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Protracted hippocampal development is associated with age-related improvements in memory during early childhood

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ABSTRACT

The hippocampus is a structure that is critical for memory. Previous studies have shown that age-related differences in specialization along the longitudinal axis of this structure (i.e., subregions) and within its internal circuitry (i.e., subfields) relate to age-related improvements in memory in school-age children and adults. However, the influence of age on hippocampal development and its relations with memory ability earlier in life remains under-investigated. This study examined effects of age and sex on hippocampal subregion (i.e., head, body, tail) and subfield (i.e., subiculum, CA1, CA2-4/DG) volumes, and their relations with memory, using a large sample of 4- to 8-year-old children. Results examining hippocampal subregions suggest influences of both age and sex on the hippocampal head during early childhood. Results examining subfields within hippocampal head suggest these age effects may arise from CA1, whereas sex differences may arise from subiculum and CA2-4/DG. Memory ability was not associated with hippocampal subregion volume but was associated with subfield volume. Specifically, within the hippocampal head, relations between memory and CA1 were moderated by age; in younger children bigger was better, whereas in older children smaller was superior. Within the hippocampal body, smaller CA1 and larger CA2-4/DG contributed to better memory performance across all ages. Together, these results shed light on hippocampal development during early childhood and support claims that the prolonged developmental trajectory of the hippocampus contributes to memory development early in life.

Introduction

The hippocampus is a complex structure comprised of multiple subfields (cornu ammonis areas 1–4, dentate gyrus, and subiculum) that are disproportionately distributed along the longitudinal axis (head, body, tail; Insausti and Amaral, 2012; Poppenk et al., 2013). Previous work examining the development of the hippocampus in school-aged children (~8 years of age and older) and adolescents has identified age- and sex-related differences in volumes of both subregions (i.e., head, body, tail; Daugherty et al., 2016; DeMaster et al., 2013; Gogtay et al., 2006; Riggins et al., 2015; Schlichting et al., 2016) and subfields (CA1-4, DG, subiculum; Daugherty et al., 2016; Lee et al., 2014; Tamnes et al., 2014). Age-related differences arise from multiple sources including: neurogenesis, synaptic growth, dendritic arborization, pruning, vascularization and myelination (Benes and Tamminga, 1994; Huttenlocher, 1990; Lenroot and Giedd, 2006). These changes have been shown to have functional relevance, as many of these studies also linked age-related differences in hippocampal volume to age-related differences in cognitive abilities such as memory (see Ghetti and Bunge, 2012 for review) and language (e.g., Lee et al., 2015). Sex differences may partially arise from effects of sex hormones as well as their collaboration with neurotransmitters and other intra- and extracellular mediators (Marrocco and McEwen, 2016; McEwen, 2010; Scharfman and MacLusky, 2017). Sex differences are important to document across development as they are thought to be associated with observed sex differences in age of onset, prevalence, and symptomatology observed in many neurodevelopmental disorders (Giedd et al., 1997).

To date, few studies have examined development of the hippocampus early in life (prior to 8 years) and its implications for memory. This is particularly unfortunate as 1) neuroanatomical data from nonhuman primate studies suggest early childhood is a period of important developmental change in the hippocampus (e.g., Lavenex and Banta Lavenex, 2013; Serres, 2001) and 2) behavioral studies in children suggest early childhood is a period of dramatic improvement in memory (e.g., Bauer et al., 2012; Drummey and Newcombe, 2002; Riggins, 2014; Sluzenski et al., 2006). Although theorists propose these developmental

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phenomena are linked (Bauer, 2006; Josselyn and Frankland, 2012; Lavenex and Banta Lavenex, 2013; Nadel and Moscovitch, 1997), empirical data are lacking.

The present study sought to address this gap by 1) systematically examining effects of age and sex on hippocampal subregions and subfields in 4- to 8-year-old children and 2) probing whether any observed differences in sex or age relate to memory ability during this developmental period. In order to set the stage for the current study, we first review findings from previous studies in humans examining age- and sex-differences in hippocampal subregions and their relations with memory, followed by findings in humans examining hippocampal subfields pertinent to these associations. Finally, findings from neuroanatomical data in nonhuman primates and behavioral studies of memory development in young children are reviewed, as this literature provided the primary motivation and hypotheses for the current study.

Subregions

Previous research suggests total hippocampal volume increases during childhood and is greater in boys compared to girls (e.g., Brown and Jernigan, 2012; Hu et al., 2013; Uematsu et al., 2012). However, hippocampal subregions (distributed along the longitudinal axis) show different developmental trajectories. Gogtay et al. (2006) first documented these regional differences in a longitudinal study, showing that between 4 and 25 years of age, anterior regions (i.e., head) decreased in size (particularly in the right hemisphere), whereas posterior regions (i.e., body and tail) increased in size (particularly in the left hemisphere). In addition, qualitative differences were observed between males and females, but statistical comparison was not possible due to the limited sample size. Furthermore, few scans were obtained during early childhood; the average age when participants were first scanned was 13 years.

Since then, cross sectional-studies have corroborated regional differences in hippocampal volume in school-aged children and adults and extended this work by relating these differences to memory performance (Daugherty et al., 2016; DeMaster et al., 2013; Riggins et al., 2015; Schlichting et al., 2016). Overall, these studies suggest age-related differences in hippocampal subregion volume, with differential changes occurring along the longitudinal axis as children move into adolescence and adulthood. Nonlinear changes have been observed in the hippocampal head, with the smallest volumes found in adults. In addition, volume of the hippocampal head has been shown to relate to performance on memory tasks, although the direction of this effect (positive or negative relation) varies across studies/age groups (cf. Riggins et al., 2015; Schlichting et al., 2016).

Finally, although most of these previous studies include sex as a covariate in the analyses, only one directly examined sex differences in hippocampal subregion volumes and reported that none were observed (Daugherty et al., 2016).

Subfields

With advances in imaging methodology, research has begun to document the effects of age and sex on hippocampal subfield (CA1-4, dentate gyrus, subiculum) development (Daugherty et al., 2017; Krogsrud et al., 2014; Lee et al., 2014; Schlichting et al., 2016; Tamnes et al., 2014). Across these studies, hippocampal subfields (typically CA1 and CA3-4/DG), showed different patterns of change (i.e., increases or decreases in volume) depending on the study and the age groups under investigation. However, across studies, volumetric differences have been related to memory performance. In two studies focusing on older children and adults (Lee et al., 2014; Daugherty et al., 2017), CA3/DG volume in the body was positively associated with memory, whereas in two studies including younger children (Schlichting et al., 2016; Tamnes et al., 2014) CA1 volume was related to memory (although the direction of this effect varied between these studies).

In a sample closest to the age range of the present study, 244 4- to 22-year-old individuals, Krogsrud et al. (2014) reported increased volume in CA1, CA2/3, CA4/DG, presubiculum, subiculum, and fimbria measured throughout the head and body of the hippocampus between 4 and ∼15 years, followed by little age-related change beyond that point. Memory was not assessed. In a sample recruited from the same cohort, Tamnes et al. (2014) examined subfield development longitudinally in 85 individuals aged 8–21 years using 170 scans. They investigated relations with memory. Nearly all subfields showed decreases in volume across development. Greater CA1 and CA2-3 volume was related to better memory performance (a finding similar to Schlichting et al., 2016).

Of these studies, many included sex as a covariate. Of those that directly examined sex differences in hippocampal subfield volumes, Daugherty et al. (2017) reported no significant effects, Schlichting et al. (2016) reported an interaction between sex and age for the subiculum in the hippocampal head, and both Tamnes et al. (2014) and Krogsrud et al. (2014) reported larger volumes in males for CA1, CA2/3, CA4/DG, and subiculum, that were driven mainly by participants under 13 years of age.

Early childhood

Of the above-mentioned studies, only three included participants younger than 6 years of age (Krogsrud et al., 2014; Riggins et al., 2015; Tamnes et al., 2014), yet none of them examined this younger age group systematically. Neuroanatomical data obtained from human and nonhuman primate tissue samples suggest developmental changes may be substantial in the hippocampus during early childhood (Eckenhoff and Rakic, 1988; Lavenex and Banta Lavenex, 2013; Serres, 2001), which some researchers propose underlie age-related changes in cognitive abilities (e.g., memory, spatial navigation) observed in this developmental stage (Bauer, 2006; Josselyn and Frankland, 2012; Lavenex and Banta Lavenex, 2013). However, to date, no studies have systematically examined hippocampal structure or its relation to cognition in humans during early childhood.

Of the cognitive abilities thought to improve due to the maturation of specific hippocampal subfields, laboratory-based studies of memory during early childhood have identified the ability to bind details of an event together and later recall these details as a significant source of change. For example, using a cohort-sequential design, Riggins (2014) examined developmental changes in children's memory for novel facts and the sources from whom those facts were learned. Results showed that memory for facts improved between 4 and 10 years of age in a linear fashion. Memory for details of these facts (i.e., the source from whom they were learned), which is thought to reflect binding, showed the greatest rates of improvement between 5 and 7 years of age. This change was evident not only in the memory for the source of the facts but also in the types of errors children made. With age, children's errors transitioned from those thought to be due to metacognitive abilities (e.g., guessing) to errors in episodic memory specificity (e.g., knowing the fact was learned in the laboratory but being unable to recall from whom it was learned). Similar findings of age-related improvements in memory during early childhood have been reported across multiple labs using several different memory paradigms (e.g., Bauer et al., 2012; Ngo et al., 2017; Sluzenski et al., 2006).

The goal of the current study was to systemically examine hippocampal development in early childhood and link age- and sex-related hippocampal differences to memory performance.

Method

Effects of age and sex on hippocampal subregion volumes (i.e., head, body, tail) were examined using T1 scans from sample of 186 4- to- 8-year-old children. These results were further probed via analysis of hippocampal subfields (subiculum, CA1, CA2-4/DG) obtained from ultra-high resolution T2 scans in a subset of the same children (n = 153). Memory was assessed using the novel fact paradigm described above (Riggins, 2014).