvements in memory during early childhood. Neuroimage 174, 127–137.

Roberts, B.M., Libby, L.A., Inhoff, M.C., Ranganath, C., 2018. Brain activity related to working memory for temporal order and object information. Behav. Brain Res. 354, 55–63.

Schlichting, M.L., Guarino, K.F., Schapiro, A.C., Turk-Browne, N.B., Preston, A.R., 2017. Hippocampal structure predicts statistical learning and associative inference abilities during development. J. Cogn. Neurosci. 29, 37–51.

Shing, Y.L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S.-C., Lindenberger, U., 2010. Episodic memory across the lifespan: the contributions of associative and strategic components. Neuroscience & Biobehavioral Reviews, Binding Processes: Neurodynamics and Functional Role in Memory and Action. 34, 1080–1091.

Sliwinski, M., Hoffman, L., Hofer, S.M., 2010. Evaluating convergence of within-person change and between-person age differences in age-heterogeneous longitudinal studies. Res. Hum. Dev. 7, 45–60.

Stiles, J., Jernigan, T.L., 2010. The basics of brain development. Neuropsychol. Rev. 20, 327–348.

Tulving, E., Markowitsch, H.J., 1998. Episodic and declarative memory: role of the hippocampus. Hippocampus 8, 198–204.

Wang, H., Yushkevich, P.A., 2013. Multi-atlas segmentation with joint label fusion and corrective learning—an open source implementation. Front. Neuroinform. 7.