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Volume of hippocampal subfields and episodic memory in childhood and adolescence

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ABSTRACT

Episodic memory critically depends on the hippocampus to bind the features of an experience into memory. Episodic memory develops in childhood and adolescence, and hippocampal changes during this period may contribute to this development. Little is known, however, about how the hippocampus contributes to episodic memory development. The hippocampus is comprised of several cytoarchitectural subfields with functional significance for episodic memory. However, hippocampal subfields have not been assessed in vivo during child development, nor has their relation with episodic memory been assessed during this period. In the present study, high-resolution T2-weighted images of the hippocampus were acquired in 39 children and adolescents aged 8 to 14 years (M = 11.30, SD = 2.38), and hippocampal subfields were segmented using a protocol previously validated in adult populations. We first validated the method in children and adolescents and examined age-related differences in hippocampal subfields and correlations between subfield volumes and episodic memory. Significant age-related increases in the subfield volume were observed into early adolescence in the right CA3/DG and CA1. The right CA3/DG subfield volumes were positively correlated with accurate episodic memory for item–color relations, and the right CA3/DG and subiculum were negatively correlated with item false alarm rates. Subfield development appears to follow a protracted developmental trajectory, and likely plays a pivotal role in episodic memory development.

Introduction

Episodic memory is the capacity to remember details about events and critically depends on the hippocampus which integrates the arbitrary features of an experience into memory (Eichenbaum and Cohen, 2001). Episodic memory develops during childhood and adolescence (Ghetti and Lee, 2011; Ofen and Shing, 2013). However, the contribution of the hippocampus to this development has received little attention.

Studies of age differences in the hippocampal volume have yielded contrasting results. Although age-related volumetric increases have been reported from childhood into young adulthood (Østby et al., 2009), other studies failed to find age differences (e.g., Giedd et al., 1996; Yurgelun-Todd et al., 2003). However, the trajectory of development may differ along the longitudinal axis of the hippocampus, even while the overall volume is relatively stable (DeMaster et al., 2013; Gogtay et al., 2006). Using different volumetric methods, DeMaster et al. (2013) and Gogtay et al. (2006) showed that with age, the hippocampal head decreased in volume while the hippocampal body increased; further, associations between volumes and episodic memory differed as a function of age and sub-region. These results raise the question of whether differences along the longitudinal axis reflect heterogeneity in hippocampal cytoarchitecture. The hippocampal formation comprises several subfields (Insausti and Amaral, 2004; Insausti, 2010), including the dentate gyrus (DG), the cornu ammonis (CA) subfields CA3, and CA1, as well as the subicular complex. Since these subfields are not uniformly distributed along the longitudinal axis, age-related differences in the subfields may help account for previous results.

To date no published study has examined age differences in the volume of hippocampal subfields and their contribution to episodic memory in children. The present study begins to address this gap by pursuing three goals. First, we sought to validate with children a subfield segmentation method previously used with adults (Ekstrom et al., 2009; Zeineh et al., 2001, 2003). Second, we sought to conduct an initial investigation of age-related differences in the volume of hippocampal subfields in the body of the hippocampus, given that most protocols developed for 3 T imaging methods yield reliable segmentation of the subfields restricted to the hippocampal body. We expected volumes of the CA1 and CA3/DG, but not the subiculum, to increase with age, consistent with the results of the only available human development subfield data coming from a post-mortem

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investigation (Insausti, 2010), as well as with results from developing macaque primates (Jabès et al., 2010). Furthermore, DG may exhibit protracted development possibly due to neurogenesis (e.g., Kalkan et al., 2013; Jabès et al., 2010; Lavenex and Lavenex, 2013; Yu et al., 2013) and myelination (Abrahám et al., 2010). Heterogeneous development of the subfields in the hippocampal body would provide initial support for the hypothesis that such development could account for age differences along the longitudinal axis reported previously (e.g., DeMaster et al., 2013; Gogtay et al., 2006). Third, we sought to explore the relation between subfield volumes and episodic memory in children. Evidence from adult humans (Kirwan and Stark, 2007; Shing et al., 2011; Yassa et al., 2011) and rodents (e.g., Hunsaker and Kesner, 2013; Sahay et al., 2011) suggests that the DG and CA3 may support encoding and retrieval of distinct event memories resistant to over-generalization (e.g., Leutgeb et al., 2007; Stark et al., 2013). Further, the protracted neurogenesis in the DG makes this field a good candidate for capturing the association between hippocampal volume and episodic memory during development. Thus, we predicted that episodic memory performance would be positively associated with CA3/DG volumes. This relationship is predicted to persist after statistically accounting for age.

Materials and methods

Participants

Thirty-nine children (19 girls) participated in the study (M = 11.30 years, SD = 2.38, range 8 to 14 years). One additional participant was excluded from analysis because we incidentally discovered a brain abnormality of clinical significance (age 9). Participants and their families were recruited from the Davis and Sacramento areas and included mostly middle class families (family income, M = 87 K, SD = 28 K). Participants were not eligible if left-handed, had a psychiatric diagnosis via parental report (e.g., ADHD, dyslexia, depression), history of head trauma, premature birth (<36 weeks), low birth weight (<5.5 lb), color-blindness, or any factor that related to participant safety in MR imaging environments. Informed consent was provided by parents and children prior to enrollment, and participants were compensated $30 for their time.

Data acquisition

MR imaging data were acquired at the UC Davis Imaging Research Center with a Siemens 3 T Siemens Trio scanner using a 32-channel head coil. The location of the hippocampus was identified bilaterally using a sagittally acquired localizing scan. A T2-weighted image of the hippocampal formation was acquired perpendicularly to the long axis of the hippocampus using a spin-echo sequence (interleaved acquisition; matrix: 161 mm × 200 mm; in-plane resolution: 0.4 mm × 0.4 mm; slices: 28; slice thickness: 1.9 mm; TR: 4200 ms; TE: 106 ms). This T2 imaging protocol was previously used with adults in the same scanner (Libby et al., 2012). One T1-weighted image was acquired sagittally using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (matrix: 256 mm × 256 mm; in-plane resolution: 1.0 mm × 1.0 mm; slices: 208; slice thickness: 1.0 mm; TR: 1900 ms; TE: 2.9 ms).

Segmentation of hippocampal subfields

Independent raters manually segmented all 39 participants' hippocampi bilaterally, resulting in separate volumes for the CA1, a joint region including the CA3 and DG (CA3/DG), and the subiculum. Segmentation was based on a protocol described in Ekstrom et al. (2009) and Zeineh et al. (2001), integrated with guidelines included in Yushkevich et al. (2010), Duvernoy (2005), and Insausti (2010). We used the ITK-SNAP image viewer and segmentation tool (www.itksnap.org) to view and segment the images. To ensure that raters traced subfields under similar viewing conditions, raters adjusted contrast levels in ITK-SNAP so that low intensity white matter voxels were seen as black and high intensity CSF voxels were seen as white.

Each rater was blind to age, gender, and memory performance of participants. Segmentation of subfields was completed for each slice within the hippocampal body. The subfields in the head and tail regions were not segmented due to concerns that partial-volume artifacts, which can occur in images with a 1.9 mm slice thickness, would prevent reliable segmentation. The boundary between the head and the body was identified based on the presence of the uncal apex: the body section began one slice posterior to the uncal apex. The body was further segmented from the tail of the hippocampus one slice anterior to the coronal slice at which the fornix separates from the hippocampus in the tail (Watson et al., 1992).

Following identification of the hippocampal body, segmentation of subfields continued caudally from the first to the last slice, using the following guidelines (Fig. 1). Segmentation of each coronal slice began with the subiculum, then the CA1, and ended with the CA3/DG. The inferior boundary of the subiculum from the parahippocampal cortex was demarcated at the nadir of the concavity in the medial wall between the collateral sulcus and hippocampus (*segment A*), which lies approximately midway between the collateral sulcus and the hippocampus. The boundary between the subiculum and CA1 was demarcated by a segment perpendicular to the gray matter ribbon at the point where the hippocampus pinches downward to form a teardrop shape (*segment B*), which also corresponds to the medial extent of the CA3/DG region. The CA3/DG boundary with the CA1 was delineated by using the following procedure adapted from Yushkevich et al. (2010). First, the longest line from the most medial and inferior extent of the CA3/DG to the most lateral point of the CA fields was drawn (*segment C*). At the midpoint of *segment C*, a perpendicular line was drawn superiorly that terminates at the most superior extent of the CA field (*segment D*). From the superior end of *segment D*, a perpendicular segment was drawn laterally (*segment E*) for a length approximately equal to the thickness of the local CA field. Finally, from the lateral end of *segment E*, we completed the 'hang-man' shape by dropping a perpendicular segment to the inferior extent of the local CA field (*segment F*). *Segment F* marks the boundary between the CA1 and CA3/DG. The alveus and fimbria were excluded from hippocampal segmentations. The internal stratified laminae identified as the visible low-intensity voxels inside the hippocampus marked the transition from the CA1 and CA3/DG. These low-intensity voxels were included within the CA1 segmentation. The overall hippocampal body volume was also computed by summing the volumes from the CA3/DG, CA1, and subiculum segmentations. We acknowledge that there are additional subfields (e.g., CA2, CA4; Duvernoy, 2005); however, most protocols including our own do not address these subfields.

Reliability of segmentation method

Before examining associations between subfields, age, and episodic memory, we took several steps to establish inter-rater reliability between two independent tracers. First, intraclass correlation coefficients (ICC; Bartko, 1966) were computed using a two-way random effects model for consistency of averaged measures. Additionally, inter-rater Dice Similarity Coefficients (DSCs; Dice, 1945) were computed to assess the absolute agreement between tracers in terms of volume and spatial position. DSC for each subfield and each participant is computed as follows: $DSC = 2|A \cap B| / (|A| + |B|)$, where A and B are the segmentation volumes provided by each of the independent tracers A and B respectively, and $|A \cap B|$ is the volume shared by both A and B. Thus, the DSC measures the proportion of spatial overlap between two raters. The coefficient ranges from 0 to 1, where 0 indicates no agreement between tracers, and 1 indicates perfect agreement in both volume and spatial position. It has been argued that $DSC \geq 0.7$ represents good to excellent agreement (Bartko, 1991; Zijdenbos et al., 1994). In developmental