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The Neural Basis of Episodic Memory in Children: an fMRI Region of Interest Analysis of Hippocampal Activation

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Abstract

It is unclear to what extent the successful formation of episodic memories in children is dependent on the integrity of the structures of the medial temporal lobe (MTL), including the hippocampus. In this study, functional magnetic resonance imaging (fMRI) data and behavioral data were examined to determine if hippocampal activation during episodic encoding predicted subsequent performance on recognition memory tests. Hippocampal activation was not correlated with recognition memory performance even when controlling for age and general cognitive ability. Younger children (ages 7-9, $N = 31$) and adolescents (ages 16-18, $N = 26$) did not differ significantly in their recognition memory accuracy on the memory tests or in the percent change in activation of the hippocampus. Consistent with the findings in adults, these data suggest that in children the hippocampus proper may play a less important role in item-specific encoding than in relational encoding.

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Introduction

Episodic memory, a type of long-term declarative memory, refers to the conscious recollection of past events coupled with a subjective experience of remembering (Tulving, 2002). Not only does episodic memory help define our sense of personal past, it is also a key mechanism that facilitates children's new learning in school, and it is a type of memory that is often compromised as a result of brain injury or disease.

Although research has greatly informed our understanding of how episodic memory functions in adults, a clear developmental perspective is lacking. This project attempts to advance our understanding of episodic memory development by elucidating the role of the hippocampus in episodic encoding in children. In this introduction, I will first review the current model of episodic memory in adults and describe how evidence from neuroimaging research fits into this framework. Then, I will review the existing behavioral, clinical, and neuroimaging data on the role of the hippocampus in episodic encoding in children.

The successful establishment of episodic memories in long-term memory, termed episodic memory encoding, appears to rely on a complex and interconnected network in the brain. Neuroimaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have examined the neural correlates of episodic encoding and implicated a network involving the prefrontal cortex (PFC) and the medial temporal lobe (MTL), a region that includes the hippocampus and its surrounding cortices (for PFC see Buckner, Kelley, & Petersen, 1999; Cabeza & Nyberg, 2000; Fletcher, Stephenson, Carpenter, Donovan, & Bullmore, 2003; Gabrieli, Poldrack, & Desmond, 1998; Habib, Nyberg, & Tulving, 2003; Kensinger, Clarke, & Corkin, 2003; Nyberg et al., 2003); for MTL see Cabeza & Nyberg, 2000; Fletcher et al., 2003; Kensinger et al., 2003; Lepage, Habib, & Tulving, 1998; Schacter &

Wagner, 1999). One proposed mechanism of action for this PFC-MTL network is that the PFC inputs vital information about an event to the MTL, where these inputs are integrated in a binding process to form episodic memories (Buckner, Logan, Donaldson, & Wheeler, 2000; Kirchhoff, Wagner, Maril, & Stern, 2000; Wagner & Davachi, 2001). In addition, several studies have also implicated parietal regions, specifically the left parietal lobe and precuneus, in episodic memory encoding (Davachi, Maril, & Wagner, 2001; Gaillard et al., 2003; Henson, Shallice, & Dolan, 1999; Saykin et al., 1999) and retrieval (Fletcher et al., 1995; Krause et al., 1999). Activations in these areas may reflect the attentional demands of visuospatial and phonological processing or perhaps the retrieval of contextual/source information (Henson et al., 1999).

Converging evidence suggests that episodic memory is dependent on the integrity of the medial temporal lobe. Lesion studies in animals, including primates, demonstrate that damage to the hippocampus results in memory deficits (Zola-Morgan, Squire, & Ramus, 1994). Neuropsychological data from humans with MTL damage also implicates the hippocampus in episodic memory functioning. The case of the well-known amnesic patient H.M. exemplifies the importance of the medial temporal lobe. At the age of 30, this man underwent bilateral removal of the medial temporal lobe for epilepsy relief (Scoville & Milner, 1957). As a result of the surgery, he exhibited a profound impairment in the ability to encode new information (Scoville & Milner, 1957). More recent data suggest that bilateral lesions limited to the hippocampus are sufficient to produce anterograde and temporally limited retrograde amnesia, although the accompanying memory deficits are less severe than those seen in H.M. (Rempel-Clower, Zola, Squire, & Amaral, 1996). This suggests that other MTL structures may also play a role in memory functioning.

Despite the clear neuropsychological evidence of the involvement of the MTL in episodic memory, many neuroimaging studies of episodic encoding have failed to demonstrate reliable MTL activation. Several explanations have arisen to account for this unexpected absence of MTL involvement. It has been suggested that the hippocampus and parahippocampal gyrus are continually active, even during periods of rest, and so do not provide an optimal baseline condition for the comparisons inherent in fMRI methodology (Stark & Squire, 2001). In fMRI paradigms, the level of brain activation during a task condition is measured by comparing it to the level of brain activation during a rest condition when the relevant brain areas are supposedly inactive. Because these MTL regions can be active during rest conditions, the activity during task conditions may be reduced, eliminated, or sign-reversed when compared to this "baseline" level of activation (Stark & Squire, 2001). Others hypothesize that fMRI and PET techniques simply lack the sensitivity to detect the small changes in blood flow in the MTL region due to a low signal-to-noise ratio that results from high susceptibility of imaging artifacts and signal drop-out in this region (Strange, Otten, Josephs, Rugg, & Dolan, 2002). Alternately, the consolidation processes of the MTL may not be as amenable to imaging as other cognitive processes (Schacter & Wagner, 1999).

In spite of these past null results, several neuroimaging studies have indeed demonstrated MTL activation in response to episodic encoding tasks (for review see Schacter & Wagner, 1999). The use of event-related fMRI paradigms, improved image resolution, and the examination of subsequent memory (SM) effects have all greatly advanced the investigation of MTL activation. SM effects are used to determine the neural correlates of successful memory encoding. Neural activity is recorded while a participant studies a sequence of items, after which recall or recognition memory for the items is tested. The neural responses in different areas of

the brain (i.e. MR signal strength in fMRI studies) elicited during study items are then contrasted based on whether the items were forgotten or remembered during the subsequent memory test. In this way, researchers can draw conclusions about which regions of the brain support successful memory encoding. In fMRI studies of episodic memory encoding, there is considerable disagreement among SM effect findings. Although the exact brain regions demonstrating SM effects differ depending on methodology and type of encoded materials, the most consistent findings across studies have implicated the left prefrontal cortex and MTL in episodic encoding (Casasanto et al., 2002; Fernandez, Brewer, Zhao, Glover, & Gabrieli, 1999; Fernandez et al., 1998; Otten & Rugg, 2001; Wagner et al., 1998). With both positive and null findings now available, researchers have begun to critically examine the nature of MTL involvement in episodic memory. The accumulation of data suggests that the answer to this puzzle lies within the anatomy of the MTL: different subcomponents of the MTL (the hippocampus and surrounding entorhinal, perirhinal, and parahippocampal cortices) may be related to different memory processes.

Using an event-related fMRI study with adults, Davachi and Wagner demonstrated that bilateral hippocampal activation was greater in a relational processing task than in a rote rehearsal task (2002). The relational processing task fostered associative learning by asking participants to order a triplet of words according to level of desirability, while the rote rehearsal task only required maintaining phonological representations of word triplets (Davachi & Wagner, 2002). A subsequent memory effect was also observed: the level of bilateral hippocampal activation in the relational processing condition, but not the rote rehearsal condition, predicted memory performance (Davachi & Wagner, 2002). In contrast, the rote rehearsal condition was associated with greater activation in the entorhinal cortex and posterior

parahippocampal gyrus, further differentiating the MTL structures (Davachi & Wagner, 2002). These results support the theory that the main function of the hippocampus is to bind together multiple features or components of an experience during relational or configural processing (Cohen, Poldrack, & Eichenbaum, 1997; Eichenbaum, 2000; Mishkin, Vargha-Khadem, & Gadian, 1998).

Previous research has shown that children generally show poorer memory for recently learned events than young adults, suggesting that some processes of memory encoding or retrieval may have a developmental time course lasting well into early adulthood (Cycowicz, Friedman, Snodgrass, & Duff, 2001; Nelson, 1997; Schneider & Pressley, 1997). However, it is unclear whether age-related differences in memory accuracy are due to structural/organizational changes in the central nervous system, the development of cognitive strategies and attentional processes, or both. To address this question, studies examining the neuroanatomy of the medial temporal lobe as well as behavioral memory performance in children over a reasonably long developmental time course are needed but lacking to date.

Research suggests that the same neural networks support episodic memory in both children and adults, although the developmental trajectory of this MTL – PFC network remains unclear. On behavioral measures, age-related increases in memory have been observed for many aspects of memory (Arterberry, Milburn, Loza, & Willert, 2001). These improvements can even be seen during the relatively restricted time period between early school age and late adolescence (Cycowicz et al., 2001; Schneider & Pressley, 1997). In general, age-related memory improvements are thought to result from developmental changes in the PFC rather than the MTL structures. Quantitative structural MRI data suggest that changes in the absolute or relative size of the MTL are modest after 2 years of age, a pattern different from that of prefrontal cortex

(Giedd et al., 1999; Giedd et al., 1996). The frontal lobes and the neural pathways between the frontal and temporal lobes continue to develop into adulthood (Gogtay et al., 2004; Menon, Boyett-Anderson, & Reiss, 2005; Paus et al., 1999). While the prefrontal cortex appears to have an extended developmental time course, the MTL may play a vital role in episodic memory from early childhood.

In a pattern of memory impairment termed developmental amnesia (DA), children with bilateral hippocampal pathology demonstrate severe impairments in episodic memory but relatively preserved semantic memory (Gadian et al., 2000; Vargha-Khadem et al., 1997; Vargha-Khadem et al., 2003). DA often results from hypoxic-ischemic events sustained early in life. Vargha-Khadem and colleagues examined three young adults who incurred extensive hippocampal damage (43-61% reduction of the hippocampal volume bilaterally) before the age of nine (Vargha-Khadem et al., 1997). These children demonstrated normal reading and spelling abilities, and normal verbal IQ (Vargha-Khadem et al., 1997). However, all three individuals demonstrated severe episodic memory impairments: none could remember daily events of their lives, and all demonstrated impaired spatial orientation and temporal orientation (Vargha-Khadem et al., 1997). Although their immediate memory was within normal limits, these patients performed in the extremely low range on delayed recall tests of word lists, stories, item pairs, and designs (Vargha-Khadem et al., 1997). The literature has shown that although children with DA have impaired recall abilities, their recognition memory is relatively spared (Baddeley, Vargha-Khadem, & Mishkin, 2001; Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001). This is further evidence for the dissociation between different forms of memory in this syndrome, although it is still unknown if the sparing of semantic memory and recognition abilities is related

to the integrity of the hippocampus or its surrounding cortices (Vargha-Khadem, Gadian, & Mishkin, 2001).

The pattern of episodic memory impairment in DA is the result of bilateral hippocampal damage sustained early in life. Vargha-Khadem and colleagues compared children who sustained hypoxic-ischemic events perinatally or within the first 3 months of life to children who sustained this type of injury between 6 and 14 years of age (Vargha-Khadem et al., 2003). Both groups of children had approximately a 40% bilateral reduction in hippocampal volume, and both groups demonstrated the typical DA cognitive profile of largely intact intelligence and academic achievement, intact semantic memory, but severely impaired episodic memory (Vargha-Khadem et al., 2003). The two groups did not differ significantly in these abilities, suggesting that the effective age of onset of DA extends from birth to adolescence (Vargha-Khadem et al., 2003). Another follow-up examination compared children with DA to children born pre-term, and determined that early hippocampal pathology in children can lead to the unique memory impairments observed in DA when the volume of the hippocampus has been reduced by 25-30% on each side (Isaacs et al., 2003). In many cases of DA, the degree of hypoxia-ischemia that the child experienced was sufficient to produce selective damage bilaterally to the hippocampus, but was not enough to result in more severe or global brain damage, and thus more severe cognitive deficits (Gadian et al., 2000).

Episodic memory impairments are also commonly observed in patients with epilepsy. Temporal lobe epilepsy is the most common type of seizure disorder, and medial temporal sclerosis, especially of the hippocampus, is a pathological marker of temporal lobe epilepsy (TLE) (Bortz, 2003). Evidence from patients with unilateral MTL lesions suggests that adults with hippocampal damage demonstrate a material specific lateralization of memory deficits:

verbal memory deficits are often associated with temporal lobe dysfunction of the left hemisphere (Milner, 1968; Powell et al., 2004; Smith, 1989). Memory impairment is a hallmark feature of MTL epilepsy, and the lateralization of the seizure focus and lesion is the strongest determinant of memory functioning in these patients (Hermann, Seidenberg, Schoenfeld, & Davies, 1997). In left temporal lobe epilepsy, learning, recall memory, and recognition memory are impaired for verbal materials such as stories, word lists, and word pairs (Dupont et al., 2000; Helmstaedter, Grunwald, Lehnertz, Gleibner, & Elger, 1997; Martin et al., 2002; Morris, Abrahams, Baddeley, & Polkey, 1995). In right TLE, memory impairments have been observed in the ability to learn, recall, and recognize nonverbal materials as measured on visuospatial memory tasks involving faces, locations, and designs (Helmstaedter, Pohl, Hufnagel, & Elger, 1991; Morris et al., 1995; Nunn, Polkey, & Morris, 1998). However, the evidence for a right temporal lobe lateralization of visuospatial memory deficits is equivocal (Bortz, 2003; Dupont et al., 2002; Hermann, Seidenberg, Schoenfeld, & Davies, 1997). Although recent imaging data suggests that most temporal lobe epilepsy patients have some degree of bilateral hippocampal involvement and thus may also have some bilateral memory consequences (Dupont et al., 2002; Reminger et al., 2004), the material-specific lateralization of verbal memory deficits in adults with left TLE remains a common and replicated finding.

However, the effects of hippocampal pathology on episodic memory functioning are less clear in the pediatric epilepsy literature. Children with temporal lobe epilepsy do not demonstrate the same material-specific lateralization as adults. Mabbott and Smith compared the memory performance of children who underwent either left or right unilateral temporal lobe excisions for seizure relief, but failed to observe material-specific memory effects on measures of story recall, verbal list learning, or design recall either before or after surgery (Mabbott & Smith, 2003). The

only memory measure on which the groups differed was face recognition, with children with right temporal lobe lesions demonstrating poorer performance (Mabbott & Smith, 2003). Indeed, the few material-specific lateralization effects that have been observed in this patient group are visual memory deficits resulting from right temporal lobe pathology. Hepworth and Smith compared children and adolescent seizure patients who underwent unilateral temporal lobectomies to controls, and found that participants with left-temporal lobe lesions were not significantly impaired on a verbal memory test of story recall (Hepworth & Smith, 2002). In contrast, the children with right temporal lobe lesions performed significantly worse than controls on a nonverbal memory test of picture location recall and required more learning trails to reach criterion than controls (Hepworth & Smith, 2002). Jambaque and colleagues studied non-surgical pediatric epilepsy patients using an extensive memory battery, and observed that left temporal patients demonstrated lower memory performance on verbal tasks while right temporal patients had lower performance on visual memory tasks (Jambaque, Dellatolas, Dulac, Ponsot, & Signoret, 1993). However, the relationship between visual memory deficits and right temporal lobe epilepsy was found to be stronger than the parallel association between verbal memory deficits and left TLE (Jambaque et al., 1993). This is the opposite of what is commonly reported in the adult literature, namely that laterality differences are most consistently observed on verbal memory tasks after left temporal lobe epilepsy.

Both across and within studies, children with epilepsy show a highly variable pattern of memory impairment. It appears that pediatric temporal lobe epilepsy patients have intact implicit memory and do not differ from control children in their conceptual or perceptual priming performance (Billingsley, McAndrews, & Smith, 2002). The data suggest that children with temporal lobe epilepsy have intact short-term memory but impaired long-term episodic memory.

Hershey and her colleagues found that both left and right TLE children were impaired on the long delay condition of a medial temporal-related memory task, but were not impaired on the short delay condition (Hershey, Craft, Glauser, & Hale, 1998). Williams and colleagues administered a list-learning task of verbal memory to a group of pediatric epilepsy patients (Williams et al., 2001). They found that the children had intact new learning abilities and intact short-term recall, but their long-term recall was impaired (Williams et al., 2001). In a review of post-operative memory outcomes in children who underwent surgery to treat epilepsy, more studies reported finding no evidence of postoperative memory decline than the number of studies that reported a decrease in memory functioning (Lah, 2004). Thus far, there is little support for the idea of negative effects of MTL pathology on memory functioning in children with epilepsy. A study of adults with early- or late-onset temporal lobe epilepsy found that those with early-onset epilepsy demonstrated widespread cognitive impairments (including both verbal and visual memory) and a reduction of white-matter tissue volume compared to both late-onset patients and controls (Hermann et al., 2002). These results suggest that childhood-onset temporal lobe epilepsy may be associated with a generalized effect on cognitive functioning and brain structure, although this pattern has not been observed directly in pediatric temporal lobe epilepsy patients.

It is unclear to what extent, and for what types of episodic encoding tasks, the MTL is activated in children. It is also unknown whether the same functional differentiation among regions of the MTL that has been suggested for adults also exists in children. Neuroimaging studies have yet to examine children's episodic memory in depth. Previous studies have instead focused on short-term memory and have used non-verbal materials (Casey et al., 1995; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000;

Thomas et al., 1999). A new avenue of research that may help elucidate the role of the MTL in children's episodic memory is associative memory. Many researchers have suggested that the role of the MTL is to construct novel associations, and Davachi and Wagner (2002) have further demonstrated that the main function of the hippocampus is relational or configural processing. Comparing children's activation patterns and memory performance on tests of verbal memory that elicit either associative encoding (encoding items by establishing associations among the items) or item-specific encoding would provide valuable insight into the functional differentiation and developmental role of the MTL.

In order to gain a better understanding of the role of the MTL in episodic encoding in a developmental context, I examined a large database of functional MRI data and behavioral data from children and adolescents to determine if hippocampal activation during episodic encoding task was related to subsequent performance on memory tests. Previous studies have examined the relationship between hippocampal volume and cognitive performance using volumetric analysis (Jackson, Connelly, Duncan, Grunewald, & Gadian, 1993; Obenaus, Yong-Hing, Tong, & Sarty, 2001; Van Paesschen, Revesz, Duncan, King, & Connelly, 1997; Vargha-Khadem et al., 1997). Fernandez and colleagues have successfully used fMRI to examine the relationship between mean activation in structures of the MTL (the entorhinal cortex and hippocampus) and the number of correct items on a cued-recall test (Fernandez et al., 1999; Fernandez et al., 1998). In the present study, I examined the relationship between activation in the defined regions of the left and right hippocampus during an episodic encoding task and subjects' subsequent performance on a corresponding recognition memory test. There were three alternative hypotheses.

1) The relationship between hippocampal activation and memory performance would be stronger for older children (ages 16 to 18) than for younger children (ages 7 to 9) due to the increased maturity and efficiency of the neural network supporting memory in the older children. Because the PFC is more developed in the older children, the MTL and PFC work in concert to integrate and then bind memories in the MTL, resulting in better memory performance.
2) The relationship between hippocampal activation and memory performance would be stronger for younger children (ages 7 to 9) than for older children (ages 16 to 18). Because of the relative immaturity of the PFC in younger children, the MTL is likely the only system supporting episodic memory, and so memory performance will rely directly on activation of the MTL structures.
3) The amount of hippocampal activation during the episodic encoding task would not be related to age or memory performance.

Examining this large sample of children and adolescents will greatly inform the debate on whether the brain-behavior relationship is the same across all subregions of the MTL in children, and will increase our understanding of the developmental course of episodic memory.

Method

Participants

Participants in this study were healthy children who had previously contributed data to a study on normal language and memory development (Chiu et al., 2006; Holland et al., 2001). Access to the data is granted by IRB protocol #CHMC 98-3-27. All participants provided assent, and a parent or legal guardian provided written informed consent at the time of participation. To be eligible for the present study, a participant must have successfully completed a structural MRI scan, and both a functional MRI scan and a recognition memory test for both the verb generation and story comprehension task in the previous episodic memory encoding study. Thirty-one 7 to 9 year olds and twenty-six 16 to 18 years olds from this pool of subjects met these criteria. There were 35 females and 22 males. Ninety-three percent of the participants were Caucasian; there were two African American children, one Hispanic child, and one Multi-Ethnic child.

Materials and Procedure

Two tasks from the database were used in the present study: a verb generation task and a story comprehension task. These tasks are incidental memory tasks. In contrast to intentional memory tasks, incidental memory tasks do not require the participant to focus his or her attention on remembering or memorizing the materials. Instead, the materials are encoded as a consequence of the task activities themselves, rather than effort on the part of the participant. The children performed the tasks while in the scanner, thus generating structural and functional MR data. In the verb generation task, children were auditorily presented with nouns and were asked to generate verbs associated with each noun. In the story comprehension task, the children listened to short stories so that they could answer questions about them later. After scanning was

completed, the children were removed from the scanner and given two recognition memory tests, one for each memory task. For the verb generation task, 19 nouns previously presented in the task were paired with 19 foils, and subjects were asked to choose which noun of the pair they had heard previously. For the story task, children were presented with various sentences either identical to or similar to the sentences they heard in the scanner, and were asked to determine whether or not they had heard each sentence during the task.

The brain imaging scans were performed using a Bruker Biospec 30/60 MRI scanner based on a 60 cm, 3.0 Tesla magnet. The structural scan of interest is a T1-weighted, 3D Modified Driven Equilibrium Fourier Transform (MDEFT) whole brain scan. This is an anatomical scan performed while the subject is relaxing in the scanner. Data were collected over the entire brain and partitioned into 4mm X 4mm X 5mm voxels of grey and white matter. A T2-weighted, gradient-echo, EPI sequence was used for the functional MRI scans (TR/TE = 3000/38ms, FOV = 25.6 x 25.6 cm, matrix = 64 x 64, slice thickness = 5mm). For both verb generation and story processing, twenty-four slices were acquired at 110 time points during the alternating 30-s periods of experimental and control task for a total imaging time of 330s. The initial 10 time points were discarded to allow for T1 relaxation effects.

FMRI image post-processing was completed using Cincinnati Children's Hospital Image Processing Software (CCHIPS), an in-house software program written in IDL (Research Systems Inc., Boulder, CO). The EPI images were corrected for geometrical distortion and Nyquist ghost artifacts using the multi-echo reference method (Schmithorst, Dardzinski, & Holland, 2001). A Hamming filter was applied to the raw EPI data prior to reconstruction in order to reduce the truncation artifacts at the edges of k-space and reduce high frequency noise in the images (Lowe & Sorenson, 1997). The data were co-registered to further reduce the effects of motion artifacts

(Thevenaz & Unser, 1998). Baseline drift was corrected for using a quadratic baseline correction on a pixel-by-pixel basis (Hu, Le, Parrish, & Erhard, 1995; Le & Hu, 1996).

Data Analysis

All data have been previously collected. After participants were selected based on the previously mentioned criteria, memory recognition test scores, structural MRI images, and functional MRI images were collected from the database. For all subjects, performance on each of the two memory tests was converted to a recognition memory accuracy score, *A prime*, which is a non-parametric measure of discriminability (Snodgrass & Corwin, 1998) calculated with the following formula: A' = 0.5 + 0.25*(H-FA)(1+H-FA) / (H)(1-FA) with H = proportion of "yes" response to studied items and FA = proportion of "yes" response to non-studied items.

In order to quantify hippocampal activation, a region of interest (ROI) was created around the hippocampus of each subject. Using Cincinnati Children's Hospital Image Processing Software (CCHIPS), a single rater carefully examined consecutive images of the MDEFT anatomical MR scan of each individual subject and manually traced out the left and right hippocampus in each image based on known anatomical markers (Bartzokis, 1998). The rater was trained by comparing ROI measurements from at least 10 non-study subjects with an experienced rater, in which the 2 rater's measurements were obtained blind to each other. High interrater reliability (intraclass correlation coefficient > .90 for all measurements) was obtained in this manner (intraclass correlation coefficients: left hippocampus = 0.97203; right hippocampus = 0.89772).

For each subject, the ROI that was created was overlaid on the fMRI data to isolate the activation that occurred in the defined hippocampal area during the memory task that the subject

was performing at the time when the fMRI data was collected. Finally, percent change in activation in the ROI over the course of the memory task was calculated for both left and right hippocampus for each subject.

Results

Fifty-seven participants were included in this sample. There were 31 children in the 7 to 9-year old group and 26 children in the 16 to 18-year old group. All analyses were conducted with $\alpha = .05$.

MRI data and memory performance data were collected for two cognitive tasks: verb generation (*verb task*) and story comprehension (*sentence task*). Because the verb task is more semantic in nature than the sentence task, the verb task and its corresponding recognition memory task provide a better measure of episodic memory. The verb task is also procedurally similar to the types of single-word stimuli memory paradigms commonly used to assess episodic memory. Consequently, the verb task is the memory task of interest in this analysis. Behavioral data for the sentence task data will be used as a control for general memory ability, and data from both tasks will be reported for completeness.

Figure 1 presents the anatomical regions significantly activated across all participants during the verb generation task as compared to a control task of bilateral finger tapping. Robust activation was observed in a number of regions, and these are presented in Table 1. Significant activation was observed in the left hippocampus across the entire sample of children. When the children were divided into the two age groups, activation in the left hippocampus was significant only for the 7 to 9-year old group. However, at a more lenient criterion level ($Z = 1.0$), activation in the left hippocampus became significant in the group of older children. Figure 2 presents the regions of significant activation for the younger and older children. This suggests that the hippocampus is indeed differentially activated by the verb generation task in the older children, although perhaps not to the same extent as in the younger children. A direct comparison of regions of significant activation in the two groups during the verb generation task found that in

general, younger children had significantly greater activation in the occipital regions (Brodmann's Area 18), left inferior temporal gyrus (BA 37), postcentral cortex (BA 2/3), and bilateral superior frontal gyrus (BA 9/10), while older children had significantly greater activation in bilateral inferior frontal gyrus (BA 44/45), left inferior parietal lobe (BA 40), and left cingulate gyrus (BA 32) (Figure 3). Interestingly, the level of left hippocampal activation during the verb generation task was not significantly different in the younger children compared to the other children. Overall, these imaging data suggest that the left hippocampus is activated during the verb generation task across all children in this sample as a group, although the level of activation only reached significance in the group of younger children. Subsequent analyses will examine these patterns of activation in more depth by investigating the relationship between hippocampal activation and memory performance in these two age groups.

Means and standard deviations of the dependent variables are presented for the two age groups in Table 2. An ANOVA was conducted to determine if the age groups differed in memory performance, hippocampal activation, or general cognitive abilities. These results are presented in Table 3. The young children and adolescents did not differ significantly on any of the variables except for Performance IQ on the Weschler Intelligence Scale for Children (WISC) – Third Edition, on which the younger children had a higher average PIQ, $F(1,55) = 4.205$, $p = .045$.

Table 1

Anatomical regions significantly activated during verb generation across the entire sample of subjects. The Talairach coordinates within representative regions are reported.

Anatomical Region	Brodmann's Area	Talairach Coordinates (X, Y, Z)
L. hippocampus		-30, -29, -15
L. parahippocampal gyrus	35/36	-38, -37, -10
L. inferior frontal gyrus	47	-38, 35, -5
L. inferior temporal gyrus		-50, -49, -5
L. inferior frontal gyrus	47	-34, 23, 0
R. inferior frontal gyrus	47	34, 19, 0
L. middle temporal gyrus	21	-58, -41, 0
L. inferior frontal gyrus	45	-38, 27, 5
R. superior temporal gyrus	22	54, -21, 5
L. superior temporal gyrus	22	-54, -37, 10
L. caudate nucleus		-14, 7, 10
L. inferior frontal gyrus	45	-46, 23, 15
L. inferior occipital gyrus	18	-34, -89, 15
R. inferior occipital gyrus	18	22, -77, 15
L. cuneus	19	-26, -85, 30
R. cuneus	19	18, -81, 30
L. inferior frontal gyrus	44	-46, 11, 25
Cingulate gyrus	32	-6, 31, 25
L. middle frontal gyrus	6	-42, -5, 40
Medial frontal gyrus	8	-6, 19, 45
L. precuneus	7	-26, -69, 45
L. middle frontal gyrus	6	-42, -1, 50
Medial frontal gyrus	6	-6, 11, 55

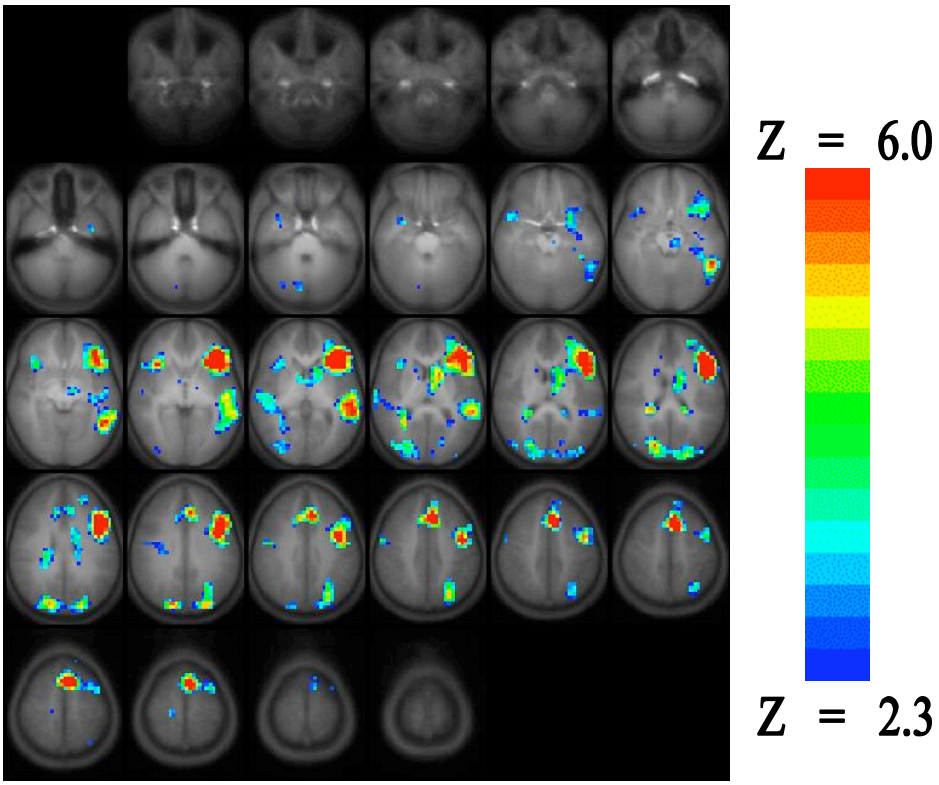

Figure 1. Composite statistical parametric map of verb generation relative to finger tapping for the entire sample of subjects. In this and all following figures, images are horizontal sections 5mm apart from z = -60 (top left) to z = +70 (bottom right). Images are in radiological convention.

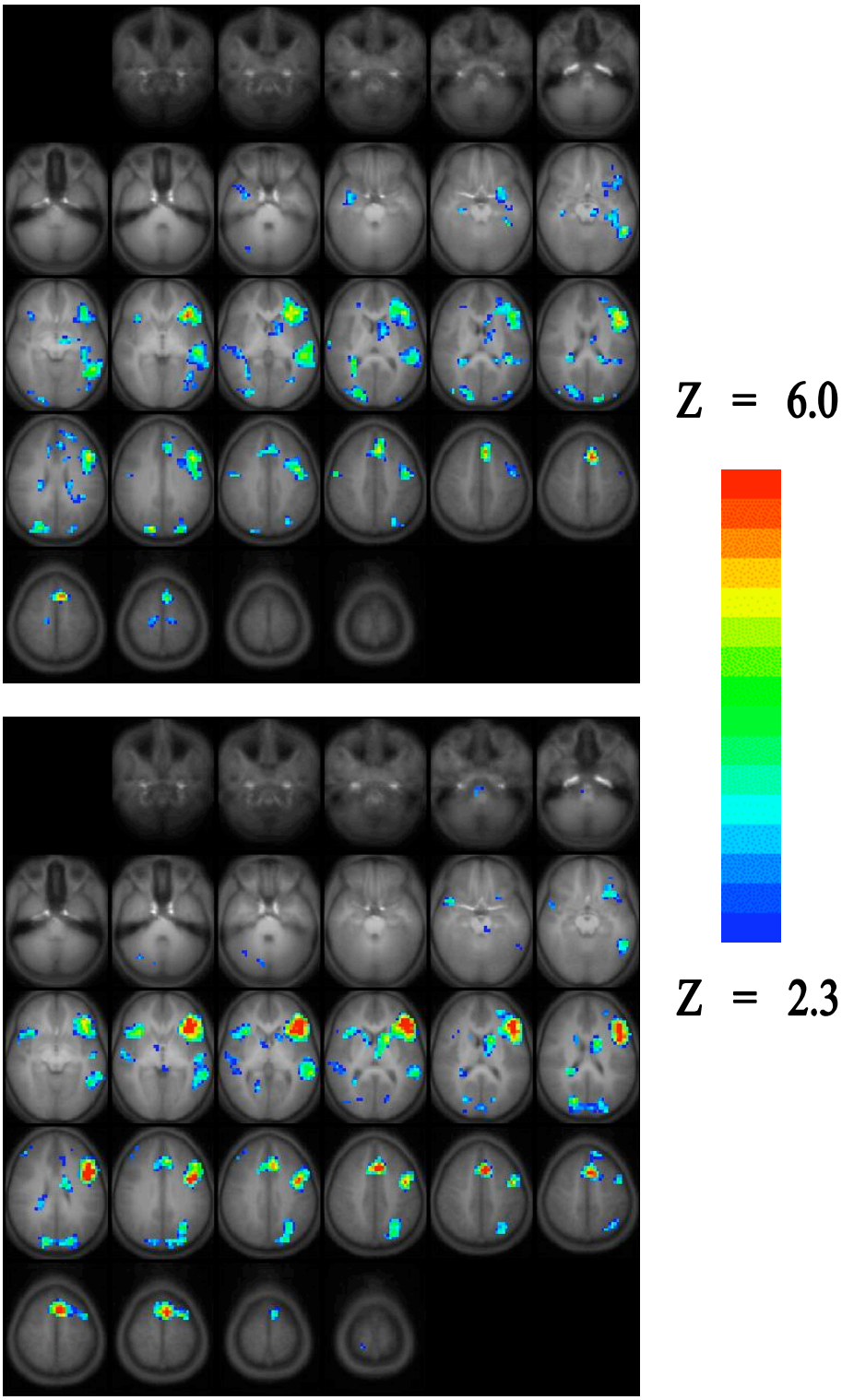

Figure 2. Composite statistical parametric map of verb generation relative to finger tapping for younger children (ages 7-9; top) and older children (ages 16-18; bottom).

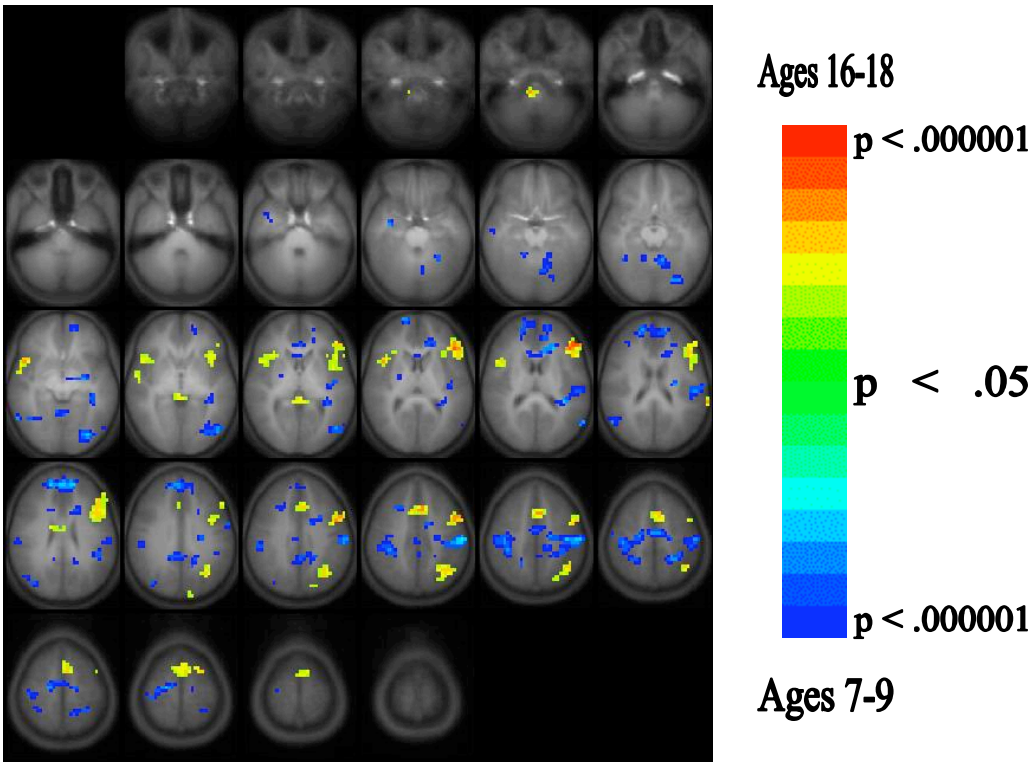

Figure 3. Composite map comparing regions of the brain that were found to be significantly activated during verb generation in the two age groups. Brain regions with significantly greater activation in the group of younger children as compared to the older children are shown in blue. Brain regions that were significantly more active during verb generation in the group of older children are shown in red/yellow.

Table 2

Group Means

		Age Group	
		Age 7-9	**Age 16-18**
		N = 31	N = 26
A' Verb Task			
	M	0.8322	0.8632
	SD	0.1243	0.1105
	Range	.5263, 1.0	.6309, 1.0
% Change Left H Verb			
	M	0.0558	0.0288
	SD	0.2394	0.3355
	Range	-0.6136, 0.6560	-0.6144, 1.1489
% Change Right H Verb			
	M	0.0751	-0.0549
	SD	0.2794	0.2352
	Range	-.5900, .9298	-.7792, .2546
% Change Whole H Verb			
	M	0.0672	-0.0130
	SD	0.2263	0.1776
	Range	-.6018, .5570	-.4524, .2305
A' Sentence Task			
	M	0.7860	0.7318
	SD	0.1888	0.1734
	Range	.1850, 1.0	.4213, 1.0
% Change Left H Sentence			
	M	0.0277	-0.0668
	SD	0.4202	0.2935
	Range	-1.1601, 1.1560	-1.2320, .2728
% Change Right H Sentence			
	M	-0.0294	-0.0036
	SD	0.3506	0.1856
	Range	-1.1375, .4254	-.4762, .3690
% Change Whole H Sentence			
	M	-0.0008	-0.0352
	SD	0.3773	0.1993
	Range	-1.1488, .7907	-.6143, .2932
WISC-III FSIQ			
	M	115.45	110.62
	SD	14.42	11.38
	Range	87, 137	91, 137
WISC-III VIQ			
	M	113.13	112.69
	SD	15.07	12.61
	Range	87, 150	88, 135
WISC-III PIQ			
	M	115.58	107.77
	SD	15.64	12.57
	Range	79, 139	89, 137

Table 3

ANOVA Results of Age Group Differences

Variable	**Source**	***SS***	***df***	***MS***	***F***	***p***
A' Verb Task	Total	0.782	56			
	Between	0.014	1	0.014	0.969	0.329
	Within	0.769	55	0.014		
% Change Left H Verb	Total	4.543	56			
	Between	0.010	1	0.010	0.126	0.724
	Within	4.533	55	0.082		
% Change Right H Verb	Total	3.963	56			
	Between	0.239	1	0.239	3.527	0.066
	Within	3.724	55	0.068		
% Change Whole H Verb	Total	2.416	56			
	Between	0.091	1	0.091	2.154	0.148
	Within	2.325	55	0.042		
A' Sentence Task	Total	1.862	56			
	Between	0.042	1	0.042	1.254	0.268
	Within	1.820	55	0.033		
% Change Left H Sentence	Total	7.578	56			
	Between	0.126	1	0.126	0.932	0.338
	Within	7.451	55	0.135		
% Change Right H Sentence	Total	4.559	56			
	Between	0.009	1	0.009	0.113	0.737
	Within	4.549	55	0.083		
% Change Whole H Sentence	Total	5.281	56			
	Between	0.017	1	0.017	0.175	0.678
	Within	5.264	55	0.096		
WISC-III FSIQ	Total	9812.561	56			
	Between	330.730	1	330.730	1.918	0.172
	Within	9481.831	55	172.397		
WISC-III VIQ	Total	10787.719	56			
	Between	2.697	1	2.697	0.014	0.907
	Within	10785.002	55	196.091		
WISC-III PIQ	Total	12148.982	56			
	Between	862.819	1	862.819	4.205	0.045
	Within	11286.164	55	205.203		

Closer examination of the data revealed that the variables of percent change in activation of the left, right, and whole hippocampus during the verb generation task each contained observations that were greater than two standard deviations from the mean. If these extreme values are outliers in the data, they could significantly influence the statistical analyses. In order to examine the effect of these data points, the three variables were Winsorized. For each variable, the most extreme five percent of values, both large and small, were replaced with the value of the next least-extreme data point. This procedure reduces the influence of the most extreme values without deleting cases from the variable. For percent change in activation of the left hippocampus, the Winsorized mean is .0437, *SD* = .1993, compared with the original variable, *M* = .0435, *SD* = .2848. For right hippocampus, the Winsorized mean is .0180, *SD* = .2095, compared to the original variable, *M* = .0158, *SD* = .2660. For whole hippocampal activation, the Winsorized variable had a mean of .0256, *SD* = .1626, compared to the original variable, *M* = .0306, *SD* = .2077. Paired samples t-tests revealed that this procedure did not result in a significant difference in the mean of any of the three Winsorized variables compared to their original variables: left, $t = -.015$, $p = .988$; right, $t = -.179$, $p = .858$; $t = .517$, $p = .607$. Also, Levene's test of homoegeneity of variance confirmed that there is an equal amount of variability in the two age groups in the original variables of left, right, and whole hippocampal activation. This evidence suggests that despite the presence of extreme values in these three variables, the Winsorization procedure does not significantly improve the power of the statistical analyses. Consequently, the original, non-Winsorized variables will be used in all further analyses.

Hierarchical multiple regression analyses were completed to investigate the relationship between hippocampal activation and memory performance for the two age groups. Age, performance on the verb generation recognition memory task, and the interaction between age

and memory performance were used to predict each type of hippocampal activation during the verb generation task (i.e. left, right, and whole hippocampus). In each analysis, recognition memory performance on the sentence task was entered into the model in the first block as a covariate. Age, verb task recognition memory performance, and the age x performance interaction term were then entered in the second block. This procedure creates two regression models, one with only the predictors from the first block, and another with the predictors from both the first and second blocks. This allows for comparison of the two models and isolates the amount of unique or additional variance in the dependent variable that is accounted for by the predictors from the second block as compared to the predictors from the first block. Although recognition memory performance on the sentence task is a variable of no interest in these analyses, it is highly correlated with memory performance on the verb task ($r = .447$, $p < .001$). Entering this variable into the regression model in block one isolates the variance in hippocampal activation that is accounted for by memory performance on the sentence task. This allows the variable to act as a covariate and serves as a control for the effects of general memory ability on hippocampal activation.

The results of these regression models are presented in Table 4. For percent change in activation of the left hippocampus, the first model which included only recognition memory for the sentence task, was not significant, $R^2 = 0.006$, adjusted $R^2 = -0.012$, F (1, 55) = .312, $p = .579$. The second model, which additionally included the three predictors of interest, was also not significant, $R^2 = 0.029$, adjusted $R^2 = -0.046$ F (3, 52) = .416, $p = .742$, and failed to reveal any predictors of hippocampal activation; none of the three variables reached significance (see Table 4). For right hippocampal activation, the first model was not significant, $R^2 = 0.006$, adjusted $R^2 = -0.012$, F (1, 55) = .312, $p = .554$. The second model was also not significant, $R^2 = 0.076$,

adjusted $R^2 = 0.005$, F (3, 52) = 1.304, p = .283, and no predictors reached significance. Finally, both models predicting change in activation of the whole hippocampus during the verb generation task were not significant and no significant predictors were identified; first model: $R^2 = 0.000$, adjusted $R^2 = -0.018$, F (1, 55) = .002, p = .969, second model: $R^2 = 0.052$, adjusted $R^2 = -0.021$, F (3, 52) = .951, p = .423.

Table 4

Summary of Hierarchical Regression Models Predicting Hippocampal Activation

		Model 1					Model 2				
Variable	Predictor	*B*	SE*B*	Beta	*t*	*p*	*B*	SE*B*	Beta	*t*	*p*
Left	A'Sentence	-0.117	0.210	-0.075	-0.558	0.579	-0.181	0.741	-0.019	-0.245	0.905
	Age						0.043	0.061	0.695	0.714	0.478
	A'Verb						0.327	0.884	0.136	0.370	0.713
	Age x A'Verb						-0.054	0.071	-0.809	-0.753	0.455
Right	A'Sentence	0.117	0.196	0.080	0.596	0.554	0.120	0.223	0.082	0.535	0.595
	Age						-0.040	0.055	-0.683	-0.720	0.475
	A'Verb						-0.534	0.805	-0.237	-0.663	0.510
	Age x A'Verb						0.031	0.065	0.505	0.482	0.632
Whole	A'Sentence	0.006	0.154	0.005	0.04	0.969	0.05	0.177	0.044	0.282	0.779
	Age						0.003	0.044	0.058	0.061	0.952
	A'Verb						-0.085	0.637	-0.048	-0.134	0.894
	Age x A'Verb						-0.012	0.051	-0.256	-0.241	0.81

Similar hierarchical regression analyses were also completed to control for the effects of general cognitive abilities rather than general memory abilities. In this set of analyses, Full Scale IQ score from the Wechsler Intelligence Scale for Children – Third Edition was entered into the models in the first block instead of sentence memory performance. As before, the three predictors of interest were added to the models in the second block. The results of these analyses are presented in Table 5. For the left hippocampus, the first model which included only the IQ

variable was not significant, $R^2 = 0.000$, adjusted $R^2 = -0.018$, F (1, 55) = .001, p = .977. The second model, which additionally included the three predictors of interest, was also insignificant, $R^2 = 0.029$, adjusted $R^2 = -0.046$ F (3, 52) = .512, p = .676, and failed to reveal any predictors of hippocampal activation (see Table 5). For right hippocampus, the first model was not significant, $R^2 = 0.027$, adjusted $R^2 = 0.09$, F (1, 55) = .1.506, p = .225. The second model was also not significant, $R^2 = 0.108$, adjusted $R^2 = 0.039$, F (3, 52) = 1.576, p = .206, and no predictors reached significance (see Table 4). Similarly, neither the first nor second model predicting whole hippocampal activation were significant, and no significant predictors emerged; first model: $R^2 = 0.010$, adjusted $R^2 = -0.008$, F (1, 55) = .546, p = .463, second model: $R^2 = 0.064$, adjusted $R^2 = -0.008$, F (3, 52) = 1.003, p = .399.

Table 5

Summary of Hierarchical Regression Models Predicting Hippocampal Activation

		Model 1					Model 2				
Variable	Predictor	*B*	SE*B*	Beta	*t*	*p*	*B*	SE*B*	Beta	*t*	*p*
Left	FSIQ	0.000	0.003	-0.004	-0.029	0.977	0.000	0.003	0.002	0.002	0.991
	Age						0.044	0.062	0.705	0.715	0.478
	A'Verb						0.309	0.922	0.128	0.336	0.738
	Age x A'Verb						-0.054	0.073	-0.816	-0.742	0.461
Right	FSIQ	-0.003	0.003	-0.163	-1.227	0.225	-0.004	0.003	-0.208	-1.147	0.148
	Age						-0.027	0.055	-0.467	-0.495	0.623
	A'Verb						-0.099	0.825	-0.044	-0.121	0.905
	Age x A'Verb						0.012	0.065	0.199	0.189	0.851
Whole	FSIQ	-0.002	0.002	-0.099	-0.739	0.463	-0.002	0.002	-0.125	-0.863	0.392
	Age						0.009	0.044	0.192	0.199	0.843
	A'Verb						0.116	0.660	0.066	0.176	0.861
	Age x A'Verb						-0.022	0.052	-0.444	-0.411	0.683

Finally, in order to determine if hippocampal activation is related to the sex of the participants, point biserial correlations were conducted. These correlations are presented in Table 6. Sex was not significantly correlated with percent change in left, right, or whole hippocampal activation during the verb generation memory task.

Table 6

Correlations Between Sex and Hippocampal Activation

		Sex
% Change Left H Verb		
	r	0.047
	p	0.727
% Change Right H Verb		
	r	0.100
	p	0.461
% Change Whole H Verb		
	r	0.093
	p	0.494

Note. Females, $N = 35$; Males, $N = 22$

Discussion

The hippocampus was activated during the verb generation task for all participants as a group. However, the level of activation was only significantly greater during verb generation compared to the control task of finger tapping for the younger children. Subsequent analyses examined group differences and attempted to elucidate the nature of the relationship between hippocampal activation and memory performance. The only group difference revealed was that the younger children tended to have higher Performance IQs than the older children. The younger children and older children performed equally well on the recognition memory test. The age groups also did not differ in the percent change in right, left, or whole hippocampal activation during the verb generation task. The sex of the participants was not significantly correlated with any of the measures of hippocampal activation.

The specific hypotheses of this study concerned the nature of the relationship between hippocampal activation during the episodic encoding task and subsequent performance on a recognition memory test. There were three alternate hypotheses about this relationship: 1) the relationship between hippocampal activation and memory performance would be stronger for older children than for younger children due to the increased maturity and efficiency of the neural network supporting memory in the older children, 2) the relationship would be stronger for younger children due to their reliance on medial temporal lobe structures while other structures are still developing, or 3) that no relationship between hippocampal activation and memory performance would be observed for either group. The results suggest that the third hypothesis is most likely accurate: no relationship was observed between hippocampal activation during the verb generation task and subsequent memory performance. Hierarchical multiple regression analyses revealed that neither age, recognition memory performance, or the

interaction between age and memory performance predicted left, right, or whole hippocampal activation during the task. Even after controlling for general memory abilities or overall cognitive abilities, the relationships remained non-significant. These null results do not appear to be caused by a lack of variability in hippocampal activation or memory performance. There was indeed a significant difference in the amount of hippocampal activation in the two age groups, as revealed in the GLM comparisons of the memory task to the control task. In addition, there was a considerable range of recognition memory performance for both age groups, as well as variability within the groups.

Although the hippocampus is indeed activated during this specific episodic encoding task for both 7-9 year olds and 16-18 years olds, age and subsequent memory performance are not sufficient to predict the amount of activation that is observed. These results suggest that in children and adolescents the hippocampus may play only a minor role in the type of episodic memory that was elicited during the verb generation task (i.e. item-specific encoding). This is consistent with the findings from other fMRI investigations of a similar verbal fluency tasks (Brown et al., 2005; Gaillard et al., 2003). In a study of 7 to 32-year olds, Brown and colleagues did not observe age-related differences in hippocampal activation or memory performance for a verb generation task (Brown et al., 2005). Similarly, Gaillard and his colleagues found no significant differences in the location or laterality of activation between adults and children for a semantic verbal fluency task (Gaillard et al., 2003). The present finding are also consistent with the adult literature regarding the functional differentiation among the substructures of the MTL, namely that the main function of the hippocampus is to bind together multiple features or components of an experience during relational or configural processing (Cohen et al., 1997; Eichenbaum, 2000; Mishkin et al., 1998). In an fMRI study with adult participants, Davachi and

Wagner observed that bilateral hippocampal activation was greater in a relational processing task than in a rote rehearsal task, lending further support to this unique role of the hippocampus (Davachi & Wagner, 2002).

Thus, the adult literature and the results of this study together suggest that in both adults and children, the hippocampus may play a less-important role in item-specific encoding compared to other types of encoding. In the present study, both younger children (ages 7 to 9) and older children/adolescents (ages 16 to 18) performed equally well on the recognition memory test and neither group demonstrated a relationship between activation and memory performance. This would seem to suggest that the functional differentiation of the hippocampus and other parts of the MTL may be established early in development, and there is evidence from the developmental amnesia (DA) literature that support this claim. Early hippocampal damage results in a profound loss of context-dependent memory abilities with relatively little improvement or recovery of function over time (Vargha-Khadem et al., 1997). This suggests that the role of the hippocampus is to process the encoding and retrieval of context-rich episodes or events, and that this function is established very early in life. However, children with DA do not exhibit the characteristic amnesic syndrome early in life, they instead appear to grow into their deficits later in childhood (Bachevalier & Vargha-Khadem, 2005). This seems to suggest that even though the hippocampus is essentially wired from birth to serve relational processing, some aspects of these context-dependent memory abilities develop gradually during childhood (Bachevalier & Vargha-Khadem, 2005). Subsequent studies will need to examine this issue in more depth with younger children.

The results of this study, and of future studies of memory development, must consider hippocampal function in the context of a system of interrelated structures that comprise the

medial temporal lobe. The findings of this study do not suggest that the MTL is unimportant or unnecessary for item-specific episodic encoding. The parahippocampal gyrus, another structure of the MTL, may in fact be more important for item-specific encoding than the hippocampus (Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002).

The present study is unique in that no neuroimaging studies have yet examined the functional specificity of the MTL in children. By isolating the percent change in activation of the hippocampus and directly relating it to subsequent memory performance, we were able to examine the neural substrate of one specific type of episodic encoding: item-based learning. However, in order to fully understand the role of the hippocampus and the MTL in the development of the memory system, investigations of additional types of episodic encoding are needed. Neuroimaging studies of children's memory thus far have focused only on short-term memory for non-verbal materials. Examining additional episodic encoding strategies such as associative encoding of verbal materials would help clarify the role of the hippocampus in memory development and would provide valuable information about the brain structures that support effective learning in children. In turn, this could have potential educational implications.

This investigation was limited by the constraints of the original study from which the imaging and behavioral data were gathered. In that study, the memory task (verb generation) and control task (finger tapping) were used to examine aspects of general memory performance in the context of language abilities. Both younger and older children performed equally well on the recognition memory test administered after scanning, suggesting that the memory task was perhaps too easy for the participants. In addition, the type of retrieval measure used in the original investigation is important to the present findings. In that study, a recognition memory test was used to ensure that the participants were completing the memory task as instructed.

Recognition memory tests do not provide detailed information about the memory performance of the participants. Consequently, it is possible that a cued recall memory test would have elicited greater age differences in performance than the recognition memory test. In an fMRI study with adult participants, Fernandez and colleagues found that the level of activation of the entorhinal cortex (an MTL structure) during a single-word episodic encoding task was significantly correlated to subsequent cued recall performance for the presented words (Fernandez et al., 1999).

However, our finding of a lack of relationship between hippocampal activation and recognition memory performance is consistent with the existing literature. Single-item episodic encoding tested in a recognition format (based on familiarity) does not appear to be dependent on the hippocampus (Aggleton & Shaw, 1996; Eldridge, Knowlton, Furmanski, Bookheimer, & Engle, 2000; Norman & O'Reilly, 2003). Children with DA demonstrate intact recognition memory despite significant hippocampal damage (Baddeley et al., 2001; Duzel et al., 2001). Future neuroimaging studies investigating the neural substrates of children's memory will need to carefully design memory paradigms that sufficiently challenge the memory abilities of children and measure their performance in more than one manner, perhaps with both cued recall and recognition.

Another possible limitation of this study is the limited age range of the participants. Children younger than 7 years old cannot reliably participate in fMRI paradigms due to the high incidence of motion artifacts in the data. Thus, the youngest children in this study were 7 years old. Although this excludes younger children from the investigation, age 7 provides a logical cut-off point because it coincides with the beginning of formal schooling for most children. In the analyses, we grouped the youngest participants (ages 7 to 9) together and grouped the oldest

participants (ages 16 to 18) together, presuming that these two groupings would show the greatest difference in memory performance and hippocampal activation. This grouping assumes that as age increases, memory performance also increases in a monotonic relationship. In theory, a relationship between memory performance and hippocampal activation may emerge for children in the middle age range (10-15). Although there does not appear to be evidence to support this idea, future studies should nevertheless include a wider and more complete age range of participants in order to examine all possible relationships.

A great deal of variability in hippocampal activation and recognition memory performance was observed both within groups and across all participants. This does not appear to be the result of poor motivation or poor cooperation on the part of the participants. All data included in the analyses were checked for motion artifacts, and post-scanning testing insured that the participants were complying with the task instructions. Instead, the high variability is consistent with the existing literature, which suggests that large individual differences exist in memory performance (Uttl, 2005), especially in children (Schneider & Pressley, 1997). In this study, recognition memory performance on a different encoding task was used in the regression analyses to control for the general memory abilities of the participants, thus isolating the effects of the memory task of interest, and ensuring that the observed variability in memory performance reflects true variation. There was also a large degree of individual variation in the amount and pattern of brain activation observed in this study. This is not unexpected, given that the hemodynamic response to MRI during encoding tasks has been shown to be highly variable, especially with young children (Casey et al., 1995). Unfortunately this variability is an inherent limitation of neuroimaging research, although using carefully designed paradigms, large samples

sizes, and statistical corrections (such as covariates) helps to alleviate this concern and isolate reliable patterns of activation.

In summary, the present results add to the literature elucidating the role of the MTL in supporting episodic memory. The results suggest that age and memory performance are not sufficient to predict variation in hippocampal activation during an item-specific encoding task. This is turn begins to suggest that the hippocampus proper plays a minor role in item-specific encoding in children and adults, and instead may be more important for relational encoding. It appears that this functional differentiation among the structures of the MTL is established early in development, although additional neuroimaging studies investigating a wider range of ages and memory processes are needed to clearly elucidate the developmental trajectory of the MTL.

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