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Hippocampal CA3-dentate gyrus volume uniquely linked to improvement in associative memory from childhood to adulthood

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ABSTRACT

Associative memory develops into adulthood and critically depends on the hippocampus. The hippocampus is a complex structure composed of subfields that are functionally-distinct, and anterior-posterior divisions along the length of the hippocampal horizontal axis that may also differ by cognitive correlates. Although each of these aspects has been considered independently, here we evaluate their relative contributions as correlates of age-related improvement in memory. Volumes of hippocampal subfields (subiculum, CA1-2, CA3-dentate gyrus) and anterior-posterior divisions (hippocampal head, body, tail) were manually segmented from high-resolution images in a sample of healthy participants (age 8–25 years). Adults had smaller CA3-dentate gyrus volume as compared to children, which accounted for 67% of the indirect effect of age predicting better associative memory via hippocampal volumes. Whereas hippocampal body volume demonstrated non-linear age differences, larger hippocampal body volume was weakly related to better associative memory only when accounting for the mutual correlation with subfields measured within that region. Thus, typical development of associative memory was largely explained by age-related differences in CA3-dentate gyrus.

Introduction

Memory functioning is critically dependent on medial temporal lobe regions, including the hippocampus (Hc; Scoville and Milner, 1957). Hc volume correlates with memory outcomes across the lifespan following an inverted-U function: smaller volumes commonly correlate with better memory outcomes among children, adolescents and young adults, whereas smaller volumes in the course of adult aging are typical indicators of memory impairment (Van Petten, 2004). Although volume-function correlations are common in the literature (Van Petten, 2004), several studies have reported age invariance of total Hc volume among children after the age of 4 years (Gogtay et al., 2006; Mattai et al., 2011; Sullivan et al., 2011), which is incongruent with the protracted development of episodic memory functions that are typically considered to be Hc-dependent (Ofen, 2012). However, the Hc is not a unitary structure; it is comprised of different tightly connected subfields and its morphometry is heterogeneous along the horizontal long axis. Each of the Hc subfields and the anterior-posterior divisions demonstrate functional specialization and are differentially implicated in neurodevelopmental disorders (Small et al., 2011). Thus, measures of Hc subfields and anterior-posterior divisions may capture unique associations between structure and function that are otherwise lost when considering the total volume. Yet, little is known of the relationship between development of memory function and the different subregions of the Hc.

The subfield divisions are the longest-standing description of Hc structure. Defined by unique cytoarchitectonic features (Duvernoy 2005), the Hc subfields include the three Cornu ammonis fields (CA1-CA3), dentate gyrus, and subiculum complex (including subiculum proper, pre- and para-subiculum). The subfields are preserved across mammalian species (Amaral and Lavenex, 2006), and based upon decades of animal and human studies, the subfields have unique functions that are each aspects of larger Hc circuits (Amaral and Lavenex, 2006; Lavenex and Lavenex, 2013). For example, in studies of adult aging, dentate gyrus volume and its functional activation is related to associative memory functions (Bender et al., 2013; Shing et al., 2011; Yassa and Stark, 2011).

Consistent with the evidence from adult aging, specificity in Hc

Abbreviations: BS 95% CI, bias-corrected bootstrapped 95% confidence intervals; CA, Cornu Ammonis; CFI, comparative fit index; DG, dentate gyrus; Hc, hippocampus; ICC, intra-class correlation coefficient; PD-TSE, proton density-weighted turbo spin echo; RMSEA, root mean square error of approximation; SEM, structural equation modeling; SRMR, standardized root mean residual; WRMR, weighted root mean residual

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subfield structure-function relations is thought to undergo changes from childhood to adulthood; yet, the few extant studies present a mixed story. Two cross-sectional studies reported CA1 and dentate gyrus volumes positively correlated with age among children and adolescents (Krogsrud et al., 2014; Lee et al., 2014), and a positive correlation with age in the subiculum in one study (Krogsrud et al., 2014) but not the other (Lee et al., 2014). Developmental differences in volume, however, appear to be non-linear within the CA1 and dentate gyrus subfields. When examining data of participants ages 4–22 years, Hc subfield volumes are age-invariant after adolescence (Krogsrud et al., 2014), whereas when comparing across nearly the entire lifespan (ages 8–82 years) smaller CA3-dentate gyrus and CA1-2 volumes correlate with age from mid-childhood to early adulthood, and subiculum volume is relatively age-invariant throughout the lifespan (Daugherty et al., 2016a). In line with the cross-sectional evidence of smaller CA1-2 and CA3-dentate gyrus volumes in childhood development, a longitudinal study of children and young adults showed shrinkage of all subfields after 2.5 years (Tamnes et al., 2014). Directly comparing the evidence from these reports is difficult due to differences in age range, Hc subfield segmentation methods, and analytic approaches. Nonetheless, development theoretically falls along a continuum across the lifespan and an inclusive account of the evidence suggests that the subfields follow different developmental trajectories that are potentially non-linear.

The plausible non-linearity in Hc subfield structural development is expected to be reflected in the structure-function relation. In a single cross-sectional study, larger CA3-dentate gyrus volumes correlated with better associative memory performance among children ages 8–14 years (Lee et al., 2014), whereas in a separate longitudinal report, shrinkage of CA2-3 and dentate gyrus predicted better verbal learning outcomes over time (Tamnes et al., 2014). As associative memory function appears to improve linearly from childhood to young adulthood (Ofen, 2012), its relation with CA3-dentate gyrus volume may follow an inverted-U function across the lifespan, similar to that with total Hc volume (Van Petten, 2004). Thus, smaller CA3-dentate gyrus volumes in childhood development may be adaptive for associative memory function whereas this is an indicator of declines in adult aging.

In lieu of subfield divisions, the unique morphometry spanning the anterior-posterior Hc axis has also captured the attention of researchers eager to assess the developing structure-function relation. The horizontal length of the Hc has a degree of functional specialization due to projections to different brain regions (Amaral and Lavenex, 2006; Duvernoy, 2005) that has been recently demonstrated in humans with resting state functional connectivity (Kahn et al., 2008; Poppenk et al., 2013; Strange et al., 2014). Definitions of anterior-posterior divisions along the Hc horizontal axis vary between studies but are generally classified either grossly as anterior–posterior relative to the uncal apex (Poppenk et al., 2013), or as the divisions termed Hc head, body and tail (Duvernoy, 2005; Poppenk et al., 2013). The definitions of these divisions and the resulting anatomical and functional characteristics are different. Yet, in most (but not all) MRI studies, the uncal apex is a common landmark to denote the transition from anterior to posterior, or between Hc head and body (e.g., Daugherty et al., 2015; Malykhin et al., 2007; Poppenk et al., 2013; also see DeMaster et al., 2014).

There is limited information regarding developmental differences in anterior-posterior Hc volumes. Some report smaller anterior regions and larger body volume in adults as compared to children (DeMaster et al., 2014) and another report in line with this identified a non-linear pattern of age-related differences among individuals aged 6–30 years (Schlichting et al., 2017), while others report a less consistent pattern of age differences in morphometry (Gogtay et al., 2006). Similar to the measurements of Hc subfields, the mixed evidence for differential age effects in anterior-posterior divisions may follow from differences in methodology. Nonetheless these few studies underscore the possible utility of characterizing developmental trajectories in volumetry along the horizontal axis of the Hc. Indeed, children and adults differ in functional activation patterns within the Hc anterior and posterior regions during source memory retrieval (DeMaster et al., 2016; DeMaster and Ghetti, 2013; DeMaster et al., 2013). Volumes of anterior and posterior divisions also correlate differentially with episodic memory function (DeMaster et al., 2014; Riggins et al., 2015). Smaller Hc head and larger posterior volumes correlate with better episodic memory in young adults (Poppenk and Moscovitch, 2011) but not among children (DeMaster et al., 2014). Thus, anterior-posterior divisions of the Hc may capture a unique aspect of memory development for which other measures of Hc structure fall short. However, the Hc subfields and anterior-posterior divisions have never been assessed simultaneously in a model of memory development, and thus their relative contributions and unique effects are unknown.

We aim to partially address the outlined limitations and explore development of the Hc subregions in relation to episodic memory function. In the present study we assessed Hc regional volumetry and associative memory in healthy participants ages 8–25 years. Hc subfields (CA1-2, CA3-dentate gyrus, and subiculum) and anterior-posterior divisions (Hc head, body, and tail) were manually demarcated on high-resolution images with high reliability. Age differences in Hc component volumes and their relation to associative memory were tested in structural equation modeling. To replicate and extend the current evidence, we first tested volumes of the Hc subfields and Hc head, body and tail in separate models. We hypothesized that Hc subfield volumes would differentially correlate with age and that smaller CA3-dentate gyrus volume would be related to better associative memory. As an alternate account, we tested the hypothesis that smaller Hc head volume with age would predict better associative memory. Finally, to account for the common measurement of the Hc, all measures were entered simultaneously into a competing hypothesis model, in which we expected CA3-dentate gyrus volume to be the stronger predictor due to its known functional specificity to associative memory function.

Material and methods

Participants

Seventy-five healthy participants (n=38 female), age 8–25 years (M=15.26, SD=4.95) underwent structural MRI and completed an associative memory test of word pairs. This sample was included in our previous report of age differences in Hc subfield volumes across nearly the entire lifespan (Daugherty et al., 2016a). All participants spoke English as a native language, were born full term, and reported no neurological injury, psychiatric disorders, or learning disabilities. Standardized IQ scores (Kaufmann Brief Intelligence Test, KBIT–2) of the whole sample indicated average intelligence (M=108.01, SD=12.28) that did not correlate with age (p=0.20). An additional 14 participants were recruited for the study and were found to perform at ceiling on the associative memory task and presented as multivariate outliers in the analysis. These participants (ages 10.87–25.32 years) were on average older than the remainder of the sample (M=19.72, SD=4.11; t (87)=−4.45, p=0.002), but did not differ in IQ or socioeconomic status (both p≥0.13). Primary hypothesis testing was conducted excluding these 14 individuals, and final models were re-assessed with their inclusion to confirm no undue bias in the analysis. All participants provided informed consent at study enrollment according to institutional requirements.

MRI acquisition

A high-resolution proton density-weighted turbo spin echo (PD-TSE) sequence was adapted from Bender et al. (2013) and acquired as part of a 1 h protocol on a 3 T Siemens Verio (Siemens Medical AG, Erlangen, Germany) full-body magnet with a 32-channel head coil. Images were acquired perpendicular to the long axis of the Hc with the

following parameters: voxel size=0.4 mm×0.4 mm×2.0 mm (30 slices); echo time=17 ms; repetition time=7150 ms; flip angle=120°; pixel bandwidth=96 Hz/pixel; turbo factor 11; FOV=280 ×512 mm.

Intracranial volume was measured from a high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: repetition time=2200 ms; echo time=4.26 ms; inversion time=1200 ms; flip angle=9.0°; pixel bandwidth=130 Hz/pixel; GRAPPA acceleration factor PE=2; interpolated voxel size 0.5 mm×0.5 mm×1.0 mm. Intracranial volume (ICV) was manually demarcated following procedures detailed in Raz et al. (Raz et al., 2004). All regional volume measures were adjusted for ICV via analysis of covariance (Jack et al., 1989). Although ICV correlated with age (0.55, $p < 0.001$), the relationship between ICV and hippocampal subfield and head, body and tail volumes did not differ by age or between sexes (all $p > 0.05$), thus the same ICV correction was applied to the entire sample.

Hippocampal subfield volumetry: subiculum, CA1-2, CA3-Dentate gyrus

Hc subfields were measured from three contiguous slices (0.4×0.4×2 mm^3, coronal) of the anterior body by a single rater (A.M.D.) with high reliability as indicated by an intra-class correlation coefficient (ICC(3); Shrout and Fleiss, 1979) following a two-week delay: left, right CA3-DG=0.88 and 0.96; left, right CA1-2=0.86 and 0.93; left, right subiculum=0.90 and 0.94. Manual tracing procedures of the Hc subfields are detailed in Bender et al. (2013; adapted from Mueller et al., 2007; Mueller and Weiner, 2009). Regions included the subiculum (including pre- and para-subiculum), area CA1 and CA2 as a single region (CA1-2), and areas CA3 and dentate gyrus as a single region (CA3-DG). See Fig. 1C for example demarcation.

Hippocampal head, body, and tail volumetry

Hc head, body and tail were manually segmented from the same images by two independent raters (A.M.D. and R.F.) with high reliability measured by an intraclass correlation coefficient with the assumption of random raters (ICC(2); Shrout and Fleiss, 1979): left, right head=0.99; left, right body=0.95, 0.89; left, right tail=0.95, 0.92. See Fig. 1A for an example of demarcation. We have developed a novel protocol for hippocampal head, body and tail demarcation (Daugherty et al., 2015), described here in brief. Regions were sampled from 15–17 contiguous slices; the most anterior slice was identified by visualization of the mammillary bodies and the range extended posterior until the pulvinar nucleus was no longer visualized and the columns of fornix were apparent. The range of the Hc head began on the most anterior slice and ended posterior to the uncal apex, when the digitations were no longer visualized. The range of the Hc body began posterior to the head and ended with the last visualization of the lamina quadrigemina, commonly on the same slice on which the fimbria fornix was visualized posterior to the pulvinar nucleus. The Hc tail range was defined as the remainder of posterior slices. The most anterior slice was identified as the same for both hemispheres, but subsequent transitions to body and tail were allowed to vary by hemisphere, as was the most posterior terminal slice. Total Hc volume was measured as the sum of the Hc head, body and tail regions, which closely agrees with other definitions used in total Hc volumetry (e.g., Raz et al., 2004).

Recognition memory paradigm

Participants completed a computerized recognition memory paradigm (adapted from Bender et al., 2010; Naveh-Benjamin, 2000). Participants studied 26 word pairs (displayed for 5 sec with 1 sec inter-trial-interval), followed immediately by a 1-min distraction task

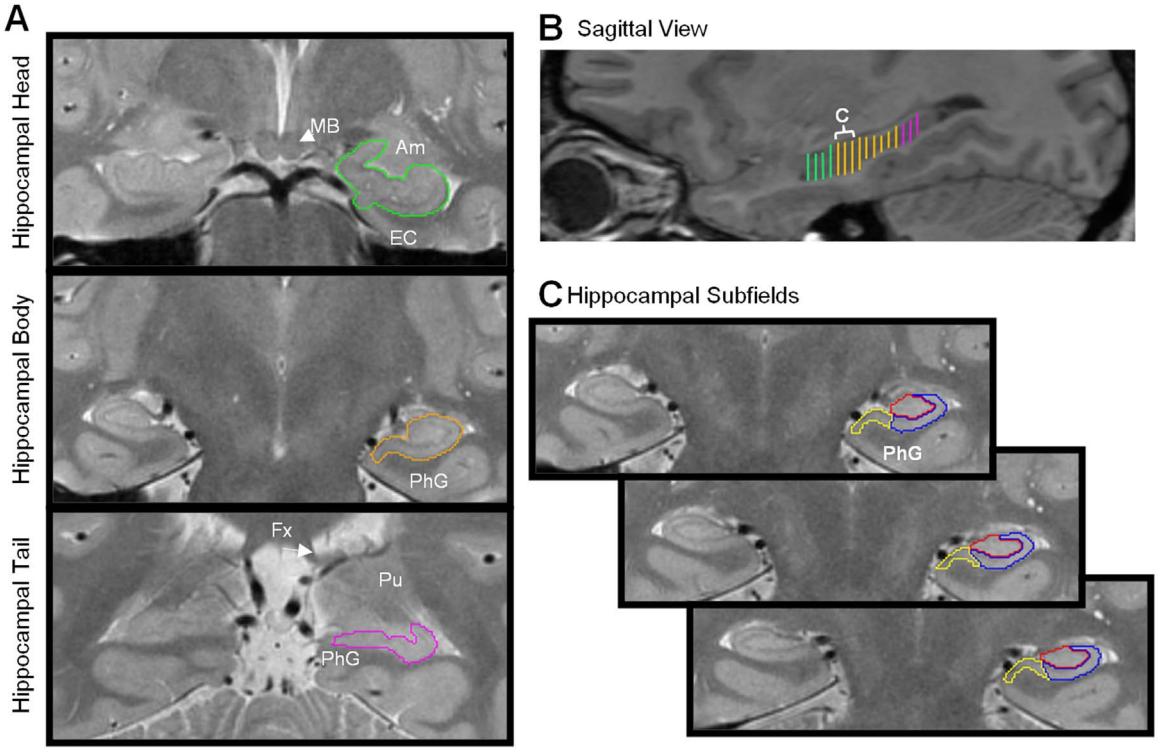

Fig. 1. Example manual tracing of hippocampal subfields and head, body, and tail on T2 proton-density weighted turbo spin echo images. Image intensities are inverted. (**A**) Example of manual tracing of hippocampal head (green), body (orange), and tail (purple). (**B**) An example sagittal T1-weighted image that displays the approximate range of head (green), body (orange) and tail (purple) measurements made from the T2-weighted images. The white bracket, labeled "C" indicates approximately the 3 slices on which the subfields were segmented in the anterior Hc body, beginning posterior to the uncal apex. (**C**) Example of manual tracing of the hippocampal subfields were made on three contiguous slices of the anterior body on T2 proton-density weighted turbo spin echo images: subiculum (yellow), CA1-2 (blue), CA3-dentate gyrus (red). Additional regions are labeled for anatomical reference: Am—amygdala; EC—entorhinal cortex; Fx—column of fornix; MB—mammillary body; PhG—parahippocampal gyrus; Pu—pulvinar nucleus.

(counting backwards from a randomly generated three digit number), and item and associative recognition memory tests. The item recognition test included 16 individual words: half were from the study list and half were unseen foil words. The associative recognition test consisted entirely of words from the study list; 8 pairs were shown unchanged from study and 8 pairs were recombined pairs of words from study. Participants completed two blocks of study and tests. The order of the study lists and the order of the item and word pair recognition tests were counterbalanced across participants. Prior to testing, participants completed a practice phase consisting of presentation of six word pairs, a distraction and the two recognition tasks.

Recognition memory paradigm stimuli

Each study list contained 26 word pairs that were composed of words chosen from the Medical Research Council psycholinguistic database (Wilson, 1988). Words were selected to be concrete nouns (concreteness≥451, scaled 100–700) composed of 3–10 letters, moderately prevalent in written language (Kucera-Francis written frequency 2–763) and commonly acquired by an early age (acquisition age score≤551, scaled 100–700). Word pairs were created to minimize semantic relatedness (relatedness=−0.1 to 0.15, scaled −1.0 to 1.0, Latent Semantic Analysis database, University of Colorado Boulder, lsa.colorado.edu).

Recognition memory discriminability index

Recognition memory performance was characterized by an index of discriminability (d′), a signal detection index based upon the proportion of correct recognition of targets and incorrect recognition of foils (false alarms; Pollack and Norman, 1964). This index is well suited for a two force-choice recognition paradigm (Stanislaw and Todorov, 1999). Separate indices were calculated for item recognition (d′ Item) and associative recognition (d′ Associative) per test block.

Data conditioning and hypothesis testing

Prior to analysis, all regional brain volumes and memory performance data were checked for skew and univariate outliers were winsorized. Average age differences and primary hypothesis testing of the relation between Hc subfield and Hc head, body and tail volumes, memory function, and age-related differences therein, were tested with latent structural equation modeling in MPlus (v7; Muthén and Muthén). Structural equation modeling (SEM) is a covariance framework that tests hypotheses based upon the pattern of shared and unique variances between multiple variables. Latent SEM is a preferred method because, unlike mean multivariate analysis methods (e.g., MANOVA), the latent estimates are independent of measurement error and the model provides a robust estimation of indirect effects through competing variables, while accounting for multivariate collinearity (Hayes and Scharkow, 2013; Raykov and Marcoulides, 2006), as we have here. Within this framework, the unique and differential effects of age predicting memory recognition via separate, correlated brain regions that are hypothesized are tested directly and rigorously. Model fit was determined by a set of indices (Hu and Bentler, 1998; Hu and Bentler, 1999; Raykov and Marcoulides, 2006): normal theory weighted χ^2 (non-significant value indicates good fit), the proportion of χ^2 to degrees of freedom as an index of parsimony (criterion less than 2), comparative fit index (CFI≥0.90 indicates excellent fit), root-mean square error of approximation (RMSEA < 0.05 supports excellent fit), and standardized root mean square residual (SRMR < 0.08 supports good fit) or weighted root mean residual for models that included a categorical variable (WRMR < 0.80 supports good fit).

Hypothesis model construction

Latent factors of Hc subfield and head, body and tail volumes were identified by left and right hemisphere measures, and item and associative memory, by block 1 and block 2 administrations. The measures were normed and intercepts fixed to 0 (except for block 1 item d' that had a free intercept), loadings of the two measures for each construct were fixed to 1 and the respective measurement variances were freely estimated. This model construction uses the commonality of the two measures to identify the latent factor while removing measurement error and thereby produces error-free estimates of the hypothesized effects. At least two measures are required to identify a latent construct apart from measurement error (i.e., left and right hemisphere volumes), and thus we do not presently test possible laterality of effects. This same construction was used to test average age differences, primary hypotheses and the competing hypothesis in separate models. Average age differences in all Hc regional volumes and recognition memory were estimated in one simple regression SEM, allowing correlations among Hc regional volumes. The model included age and age^2 (both terms centered at the sample mean) as correlated terms, and significance of the quadratic age term while accounting for possible linear effects of age was conservatively taken as evidence of non-linearity. Following which, two primary hypothesis models were constructed to test age-related differences in Hc regional volume and memory discriminability: one model included the Hc subfield volumes pertaining to our primary hypothesis, the other model included Hc head, body and tail as an alternate hypothesis. A third, competing hypothesis model included age-related differences in Hc subfield volumes, Hc head, body and tail volumes, and memory discriminability. In the first two models, we directly evaluated standing hypotheses within the literature, and in the third we tested whether volumes of the Hc subfields or Hc head, body and tail were the better predictor of age-related differences in memory. Because the regions are treated as unique, but correlated, measures within the Competitive Hypothesis model, the interpretation of effects pertaining to each Hc subfield and Hc head, body and tail can be considered independently. Within these three hypothesis models, indirect effects were evaluated according to the James and Brett (1984) method, in which a significant effect establishes an association between age and memory discriminability via regional Hc volumes. During model construction and hypothesis testing, non-significant paths were constrained to zero. All comparisons of differential age effects and correlations with memory performance across Hc subfields and Hc head, body, and tail were made simultaneously within the specified models, obviating the need for correction for multiple comparisons, and significance testing was set a $p < 0.05$.

Results

Average age differences in Hc regional volumes

In an initial analysis, the head, body and tail measures were summed to calculate total Hc volume in the left and right hemispheres and were submitted to a repeated measure general linear model. Total Hc volume was confirmed to show no age differences ($F(1, 71)=1.50$, $p=0.22$), Hc volumes were similar between hemispheres ($F(1, 71)=0.75$, $p=0.39$) and age effects did not differentiate between hemispheres ($F(1, 71)=0.72$, $p=0.40$). In contrast to total Hc volume, age-related differences in volumes differed between Hc subfields and Hc head, body and tail. Average age differences in Hc subfields and Hc head, body and tail were estimated in SEM with excellent fit: $\chi^2(135)=127.32$, $p=0.67$; CFI=1.00; RMSEA=0.00; WRMR=0.61. The model controlled for the correlations among Hc head, body and tail and subfields. Adults had smaller CA3-DG volumes as compared to children following a linear function (age β=−0.34, p=0.02; age^2 β=0.07, p=0.62; R^2=0.12), and CA1-2 volume demonstrated a non-linear trend of smaller volumes in adolescents as compared to children and adults (age^2 β=0.34, p=0.01; age β=0.07, p=0.56; R^2=0.12), but subiculum volume was age-invariant (age β=−0.14, p=0.37; age^2 β=−0.12, p=0.39; R^2=0.04). Non-linear age differences were also identified in Hc body volume (age^2 β=0.30, p=0.01; age β=0.21, p=0.10; R^2=0.14)—

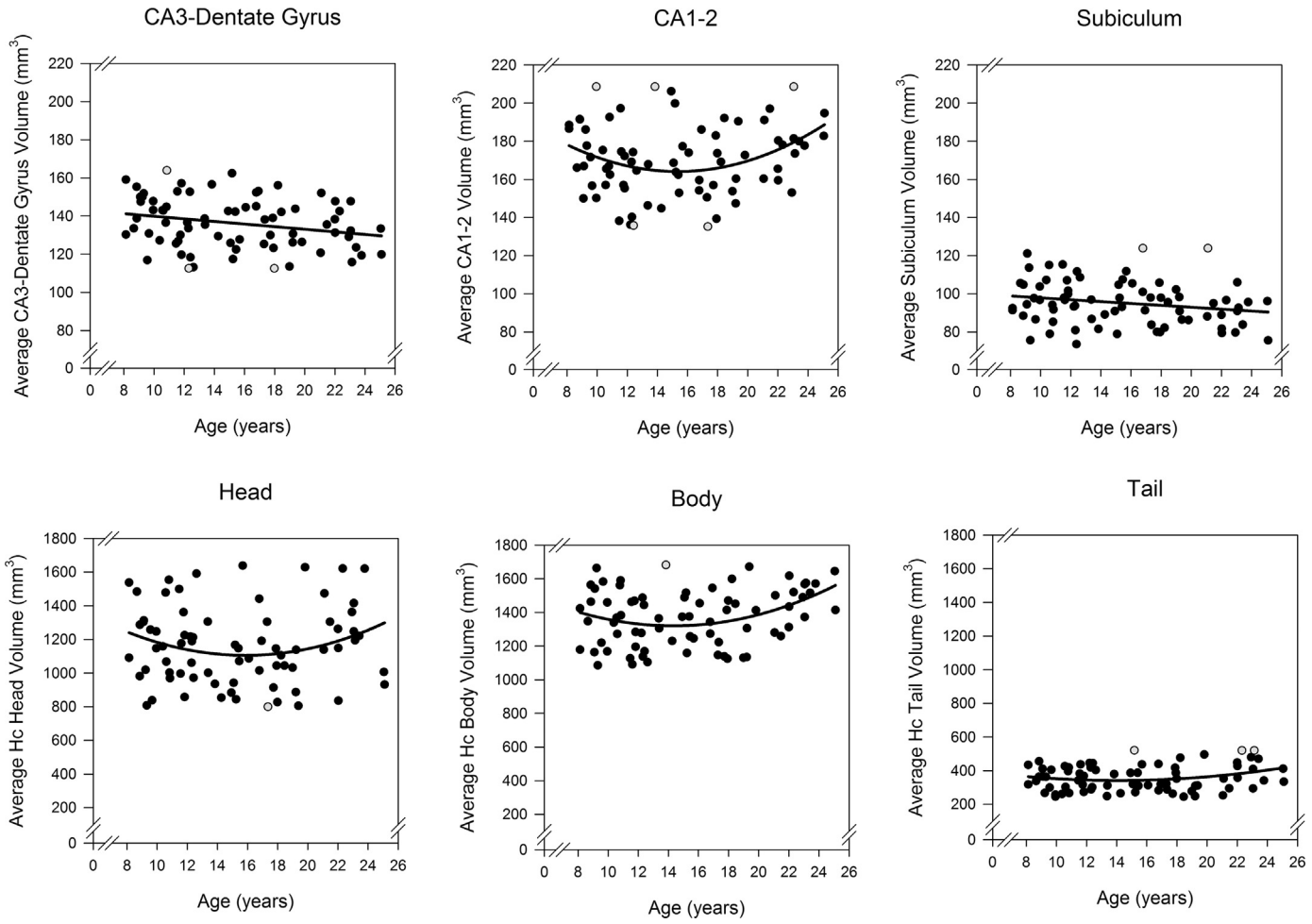

Fig. 2. Age differences in volumes of hippocampal subfields and hippocampal anterior-posterior divisions. (**A**) CA3-dentate gyrus (age p=0.02; age^2 p=0.62; R^2=0.12), (**B**) CA1-2 (age p=0.56; age^2 p=0.01; R^2=0.12), (**C**) subiculum (age p=0.37; ge^2 p=0.39; R^2=0.04); (**D**) hippocampal head (age p=0.65; age^2 p=0.11; R^2=0.05), (**E**) hippocampal body (age p=0.10; age^2 p=0.01; R^2=0.14), (**F**) hippocampal tail (age p=0.26; age^2 p=0.06; R^2=0.10). Standardized effect coefficients are reported from the latent modeling that estimated linear and quadratic age differences in all regions simultaneously, accounting for correlations among subregions. Points labeled with gray represent univariate outliers that were winsorized. All volumes were corrected for intracranial volume. For plots of age differences in hippocampal subregion volumes that were not corrected for intracranial volume, see Supplementary material Fig. S1.

Table 1
Pearson correlations among observed variables.

		1	2	3	4	5	6	7	8	9
1	Age	1.00								
2	Hc Head Volume	0.03	1.00							
3	Hc Body Volume	0.22	0.01	1.00						
4	Hc Tail Volume	0.16	**0.36**	*0.30*	1.00					
5	CA1-2 Volume	0.10	0.00	**0.57**	0.14	1.00				
6	Subiculum Volume	−0.21	**0.37**	−0.10	−0.05	−0.06	1.00			
7	CA3-DG Volume	*−0.25*	−0.01	**0.37**	0.08	**0.40**	0.03	1.00		
8	Item d'	0.10	0.12	−0.01	0.00	0.10	0.11	0.09	1.00	
9	Associative d'	**0.49**	0.07	0.10	0.13	0.00	0.03	*−0.24*	**0.43**	1.00

Note: Memory recognition d' scores are averages of two block administrations, and volumes of hippocampal subfields and head, body and tail regions are averages of left and right hemispheres, corrected for intracranial volume. Significance indicated as: **r≥|0.36|, p≤0.001,** *r≥|0.24|, p < 0.05*. CA—Cornu ammonis; DG—dentate gyrus; Hc—hippocampus.

body volume was smaller among adolescents as compared to children and adults. Non-significant trends for the same pattern of non-linearity were identified in the Hc head (age β=0.06, p=0.65; age^2 β=0.21, p=0.11; R^2=0.05) and tail volumes (age β=0.17, p=0.56; age^2 β=0.26, p=0.06; R^2=0.10). See Fig. 2 for age differences in Hc subfield and head, body and tail volumes. For age differences in Hc subregion volumes that were not corrected for ICV, see Supplementary material (Fig. S1). Sex was included as a covariate in the model and was unrelated to volumes of Hc subfields (all p≥0.35). A non-significant trend indicated males had smaller Hc tail volumes (r=−0.28, p=0.08), but there were no sex differences in Hc head (r=−0.18, p=0.26) or body volumes (r=−0.16, p=0.29). Therefore, sex was retained as a control variable in models that included Hc tail volumes, but was omitted from the primary hypothesis model that included only subfield volumes. See Table 1 for correlations between observed variables.

Average age differences in recognition memory

In the same model that included Hc regional volumes, linear and non-linear age differences in recognition memory were also examined.

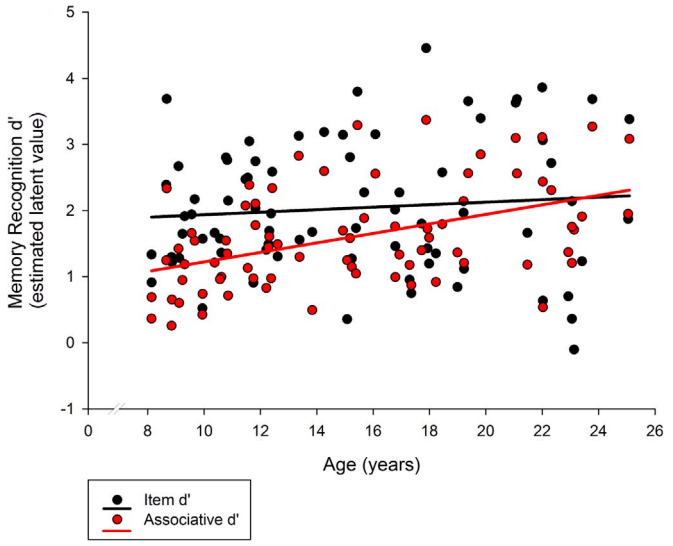

Fig. 3. Age differences in memory recognition (d′) for item (age p=0.68; age^2 p=0.87; R^2=0.003) and associative pairs (age p < 0.001; age^2 p=0.93; R^2=0.41). Values for memory recognition are latent estimates per each individual that were extracted from the structural equation model. Regression lines were fit. Black represents memory for items and red represents memory for associative pairs.

Participants studied lists of word pairs and were later tested for recognition of individual words (item) and pairs of words (associative). As expected, older age was linearly related to better associative recognition (age β=0.64, p < 0.001; age^2 β=0.01, p=0.93; R^2=0.41) but not item recognition (age β=0.05, p=0.68; age^2 β=−0.02, p=0.87; R^2=0.003**;** Fig. 3). Sex was unrelated to either index of memory (both p≥0.26).

Smaller CA3-DG accounts for age-related improvement in associative memory

In the primary hypothesis model we tested the relation between variability in Hc subfield volumes and associative memory. This model that only included volumes of the Hc subfields had excellent fit (see Table 2) and standardized effects are reported. To avoid spurious effects due to small sample size, tests of indirect effects were bootstrapped with bias-correction (5000 iterations of the whole sample; (Hayes and Scharkow, 2013) to estimate 95% confidence intervals (BS 95% CI) of unstandardized effects.

Better associative memory was explained by smaller CA3-DG volume (β=−0.46, p=0.002; R^2=0.21; see Fig. 4A), but not by differences in CA1-2 (β=0.49, p=0.10, path constrained) or subiculum (β=0.09, p=0.62, path constrained). Age was indirectly related to better associative memory via smaller CA3-DG volume (indirect effect=0.19, p=0.04; BS 95% CI: 0.01/0.09; Fig. 5). The effect was specific to associative memory, as differences in Hc subfield volumes did not explain individual differences in item memory (all p≥0.38, paths constrained). The model specifically tested a hypothesized indirect effect of age on memory via brain volumes, and the independent correlation of age with memory was constrained. When age was allowed to correlate with associative recognition (r=0.56, p < 0.001), smaller CA3-DG remained uniquely related to better associative recognition (β=−0.28, p=0.049), albeit attenuated, which suggests that individual differences in CA3-DG volume predicting associative recognition are partially related to age. The hypothesized model was assessed with Hc subfield volumes that were not corrected for ICV, and the same pattern of results were identified: age predicted smaller CA3-DG volume (age β=−0.37, p=0.002) that in turn predicted better associative memory recognition (β=−0.43, p=0.003; indirect effect=0.16, p=0.06; BS 95% CI: 0.01/0.09). Thus, smaller CA3-DG volumes with age partially explained the age-related improvement in associative memory.

Table 2
Fit indices of hypothesized models.

Fit index	Fit criterion	Model		
		Hc subfields	Hc head, body, tail	Competitive hypothesis
χ2 (p-value)	p > 0.05	62.19 (0.27)	64.79 (0.52)	150.67 (0.47)
χ2/d.f.	< 2	1.11	0.98	1.00
CFI	≥0.90	0.97	1.00	0.99
RMSEA	≤0.05	0.04	0.00	0.01
SRMR (WRMR)[a]	< 0.08 (< 0.80)	0.10	(0.71)[a]	(0.75)[a]

Note: Fit criteria demonstrate good model fit (Hu and Bentler, 1998, 1999; Raykov and Marcoulides, 2006). d.f.—degrees of freedom; CFI—comparative fit index; RMSEA—root mean square error of approximation; SRMR—standardized root mean residual; WRMR—weighted root mean residual.

[a] WRMR was estimated in lieu of SRMR for models that included sex as a categorical covariate.

Reverse effects model

As a final test of the direction of effects, all regression paths were reversed and estimated as a Reverse Effects model that included volumes corrected for ICV. This model fit similar to the hypothesized model: χ^2 (52)=63.54, p=0.13; CFI=0.94; RMSEA=0.05; SRMR=0.10. The reverse path of CA3-DG volume regressed on associative recognition was not significant (β=−0.20, p=0.10) and therefore the direction of effects of volume predicting performance was further supported. Relying on cross-sectional data, we cannot confidently test causality, but we can determine the direction of an association between two constructs with greater certainty.

Differences in Hc head, body, tail volumes do not account for individual differences in memory

In a second model, we tested the alternative hypothesis that differences in Hc head, body and tail volumes would account for variability in associative memory. Hc head, body and tail volumes were unrelated to differences in item (all p≥0.27) and associative memory (all p≥0.28) and these paths were constrained in the final model (Fig. 4B) that had excellent fit (see Table 2), further supporting no unique relationship between volumes of these regions and memory function.

Competitive hypothesis testing: CA3-dentate gyrus volume is the largest predictor of age differences in associative memory

Although we treat these methods separately, volumes of the Hc subfields and Hc head, body and tail regions are related measures of the same structure, and we can better evaluate the selectivity of cognitive correlates by including all measures in a single model. We hypothesized that given the known functional specificity of the Hc subfields, CA3-DG volume would be a stronger correlate of associative memory across development as compared to Hc head, body and tail volumes. The competitive hypothesis model fit well (see Table 2) and demonstrated that age-related improvement in associative memory was primarily explained by smaller CA3-DG volume with age. Linear age-related improvement in associative memory was explained by combined differences in CA3-DG and Hc body volumes (total indirect effect=0.46, p=0.001; BS 95% CI: 0.02/0.13). When comparing the specific paths, age differences in CA3-DG accounted for 67% of the indirect effect of age on associative memory (indirect effect=0.31, p=0.01; BS 95% CI: 0.01/0.12; see Fig. 5). The remainder was related to linear age differences in Hc body volume, however, this did not reach significance (indirect effect=0.15, p=0.09; BS 95% CI: 0.002/0.07), and

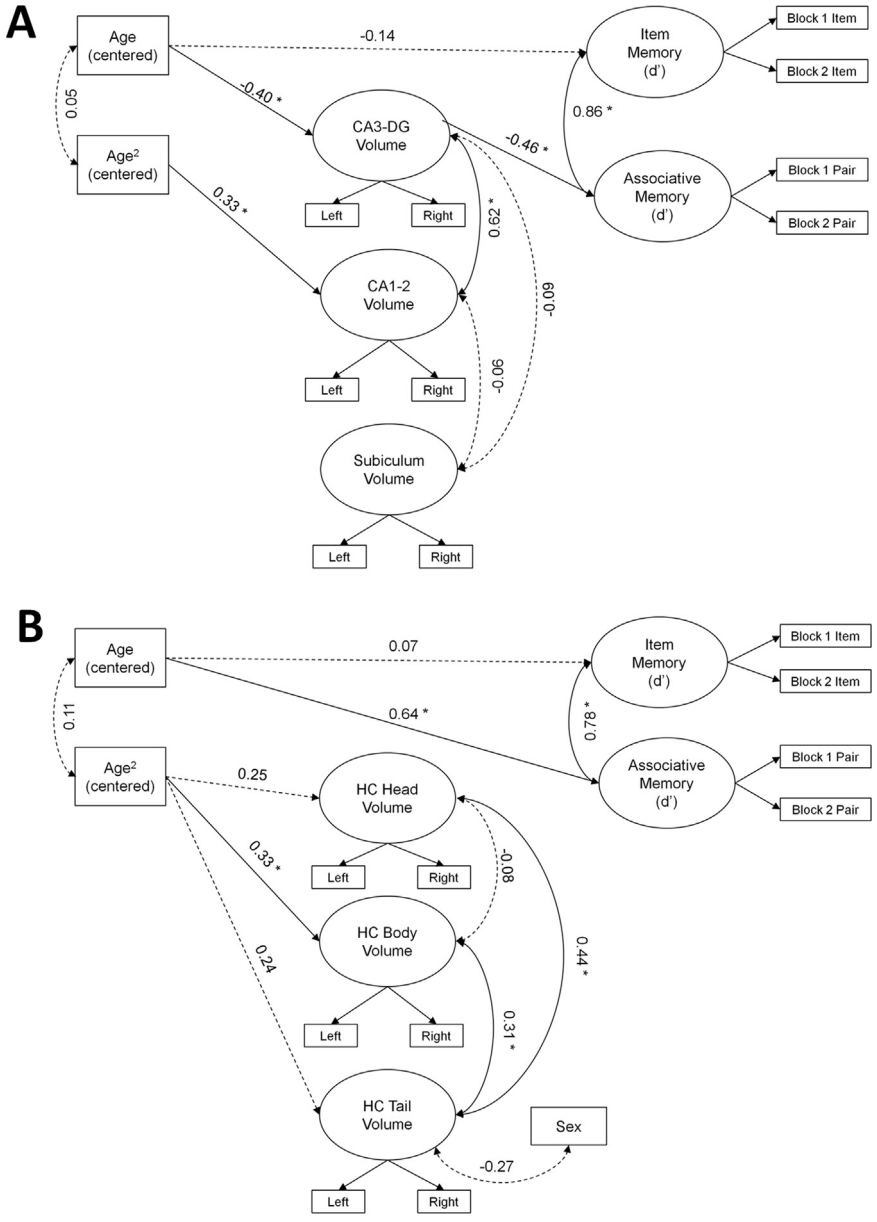

Fig. 4. Primary hypothesis models testing age-related differences in hippocampal regional volumes as predicting differences in recognition memory. **(A)** Hippocampal subfield (subiculum, CA3-dentate gyrus, and CA1-2) volumes predicting differences in recognition memory (indirect age effect p=0.04; R^2=0.21). **(B)** Hippocampal head, body and tail volumes did not predict differences in recognition memory (indirect age effect $p \geq 0.05$, non-significant paths were constrained). All coefficients are standardized. * indicates a significant effect, $p < 0.05$. Paths marked with broken lines indicate non-significant covariate effects.

non-linear age differences in Hc body volume did not account for age-related improvement in associative memory (indirect effect=0.14, p=0.10; BS 95% CI: 0.002/0.02). Notably, Hc body volume alone did not account for memory recognition (refer to alternative hypothesis model, Fig. 4B) and only reached significance (β=0.57, p=0.01) when accounting for its high correlation with CA3-DG (r=0.80, p < 0.001) and CA1-2 (r=0.70, p < 0.001) volumes measured in this region. The same analysis with Hc subregion volumes not corrected for ICV produced a similar result: smaller CA3-DG volume predicted better associative memory (β=−0.77, p=0.001) as did larger Hc body volume (β=0.61, p=0.01), and both regions contributed to the indirect effect of age on associative memory (total indirect=0.09, p=0.001; BS 95% CI: 0.02/0.14). Thus, smaller CA3-DG volume with age was a stronger predictor than Hc body volume of age-related improvement in associative memory.

Reverse effect model

The reverse model with volumes adjusted for ICV had modestly worse fit than the hypothesized model: χ^2 (151)=162.63, p=0.24; CFI=0.90; RMSEA=0.03; WRMR=0.83. Reverse pathways of CA3-DG (p=0.23) and Hc body volumes (p=0.66) regressed on associative memory recognition were not significant. Taken together, the cumulative evidence presented here suggest that between childhood and adulthood, older age accounts for smaller CA3-DG volume that in turn explains age-related improvement in associative memory.

Accounting for possible bias of effects identified in final models

Several cases that presented as multivariate outliers were removed from primary hypothesis testing and to guard against analytic bias, we conducted complementary analyses with alternate sample selection.

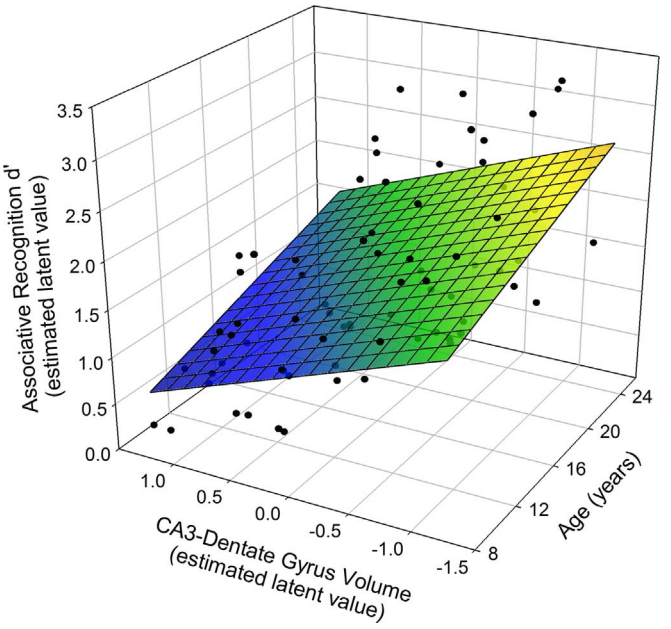

Fig. 5. Plot of the relation between age, CA3-dentate gyrus volume, and associative recognition (d'). A regression plane was fit to the three dimensional scatter plot, the plane is color coded to demonstrate the three-way interaction between age, CA3-dentate gyrus volume and associative recognition—blue corresponds to children who had large CA3-dentate gyrus volumes and poor associative recognition; yellow represents adults with smaller CA3-dentate gyrus volumes and better associative recognition. Scales for CA3-dentate gyrus volume and associative d' are latent values for each individual extracted from the structural equation model of these effects. The indirect effect of age on associative recognition via CA3-dentate gyrus explained 67% of the total indirect effect of age on associative memory in the competing hypotheses model that included the Hc head, body, and tail volumes.

First, we reassessed the final models that returned significant effects in the total sample (N=89), including the 14 participants who performed at ceiling on the associative memory task. The pattern of effects was replicated in the Hc subfields model: age predicted smaller CA3-DG volume (β=−0.28, p=0.02) that in turn accounted for better associative memory (β=−0.28, p=0.02). The indirect effect of age on associative memory recognition via CA3-DG volume (0.08, p=0.13; BS 95% CI: 0.001/0.16) was attenuated as compared to the original analysis, but was supported by BS 95% CI that did not overlap with zero. This model estimated in the total sample had acceptable fit (χ^2 (56)=80.65, p=0.02; CFI=0.91; RMSEA=0.07; SRMR=0.11); yet, the indices indicate that the model is a sub-optimal account of the variance, potentially among participants performing at ceiling across the sampled age span (ages 10.87–25.32 years). The pattern of effects was also replicated in the Hc head, body and tail model: volumes were confirmed to be unrelated to item (all p≥0.13) and associative (all p≥0.21) memory recognition. Thus, in this complementary set of analyses the evidence supported CA3-DG as a correlate of age-related differences in associative memory, whereas there was little evidence supporting the contribution of Hc head, body and tail volumes.

Second, because young adults were more likely than children and adolescents to perform at ceiling and thus more likely to be removed from our primary hypothesis testing, the reported analyses are vulnerable to a possible age-related bias. To gauge this possibility, we reassessed the models adopting another procedure that excluded individuals who performed within the 90th percentile on the associative memory task defined within child, adolescent and adult age groups. This procedure excluded a similar number of high-performing younger and older individuals (n=8 children and adolescents, n=10 adults), including those at performance ceiling. This repeated analysis (N=71) identified the same pattern of results. Age was associated with smaller CA3-DG volume (age β=−0.45, p=0.001) that in turn predicted better associative memory performance (β=−0.75, p < 0.001; indirect effect=0.33, p=0.01, BS 95% CI: 0.01/0.12). Age also predicted larger Hc body volume (age β=0.23, p=0.05; age^2 β=0.24, p=0.04) that in turn was associated with better associative recognition (β=0.57, p=0.01; indirect effect=0.13, p=0.12, BS 95% CI: 0.00/0.08), and this remained the weaker contributor to age-related differences in associative memory.

Discussion

The hippocampus is a complex structure composed of various subfields and anterior-posterior divisions, and differential development of these subregions has been proposed to partially explain the mixed and protracted development of memory function into adulthood. Here we uniquely assessed age-related differences in Hc subfields and Hc head, body and tail volumes simultaneously, juxtaposing the evidence for these alternate measures of hippocampal structure and their relative contributions to memory function. We find young adults had smaller CA3-DG volume as compared to children following a linear trend, non-linear age differences in CA1-2 volume in which adolescents had smaller volumes, and subiculum volume was age invariant. Hc body volume also demonstrated non-linear age differences with smaller volumes among adolescents, and a non-significant trend for the same in Hc head volume, whereas Hc tail volumes were unrelated to age. Intriguingly, smaller CA3-DG volume uniquely accounted for age-related improvement in associative memory recognition. There was minimal evidence of anterior-posterior volume differences accounting for recognition, and larger Hc body volume predicted better associative memory only when accounting for its correlation with CA3-DG and CA1-2 volumes measured in that region. Indeed, smaller CA3-DG volume accounted for 67% of the indirect effect of age predicting improvement in associative memory whereas the remainder of the effect related to Hc body volume failed to reach significance. Therefore, CA3-DG volume appears to be a more sensitive correlate to associative memory during development than volumes of the other subfields or Hc head, body and tail.

Our finding of CA3-DG volume accounting for associative memory is consistent with prior evidence from studies of childhood development (Lee et al., 2014; Tamnes et al., 2014) and aging (Bender et al., 2013; Shing et al., 2011; Yassa et al., 2011b). Unlike item memory that develops early, complex associative memory functions develop after mid-childhood into young adulthood (Ofen, 2012). Pattern separation and completion functions of the CA3 and dentate gyrus are a posited mechanism of associative memory (Rolls, 2013). In this regard, volumetry of the subfields may be a proxy for cumulative microstructural changes, such as neurogenesis and synaptic pruning—the putative neural basis of associative memory binding and reconstitution (Johnston et al., 2016; Rolls, 2016).

Thus, it is intriguing that we find age negatively correlated with CA3-DG volume here. This is in line with our previous report of age differences across nearly the entire lifespan (Daugherty et al., 2016a) and the only longitudinal study of Hc subfield volumes in childhood to date (Tamnes et al., 2014). In that study, dentate gyrus shrinkage over 2.5 years in children and adolescents explained improvement in a verbal learning task (Tamnes et al., 2014). Thus, smaller CA3-DG volume during childhood development may be functionally adaptive. The paradox of pattern separation and memory robustness has been speculated upon in the context of adult aging (Johnston et al., 2016), and it is plausible that a similar balance between neurogenesis and synaptic pruning is seen here in childhood development to explain smaller volumes in relation to improved associative memory. Several cortical and subcortical brain regions demonstrate shrinkage in the course of development (Lenroot et al., 2007; Tamnes et al., 2010) and we find a similar pattern here in age-related differences in CA3-DG volume. This supports a hypothesis of protracted development of Hc-dependent memory functions, such as complex associative memory

(Ofen, 2012; Ofen and Shing, 2013). However, the effect is only identified when studying the subfields and there was no indication of the same negative correlation with age unique to any of the larger Hc head, body and tail volumes. Therefore, the CA3-DG subfields appear to be critical neural substrates of associative memory that develop into adulthood.

Whereas we replicate these previous studies, our finding is inconsistent with another cross-sectional report of a non-linear positive association of age with dentate gyrus volume into adolescence (Lee et al., 2014) that did not include adults in the analysis. Methodological differences for Hc subfield segmentation between that study and ours notwithstanding, differences in sampled age range may be one source of discrepancy. The different age ranges sampled may capture different age-related variability in hippocampal structure and memory function. This is expected to be further influenced by the use of cross-sectional study design that conflates between person differences with estimates of age effects (Lindenberger et al., 2011). Indeed, this is a limitation of any cross-sectional study of development, including ours. We find a pattern of smaller CA3-DG volume and invariance of subiculum volume with age that is similar to our previous lifespan report (Daugherty et al., 2016a). However, the non-linear pattern of age differences in CA1-2 volume identified here is incongruent with our previous report that included the majority of the adult lifespan. While there may be higher order non-linearity of age differences in this region due to dynamic microstructural changes (Bastian et al., 2016) this incongruence is likely an artifact of differences in the sampled age span and approximation of change from cross-sectional studies that is confounded by individual differences. This reasserts the need for longitudinal studies that can provide true estimates of change and valid tests of its mediators (Lindenberger et al., 2011; Maxwell and Cole, 2007). Yet, our evidence is at least partially in line with the single extant longitudinal study that similarly finds dentate gyrus shrinkage in normally developing children (Tamnes et al., 2014).

As an alternative account to subfield-specific effects, we tested possible associations between Hc head, body and tail volumes and memory function to account for age-related differences therein. Although the anterior-posterior divisions have gained popularity in the study of developing Hc structure-function relations, the evidence is mixed. For example, smaller anterior Hc and larger posterior Hc volumes correlate with better episodic memory in adults (Poppenk and Moscovitch, 2011), but volumes do not correlate with memory performance in children (DeMaster et al., 2014). Similarly, functional activation of the anterior Hc from source memory retrieval is only observed in adults and not found in younger children, although the difference in activation between adults and children is most robust in posterior regions (DeMaster et al., 2016, 2013; DeMaster and Ghetti, 2013). Here, we find non-linear age differences in Hc body volume, but Hc head, body and tail volumes did not alone explain individual differences in memory. Only when accounting for the correlation between Hc body volume and the subfield volumes measured in that region, larger body volume weakly predicted better associative memory. Yet, even when considering this, the indirect effect of age on associative memory was largely via smaller CA3-DG volume.

Interpreting the source of age-related differences in brain volumes is difficult, chiefly because volume is a crude proxy measure of microstructure defined by several cellular mechanics that each have different relevance across the lifespan. For example, persistent neurogenesis into senium is a unique feature of the dentate gyrus, but the rate of neurogenesis and its relation to the robustness of memory varies over the life course (Johnston et al., 2016). Because of the poor specificity to particular cell mechanics, interpretation of volume measures largely depends upon anatomical definition—i.e., the boundaries from which it was measured. Functions of the subfields are directly related to their distinct cytoarchitecture (Amaral and Lavenex, 2006; Lavenex and Lavenex, 2013) and the boundaries drawn on MRI approximate the divisions of these microstructural features. Thus, volumes from these definitions may more closely represent the structural composition of the Hc subfields from which we infer mechanistic properties and test cognitive correlates. Unlike the subfields, the anterior-posterior specialization is most distinct vis-à-vis extra-hippocampal functional projections and gene expression (Fanselow and Dong, 2010) and their division falls along a gradient instead of discrete microstructural boundaries (Strange et al., 2014). The definitions of Hc head, body and tail regions employed here are based on strict structural landmarks but may be a distant approximation of the gradient in functional projections along the horizontal axis. Thus, volumetry may be a poor proxy measure of the complexity in the Hc long axis and other methods—e.g., functional connectivity and morphometry from high-resolution imaging—may have better sensitivity. A convergence of these various methods in future studies may provide insights on how to best measure the developing hippocampus.

The findings reported here should be interpreted considering several other limitations. First, the Hc subfields were measured from only 3 contiguous slices of the anterior body. We used an established protocol that is highly reliable and has produced similar results between comparable samples (Shing et al., 2011, Bender et al., 2013, Daugherty et al., 2016a). However, our interpretations are limited to that portion of the Hc. Given the interest in anterior-posterior heterogeneity, it is a worthwhile goal to extend the subfield measurements throughout the horizontal length. Many protocols for Hc subfield segmentation exist but provide highly discrepant results, and it is the current thinking that a single harmonized protocol can be adopted at a future date (Yushkevich et al., 2015). Thus, in the future, we hope to extend our measurements and address additional hypotheses of differential involvement of the subfields in anterior versus posterior regions.

A second limitation is that the Hc head, body, and tail divisions may under-represent the age-related variability in the structure by averaging across large volumes. The landmarks used to make these divisions are accepted in the literature and produce reliable volumes (Daugherty et al., 2015). However, use of the uncal apex as a landmark may have included a portion of the anterior body within the Hc head measurement (Duvernoy, 2005). The current definitions exclude the portion of Hc head anterior to the mammillary bodies due to the difficulty of segmentation at the level of the amygdala, as well as a portion of the posterior tail; thereby, we may underestimate age-related variability that is localized to the most anterior and posterior aspects of the Hc (see Gogtay et al., 2006). As previously discussed, these gross divisions may be a poor approximation of the complexity in the horizontal axis. A longitudinal study that explicitly modeled the anterior-posterior gradient found a mixture of positive and negative, yet significant change in morphometry (Gogtay et al., 2006). By the virtue of representing this gradient by only three subregions, our protocol averages this variability within a region and therefore may be less sensitive to age-related differences therein.

Third, we do not presently test possible laterality of age differences in hippocampal structure and its relation to memory function. We chose to employ a latent modeling approach to test the hypotheses laid out here, which allowed latent estimates that were, by definition, free of measurement error and identified unique Hc subregion effects, while accounting for correlations among the different Hc measures. To accomplish these robust features of the analysis, we identified latent constructs by the common variance of the left and right hemispheres, which precluded analyses of possible laterality. Some have reported age effects and correlations with memory that differentiate by hemisphere in the Hc subfields (e.g., Lee et al., 2014) and Hc head, body and tail (e.g., DeMaster et al., 2014), but the pattern of laterality is inconsistent. Here we find no evidence of hemispheric differences in total Hc volumes or age differences therein, but we do not presently test this hypothesis with the Hc subregion measures.

Fourth, hypotheses were tested only with an associative memory task and demonstrate select effects with the CA3-DG, which is in agreement with extant literature (Bender et al., 2013; Shing et al.,

2011; Yassa et al., 2011a, 2011b). However, the subfields, and possibly the Hc head, body and tail, serve additional cognitive functions and a more extensive battery of tests should be considered in the future. Our research group has also reported a relation between CA1-2 volume and immediate recall on episodic memory tasks in adults (Bender et al., 2013), as well as correlations of CA1-2 and subiculum with spatial navigation ability (Daugherty et al., 2016b). Thus, the null effects reported here likely reflect the test selection and functional specificity of the Hc subfields, and additional cognitive correlates are expected. When determining additional cognitive assessments for the study of development, future studies may consider choosing a task that is not vulnerable to ceiling effects, as we had here. This is a methodological challenge in studies including children and adults, and we expect that the effects reported here would be more pronounced without this statistical bias.

Finally, the cross-sectional design limits testing age differences in memory and its mediation by the subregional volumes (Maxwell and Cole, 2007). Longitudinal studies are necessary for true estimates of change and its mediators during development (Lindenberger et al., 2011; Maxwell and Cole, 2007). Mediation tests in structural equation modeling with bias-corrected bootstrapped 95% confidence intervals is the current best practice (Hayes and Scharkow, 2013), but it cannot overcome the limitation of a cross-sectional design testing time-dependent effects. Moreover, the model testing the indirect effects of age on memory via Hc subregion volumes is an incomplete account of memory development. Several additional factors, including other brain regions and cognitive functions, and age-related differences therein, are expected to exert an influence (Ofen, 2012), as well as health and environmental factors that may impact brain structure and function beyond the effects of age alone (Walker et al., 2011; Yu et al. in press). An exhaustive account of memory development is beyond the means of this study and the reported models may be biased from omitted variables. Nonetheless, the evidence we provide here from a robust analytic approach lends insight into the development of associative memory in relation to hippocampal structure.

Conclusion

Here, we demonstrate a negative correlation of age and CA3-DG volume that accounted for age-related improvement in associative memory specifically. Item recognition was age-invariant, as is expected after mid-childhood, and was unrelated to all measures of the Hc subregions. Volumes of the other subfields and Hc head, body and tail did not account for associative memory function. Thus, age-related reduction in CA3-DG volume appears to be a feature of typical memory development.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2017.03.047.

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