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Developmental differences in relations between episodic memory and hippocampal subregion
volume during early childhood

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Abstract

Episodic memory shows striking improvement during early childhood. However, neural contributions to these behavioral changes are not well understood. The present study examined associations between episodic memory and volume of subregions (head, body, tail) of the hippocampus—a structure known to support episodic memory in school-aged children and adults—during early childhood (n=45). Results revealed significant positive relations between episodic memory and volume of the hippocampal head in both the left and right hemispheres for 6- but not 4-year-old children, suggesting brain-behavior relations vary across development. These findings add new information regarding neural mechanisms of change in memory development during early childhood and suggest developmental differences in hippocampal subregions may contribute to age-related differences in episodic memory ability.

Keywords: episodic memory, hippocampus, hippocampal subregions, early childhood, source memory

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Episodic memory is the ability to remember a past experience and details about the context in which it occurred (e.g., when, where, and how events unfolded). Previous research suggests that episodic memory improves dramatically during early childhood. For example, although very young children (e.g., 3-4 years) can form memories for real-life events and report on them accurately after brief delays, the majority of these memories are lost over increasing delay intervals (days or years; e.g., Bauer, 2007; Hamond & Fivush, 1991). Collectively, studies such as these suggest that that important changes occur during early childhood that ultimately lead to improvements in episodic memory.

Laboratory-based studies examining episodic memory during early childhood have suggested that memory improvements during this period are, in large part, due to children's increased ability to remember relations among co-occurring stimuli. For example, in one study, 4- and 6-year-old children and adults viewed complex pictures and were subsequently tested on memory for isolated picture parts and part combinations (Sluzenski et al., 2004). Results revealed that although memory for picture parts was similar across all three groups, there were age-related improvements in memory for combinations between 4 and 6 years. Similar improvements have been reported in studies examining children's ability to remember the source from whom they learned novel facts (Drumme & Newcombe, 2002; Riggins, 2014) or the location in which an object was encountered (Bauer et al., 2012). Together, these findings suggest that early childhood marks an important transition in episodic memory, specifically, in children's ability to remember relations between stimuli. However, the neural mechanisms underlying this change remain unclear.

Evidence from school-aged children and adults demonstrates that episodic memory in general and the specific ability to recall relations between stimuli rely on the hippocampus (see Ghetti & Bunge, 2012 and Spaniol et al., 2009 for reviews). Evidence supporting this brain-behavior relation comes from multiple sources including studies examining patients with damage to the hippocampus, associations between hippocampal structure and memory behavior, and hippocampal function during memory tasks. For example, fMRI studies in typical individuals show engagement of the hippocampus during episodic memory tasks in children as young as 7 years of age (Ghetti & Bunge, 2012) and throughout adulthood (Spaniol et al., 2009).

The hippocampus is known to undergo developmental changes during early childhood (e.g., data from nonhuman primates suggests that synaptic connectivity within this structure does not reach maturity until 5-7 years of age, see Lavenex & Banta Lavenex, 2013; Serres, 2001), and MRI studies in humans have reported age-related differences in hippocampal volume across middle and late childhood (e.g., Grieve, Korgaonkar, Clark, & Williams, 2011; Østby et al., 2009; Pfluger et al., 1999; Uematsu et al., 2012; Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). These findings have led to the proposal that improvements in memory may be related to changes in the hippocampus (Ghetti & Bunge, 2012), and cross-sectional studies of typically developing school-aged children have shown relations between hippocampal volume and performance on delayed recall tasks in school-aged children (e.g., Østby, Tamnes, Fjell, Walhovd, 2012).

In addition to studies examining the role of the hippocampus as a whole, regional specificity has also been demonstrated in terms of hippocampal function. Such specificity arises due to the fact that subregions (head, body, tail) of the hippocampus are differentially involved in various cognitive tasks as a result of 1) differential distribution of subfields and 2) differences in

connectivity with cortical regions within these subregions (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). These regional differences show developmental differences. DeMaster and colleagues (2014) reported that better performance on an episodic memory task in adults was associated with smaller right hippocampal head and larger right hippocampal body, whereas in school-aged children performance was associated with larger left hippocampal tail. Their findings suggested that developmental differences in hippocampal subregions contribute to age-related differences in episodic memory and provided further evidence supporting the idea that hippocampal-memory relations vary across development.

In sum, findings from previous research suggest that individual differences in memory ability are related to variations in hippocampal volume, but that these associations differ as a function of the 1) developmental state of the individual, and 2) specific subregion of the hippocampus being examined. The goal of the present study was to examine how age-related differences in episodic memory during early childhood are related to volumetric differences in the hippocampus. To accomplish this goal, we examined correlations between hippocampal volume and episodic memory separately in 4- and 6-year-old children. This represents the first investigation of hippocampal-memory relations in early childhood, which is a period of rapid behavioral development. Based on previous research we predicted that different brain-behavior relations would exist between 4- and 6-year-old children, who vary in episodic memory ability. However, given the lack of previous data regarding normative developmental changes of head, body, and tail specifically between 4 and 6 years of age, specific hypotheses were not generated regarding the pattern of correlations within either group.

Method

The University Institutional Review Board approved all procedures. Participants were compensated for participation.

Participants

Participants were recruited through a University maintained database. Informed consent was obtained from legal guardians. All children were full-term, native English speakers, free of neurological damage, and had no history of developmental disorders as determined by a parent-report.

A total of 75 4- (n=36, 22 female, 14 male) and 6- (n=39, 23 female, 16 male) year-old children participated. Of these children, 59 contributed MRI data (25 4-year-old, 34 6-year-old children), 52 contributed memory data (29 4-year-old, 23 6-year-old children), and 45 contributed both memory and MRI data (22 4-year-old, 23 6-year-old children). Reasons for attrition are as follows: 2 withdrew from the study, 3 were determined to be ineligible after enrollment (i.e., due to a history of seizures, behavioral problems, or limited knowledge of English), 3 did not complete the MRI scan, 6 had excessive head motion during the MRI scan, 1 had a structural abnormality, and 18 were not administered the memory assessment that is the focus of this paper.

Procedure

Children visited the laboratory on 3 different occasions. They completed training in a mock MRI, structural and functional MRI scanning, and behavioral testing, which consisted of assessment of memory, executive function, theory of mind, and IQ. Only data from the episodic memory assessment and structural MRI scan are included in the present report. The average delay between memory assessment and the MRI scan was 10.76 days ($SD = 9.05$ days), which did not differ between the age groups, $p=.33$.

Behavioral assessments

Memory for contextual details was examined using a source memory paradigm (Riggins & Rollins, in press). In this paradigm, children were shown 36 items in one of two different locations. Items consisted of 54 age-appropriate, commercially available toys. Thirty-six of the items were presented at both encoding and retrieval and an additional 18 were presented as novel items during retrieval. During encoding, each item was randomly associated with one of three novel actions (i.e., hug it, put it on your head, beat on it like a drum). Items were randomly divided into 6 sets of 9 items, to ease counterbalancing across subjects. Each action was presented 3 times per set. Location and item set order were counterbalanced between participants and items within sets were randomly presented. Locations were two rooms designed to be child-friendly and engaging and significant features of each room were made salient when the child entered the room (e.g., children unrolled the rug and placed it on the floor). Each room had a stuffed “character” associated with it to increase the salience of the context. Children were first shown each item and asked to interact with it in order to gain their attention and interest. Then the experimenter modeled the action associated with the object and required the child to imitate the action. All items in location 1 were shown before the child moved to location 2.

After a delay of approximately 1 hour, children were presented with the target items seen during encoding and 18 novel items. Items were presented one at a time and the children were asked to make old/new judgments. For items identified “old,” children were also asked what action was paired with the item during encoding and which location they encountered it in. These measures were averaged together and served as the dependent measure of episodic memory. For items identified as “new,” children were asked to place the item into a “new item” bin. Verbal or behavioral responses (pointing or placing the item in the room) were acceptable.

In addition to age-appropriate instructions, five training trials were administered to ensure all children understood the task at encoding and retrieval.

MRI Acquisition and Analyses

High-resolution structural MRI images were acquired from a Siemens 3.0-T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions) via a 12-channel coil with a T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence with standard parameters (176 contiguous sagittal slices, voxel size= $1.0 \times 1.0 \times 1.0$ mm; repetition time/echo time/inversion time = 1900/2.52/900 ms; flip angle= 9° ; pixel matrix= 256 x 256) while children viewed a movie of their choosing. Children were given motion training prior to scanning and head movement was minimized using padding around the head. Images were analyzed using FreeSurfer Version 5.1.0, a standard automatic volumetric segmentation program (surfer.nmr.mgh.harvard.edu) using a Linux terminal (RedHat 6.3) on a Macintosh computer. Freesurfer segmentation has been extensively described elsewhere (Fischl, 2012) and its calculations of subcortical volumes have been shown to be comparable to manual segmentation (Lehmann et al., 2010; Morey et al., 2009a;b). Use of FreeSurfer has also been validated in children as young as 4 years of age (Ghosh et al., 2010) and has been used in previous developmental investigations examining relations between hippocampal volume and memory (Østby et al., 2012). T1-weighted images of each participant were compared to a probabilistic atlas, generating new surface maps of gray matter, white matter and pial boundaries. Reconstruction and volumetric calculations were automatized. Resulting volumes were aligned into anterior commissure –posterior commissure (AC-PC) space, allowing for assessment of hippocampal volumes without distortions introduced by reorientation (Poppenek & Moscovitch, 2011). Manual quality control checks were performed at multiple steps during the procedure.

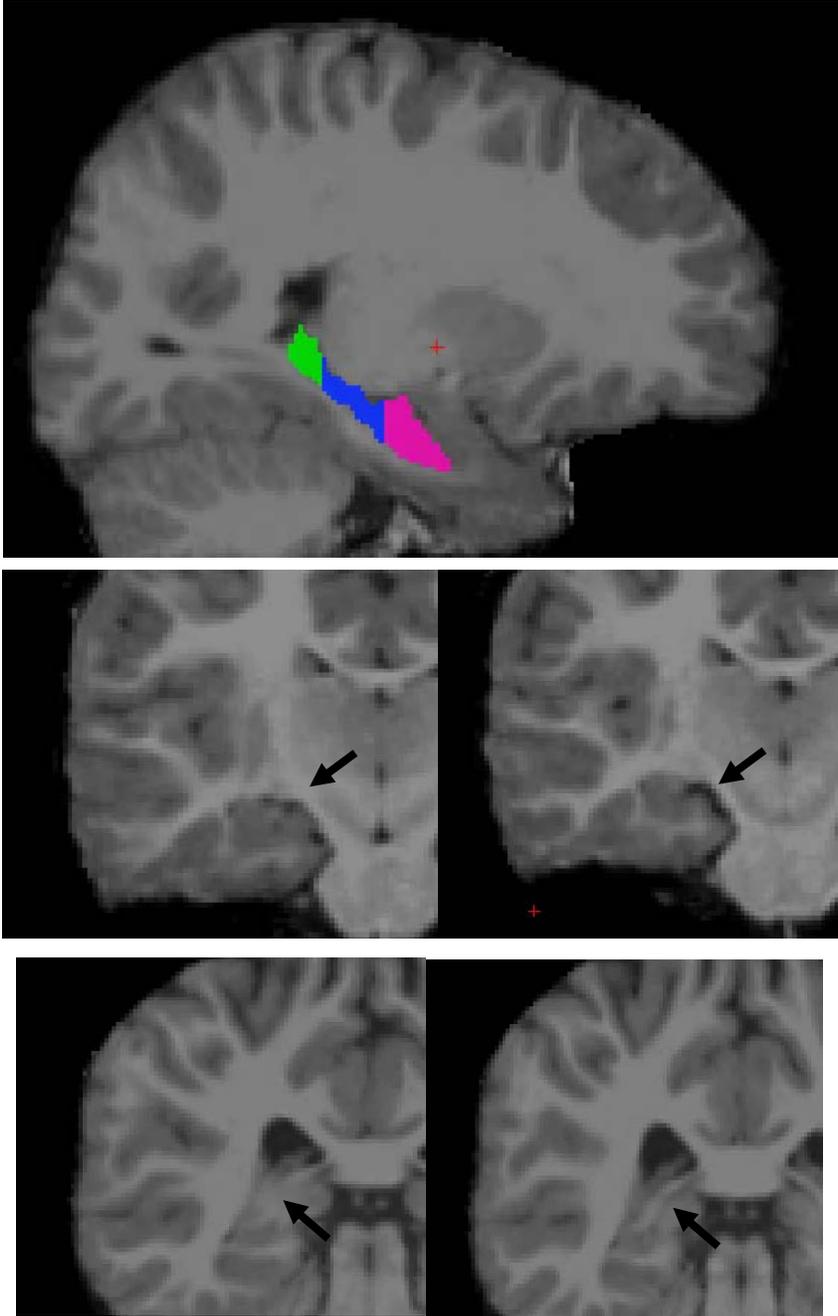
Minor edits to the cortical surface were made when it was necessary to exclude skull or dura from inclusion in the pial boundary (approximately 50% of the sample, on typically less than 20 slices per participant). These edits did not impact the subcortical segmentation resulting in hippocampal volumes, and given similar findings between raw and ICV-corrected hippocampal volumes, cannot account for the main finding of relations between hippocampal volume and memory performance. Manual edits were performed on 12% of the hippocampal segmentations (n=7, 5 6-year-old and 2 4-year-old children) in order to correct minor over- or under-inclusions using standard anatomical landmarks. Findings were identical when these children were removed from analyses; thus, only findings from the full sample are reported.

Resulting hippocampal volumes were manually segmented into 3 subregions (i.e., head, body and tail) using the uncal apex (Figure 1A). This landmark is easily recognized, unambiguous, and has been promoted as a standard reference in the field (Weiss et al., 2005; see also Duvernoy, 2005 and Gloor, 1997). In the coronal view, the most anterior slice of the hippocampus was identified by FreeSurfer and marked the anterior boundary of the hippocampal head. The posterior boundary of the hippocampal head was identified by moving caudally through the image and selecting the most posterior slice in which the uncal apex was visible (Figure 1B-C). Given there is some suggestion that this method includes portions of the body into the head (Duvernoy, 2005; Mai et al., 2008 as cited in DeMaster et al., 2014), we also investigated volumes of hippocampal head using an alternative anatomical landmark (i.e., when the digitations on the dorsal edge of the hippocampus are no longer apparent and it begins to round into a tear drop shape, see DeMaster et al., 2014 and supplementary material for details).

The most anterior slice of the hippocampal tail was identified as the slice at which the fornix separates from the hippocampus and becomes clearly visible (Watson et al., 1992, Figure

1D-E). The posterior slice of the hippocampal tail was identified automatically using parcellation algorithms for the whole hippocampus in FreeSurfer. Raters were blind to participant age and sex. Inter-rater reliability of landmark identification was computed for all participants. There was 97% agreement (within 2 slices) between raters for the slices selected as the end of the hippocampal head and beginning of the hippocampal tail in both left and right hemispheres. In addition, two-way mixed intra-class correlations (ICCs) were used to evaluate consistency between raters. In the right hemisphere, ICCs for volumes of the head and tail were .86 and .98 for 4 year olds and .98 and .97 for 6 year olds; and in the left hemisphere, .90 and .87 for 4 year olds and .98 and .98 for 6 year olds. No significant differences were identified between ICCs for 4- and 6-year-old children, ($ps=.16-.76$) (Feldt, Woodruff, & Salih,, 1987).

Figure 1. A) Head (pink), body (blue), and tail (green) for an individual participant. B) Slice illustrating where uncal apex is visible which marked the end of the head of the hippocampus, C) the next posterior slice where the uncal apex is no longer visible. D) Slice illustrating a portion of the body anterior to where the fornix separates from the hippocampus, E) the next posterior slice where the fornix is separated from the hippocampus.



Finally, in order to account for variation in hippocampal volumes resulting from age related differences in brain size, we adjusted hippocampal volumes using intracranial volume (ICV) using the method reported in Raz et al., 2005. All analyses, figures, and descriptive statistics reflect these ICV-adjusted volumes. Although hippocampal volume was correlated

with ICV, memory performance was not. Thus, results regarding associations between memory and subregion volume were similar if raw volumes were used instead.

Results

To examine memory differences between 4- and 6-year-old children, we compared performance between the age groups on 1) recognition of old stimuli, 2) correct rejection of new stimuli, 3) d' (sensitivity index) and 4) recall of contextual details for items correctly recognized as old (i.e., the location where old items were originally encountered and the action associated with them) using one-way ANOVAs with Age Group as a between subjects factor. Results revealed that there was no difference between 4- and 6-year-old children's ability to recognize stimuli as old or to correctly reject new stimuli (including d'), but 4-year-old children recalled marginally fewer contextual details compared to 6-year-old children (see Table 1). This pattern of findings was identical in the subset of children who contributed useable MRI data.

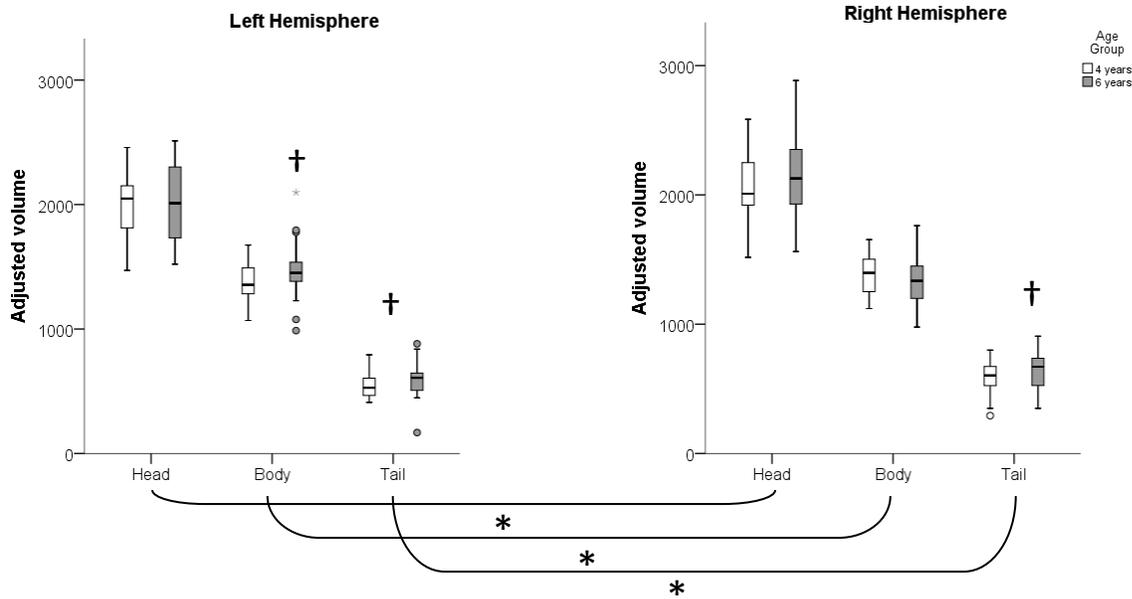
Table 1. Average behavioral performance for 4- and 6-year-old children on the memory task.

	4 year olds ($n=29$)		6 year olds ($n=23$)		Group difference
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	
Hits	96.54%	9.07%	99.88%	0.58%	<i>ns</i>
Correct Rejections	92.16%	21.44%	98.79%	5.79%	<i>ns</i>
d'	3.98	1.53	4.56	.37	<i>ns</i>
Contextual Details	42.45%	12.51%	49.55%	15.11%	$F(1,50) = 3.44, p=.07$

Differences in volumes of hippocampal subregions were examined using a 2 Age Group (4, 6 year) x 2 Hemisphere (left, right) x 3 Subregion (head, body, tail) RM-ANOVA with Age

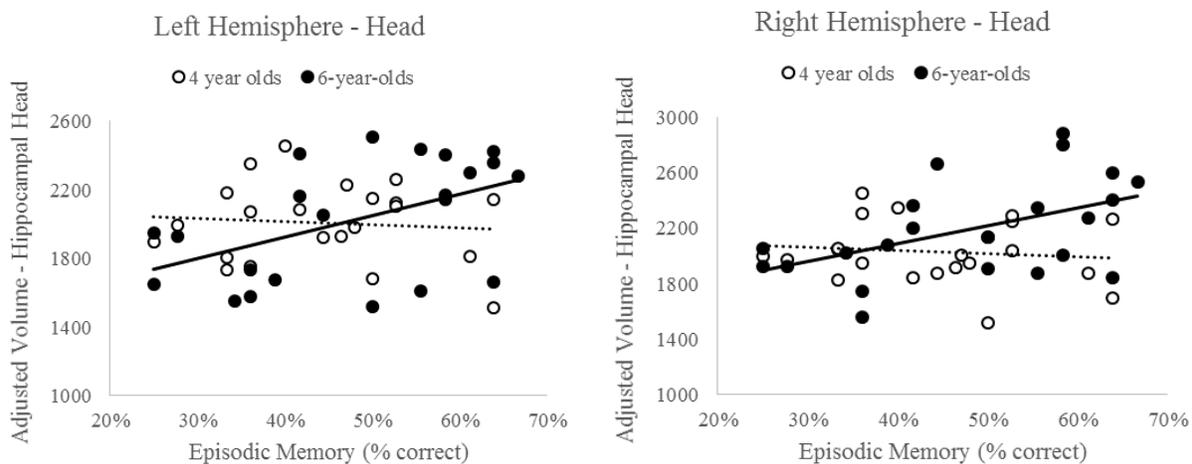
Group as a between subjects factor. This revealed a marginal main effect of Age, $F(1, 57) = 3.61, p=.06$, a main effect of Hemisphere, $F(1, 57) = 9.72, p<.01$, Subregion, $F(2, 114) = 834.47, p<.001$, and interactions between Hemisphere x Subregion, $F(2, 114) = 8.84, p=.001$, and Hemisphere x Subregion x Age Group, $F(2, 114) = 5.93, p<.01$. Follow-up analyses were conducted for each subregion separately (Figure 2). For the hippocampal head there was a main effect of Hemisphere, $F(1, 57) = 11.35, p=.001$, with volumes in right hemisphere greater than those in the left. For the body there was a main effect of Hemisphere, $F(1, 57) = 5.84, p<.01$, that was qualified by a significant interaction with Age Group, $F(1, 57) = 10.95, p<.01$. Volume of the hippocampal body was marginally larger in the 6-year-old children in the left hemisphere, $F(1,57) = 3.27, p=.08$, whereas there was no difference in volume between the groups in the right hemisphere, $p=.25$. Finally, for the tail, there was a main effect of Hemisphere, $F(1, 57) = 6.66, p=.01$, with volumes in the right hemisphere greater than those in the left and a marginal effect of Age Group, $F(1, 57) = 3.43, p=.07$, with volumes in 6 year olds marginally larger than those in 4 year olds.

Figure 2. Adjusted hippocampal volumes in left and right hemispheres for 4- and 6-year-old children. * indicates significantly larger volumes in right compared to left hemispheres, $p<.05$. † indicates marginally larger volumes in 6- compared to 4-year-old children, $p\leq.08$.



Relations between episodic memory performance and adjusted hippocampal volumes were examined separately for 4- and 6-year-old children. Results revealed significant positive relations between episodic memory and hippocampal head in both the left $r(22) = .50, p < .05$, and right, $r(22) = .49, p < .05$, hemispheres for 6-year-old children (Figure 3). These relations were not observed in 4-year-old children (for left, $r(22) = -.09, p = .69$, or right head, $r(22) = -.11, p = .62$) nor with the other subregions in either age group, $ps = .12-.72$. Comparison of correlation values between Age Groups (Fisher's r -to- z) revealed significantly larger correlation values in 6- compared to 4-year-old children in the head in right and left hemispheres, $zs = 1.97$, and 1.99 respectively, $ps < .05$. The pattern of significant relations was identical when the alternative boundary of the disappearance of the digitations was used for the head (see supplementary materials for details).

Figure 3. Associations between episodic memory and volume of the hippocampal head in left and right hemispheres for 4- and 6-year-old children. Only relations for 6-year-old children were significant. Correlation values were significantly greater in 6- versus 4-year-old children, $ps < .05$.



Discussion

The goal of the present study was to examine how age-related differences in episodic memory during early childhood are related to volumetric differences in the hippocampus. Results revealed differential relations between 4- and 6-year-old children's hippocampal subregion volumes and their ability to recall contextual details (i.e., location and action) associated with an event. Specifically, significant positive associations were observed between volume of the head of the hippocampus bilaterally and episodic memory in 6- but not 4-year-old children. Moreover, the association between memory and hippocampal head volume was significantly greater in 6- compared to 4-year-old children, suggesting brain-behavior relations between episodic memory and hippocampal subregions may emerge across development as the hippocampus matures and memory improves. These behavioral findings are consistent with previous research showing episodic memory increases during early childhood (e.g., Bauer et al., 2012; Drumme & Newcombe, 2002; Riggins, 2014; Sluzenski et al., 2004). However, they also add new information regarding neural underpinnings of memory during early childhood by

demonstrating differential relations between hippocampal subregion volumes and episodic memory performance during early childhood.

Data supporting the association between developmental improvements in episodic memory and hippocampal development are important for several reasons. First, behavioral research suggests that early childhood is a time of rapid change in episodic memory (e.g., Sluzenski et al., 2004). Collectively, these studies show that 4-year-old children have difficulty recalling contextual details associated with previously experienced stimuli, despite the fact that they are able to reliably distinguish them from new stimuli. However, after 6 years of age, children are significantly more accurate in recalling contextual details across a variety of tasks. Our findings provide some of the first empirical evidence that the emergence of this ability to recall contextual details may arise from changes in the neural structures supporting memory in early childhood.

Thus, a subsequent question of interest becomes: what exactly is changing that results in these developmental differences? The current study found a relation between hippocampal head size and memory performance in 6-year-old, but not 4-year-old children, despite the fact that there was no increase in the relative size of the hippocampal head between 4 and 6 years. Therefore, general increases in size of the hippocampal head are not likely driving the developmental differences seen at the behavioral level. Rather, it is likely that the function or role of this region of the hippocampus in episodic memory changes with development. In addition, in the present report, there were marginal increases in volume between 4 and 6 years in posterior regions (i.e., left body, and tail bilaterally), which cannot be attributed to overall increases in brain size between 4 and 6 years given that variation in ICV was taken into account. It is also possible that changes in a single region cannot account for the complicated effects

observed at the behavioral level, but rather these changes result from the interaction between multiple subregions. Although brain-behavior correlations were observed bilaterally in 6 year olds, there were volumetric differences between the left and right hemispheres across subjects with greater volumes present in the right hemisphere for the head and tail subregions, and greater volume in the left hemisphere for the body. It is also possible that these hemispheric differences contribute to developmental differences in behavior. Hemispheric differences have been reported in some, but not all, previous studies. Unfortunately the consistency of these effects is unclear given the age groups sampled and methods used to evaluate these differences (cf. Daugherty, Yu, Flinn, & Ofen, 2015; DeMaster et al., 2014; Gogtay et al., 2006). Thus, examination of the interaction between hippocampal subregions across left and right hemispheres represents an exciting avenue for future research.

Relations between volume of the hippocampal head and memory performance in 6-year-old children reported here differ from previously reported relations between episodic memory and volume of the left hippocampal *tail* in 8- to 11-year-old children (DeMaster et al., 2014) and previous research in adults that suggests that memory for location is associated more with posterior hippocampus (e.g., Maguire et al., 2000; Ryan et al., 2010). One possibility is that these differences are due to the fact that these age groups sample different points on the developmental trajectory. The difference may also arise because the source memory task used in this study differed significantly from tasks used in adults and school-aged children (e.g., spatial navigation tasks in Maguire et al., 2000; or spatial relations between objects/object arrays on a computer screen (e.g., DeMaster et al., 2014; Ryan et al., 2010). This question awaits further testing.

The reason for the lack of a relation in 4-year-old children is unclear. Given that 4-year-old children were able to recall contextual details on some trials (i.e., the decrement in performance was not absolute) this lack of relation may reflect weak or unreliable reliance on similar circuitry or perhaps recruitment of alternative structure(s)/circuitry (e.g., parahippocampal or perirhinal cortices), which are supporting their completion of the task. Research in adults with damage to the hippocampus (Diana et al., 2010) and elderly patients with dementia (Bastin et al., 2013) suggest that cortices surrounding the hippocampus (e.g., perirhinal cortex), can support memory for contextual details under circumstances in which the details are unitized with the item (i.e., become ‘features’ of the item; see Diana et al., 2010 for elaboration). Another important avenue for future research will be to examine other routes through which episodic-like details can be recalled, and importantly, their developmental trajectories.

There are several limitations of the current work. First, functionality of the hippocampus was not assessed, rather volume served as a proxy measure of function. Thus, discussion regarding what the volume differences mean in terms of function remain speculative, although they are consistent with recent fMRI studies in school-age children that suggest functional reorganization within the medial temporal lobe during development (DeMaster, Pathman, & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010). Second, in the present study we did not have sufficient power or strong a priori justification to examine differences in relations between episodic memory and hippocampal volume as a function of sex, despite previous suggestions that differences may arise as a function of this variable (e.g., Gogtay et al., 2006). Finally, although the hippocampus is critical for episodic memory, studies in school-age children (Ghetti & Bunge, 2012) and adults (Spaniol et al., 2009) reveal the involvement of multiple cortical regions (e.g., prefrontal and posterior parietal cortex). Knowledge regarding how these

cortical regions become integrated with the hippocampus during early childhood is needed to fully characterize our understanding of how memory changes over the first few years of life. Despite these limitations, the present study provides an initial step toward describing neural changes that may account for the dramatic improvements observed in behavioral studies of episodic memory in early childhood. These results contribute to a growing literature suggesting age-related changes in the hippocampus contribute to age-related changes in episodic memory including the period of early childhood.

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