Age-related effects on the anterior and posterior hippocampal volumes in 6-21 year olds: a model selection approach

Short Title: Age effects on hippocampal volume

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ABSTRACT

Although recent studies support significant differences in intrinsic structure, function, and connectivity along the longitudinal axis of the hippocampus, few studies have investigated the normative development of this dimension. In addition, factors known to influence hippocampal structure, such as sex or puberty, have yet to be characterized when assessing age-related effects on its subregions. This study addresses this gap by investigating the relationship of the anterior (antHC) and posterior (postHC) hippocampus volumes with age, and how these are moderated by sex or puberty, in structural magnetic resonance imaging scans from 183 typically developing participants aged 6-21 years. Based on previous literature, we first anticipated that non-linear models would best represent the relationship between age and the antHC and postHC volumes. We found that age-related effects are region-specific, such that the antHC volume remains stable with increasing age, while the postHC shows a cubic function characterized by overall volume increase with age but a slower rate during adolescence. Second, we hypothesized that models which include biological sex or pubertal status would best describe these relationships. Contrary to expectation, models comprising either biological sex or pubertal status did not significantly improve model performance. Further longitudinal research is needed to evaluate their effects on the antHC and postHC development.

KEYWORDS: hippocampus, adolescence, development, gray matter, puberty

INTRODUCTION

The human hippocampus is structurally and functionally distinct along its longitudinal axis (Adnan et al., 2016; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), with implications for understanding the key roles it plays in episodic memory processes (Burgess, Maguire, & O'Keefe, 2002; Nadel & Moscovitch, 1997; Preston A.R. & Wagner, 2007; Sekeres, Winocur, & Moscovitch, 2018). Emerging evidence suggests that the anterior hippocampus (antHC) is responsible for the encoding and retrieval of gist-like memory, while the posterior hippocampus (postHC) is involved in detailed memory and spatial navigation (Brunec et al., 2018; Poppenk et al., 2013; Poppenk & Moscovitch, 2011; Sekeres et al., 2018). In addition, differential anatomic and functional connectivity of these sub-regions to cortex indicate that they undergird distinct networks and cognitive representations (Barnett et al., 2021; Ranganath & Ritchey, 2012; Sheldon, Fenerci, & Gurguryan, 2019). Although there has been recent interest in using functional magnetic resonance imaging to characterize distinctions in activation and connectivity present along its longitudinal axis in children and adolescents (D. M. Demaster & Ghetti, 2013; Schlichting, Guarino, Schapiro, Turk-Browne, & Preston, 2017; Selmeczy, Fandakova, Grimm, Bunge, & Ghetti, 2019), much less research has focused on patterns of structural development of the antHC and postHC.

There are two schemes by which the hippocampus can be divided along its longitudinal axis: the tripartite model (head, body, tail) and the bipartite model (antHC and postHC). In the latter model, the hippocampal body and tail form the postHC. Two longitudinal studies investigated the hippocampus along its longitudinal axis based on the tripartite model and characterized non-linear development from childhood to adolescence (Lee et al., 2020) and to adulthood (Gogtay et al., 2006). The two longitudinal studies and other cross-sectional research indicate volumetric decreases in the hippocampal head (Gogtay et al., 2006; Lee et al., 2020; Schlichting et al., 2017) and increases in the hippocampal body (Daugherty, Flinn, & Ofen, 2017; Gogtay et al., 2006; Schlichting et al., 2017). Furthermore, there is evidence of distinct developmental associations of the antHC and postHC correlate with behaviour (Lee

et al., 2020). Importantly, these studies contribute to a growing body of evidence for the unique development of the antHC and postHC.

In addition, there is growing evidence that sex and puberty may influence hippocampal development —see reviews (Kight & McCarthy, 2020; Peper, Hulshoff Pol, Crone, & van Honk, 2011). Fish and colleagues found sex differences in hippocampal developmental trajectories from ages 5-25 years using non-linear shape modelling (Fish et al., 2020). In contrast, Lynch and colleagues showed greater age-related differences in females compared to males over ages 1-22 in the hippocampal body (Lynch et al., 2019). Puberty also impacts hippocampal developmental trajectories in both sexes (Goddings et al., 2014; Wierenga et al., 2018), but these have not been investigated for the antHC and postHC. In the transition from childhood to adolescence, hippocampal function in the tripartite model with age and puberty have shown that both uniquely contributed to improvement of relational memory (Selmeczy et al., 2019). This evidence suggests that sex and puberty are important factors when considering age models, and these have yet to be explicitly evaluated for the antHC and postHC volumes.

In the current study, we used a cross-sectional design to investigate age-related effects on the antHC and postHC volumes using a large structural neuroimaging dataset from the Child Mind Institute spanning 6 to 21 years of age. Based on prior findings, we hypothesized non-linear age-related effects on the antHC and postHC volumes across this developmental period. Given previous evidence of the possible influence of sex or puberty, we also hypothesized that models best describing such effects would include these factors. However, recognizing that such statistical models may obscure subtle differences, we also report findings separately for males and females, as well as for different pubertal stages for the antHC and postHC.

METHODS

Participants

Our study was approved by the Research Ethics Board at the University of Toronto. We analyzed structural neuroimaging data from typically developing children from the Child Mind Institute Healthy Brain Network (HBN) database (Alexander et al., 2017). Prior to starting the study, written consent was obtained from participants 18 years and older and their legal guardians if participants were younger than 18 years old (Alexander et al., 2017). We included typically developing participants aged 6-21 years from releases 1-9 from the Child Mind Institute restricting inclusion to those who had phenotypic data available. We aimed to achieve a rectangular distribution around ages and roughly equal numbers of females and males. Given the paucity of data in the lowest and highest age ranges and to avoid bias in the sample, we randomly selected participants with relevant neuroimaging and pubertal data up to a maximum of 28 per year of age (Supplementary Tables 1.1 and 1.2). We excluded participants missing pubertal scores (n=49) and those with incomplete neuroimaging data (n=9).

Pubertal assessment

The researchers at the Child Mind Health Institute administered either two pubertal scales: the Pubertal Developmental Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988) and the Tanner Staging Assessment (TANN) (Marshall & Tanner, 1969, 1970). Participants 11 years and older completed self-report measures and parent-report measures were available for participants aged 6-10 years. No participants completed both scales. The PDS uses a series of questions and reports pubertal development on five indices related to gonadal, adrenal, and growth factors that alter the body during puberty. Development on each characteristic is rated on a 4-point scale, such that a rating of 1 indicates “no development” and a rating of 4 indicates “complete development”. Averaging the responses to questions 1-5, we categorized a score of 1-1.9 as “pre-puberty”, 2-3.9 as “puberty” and a score of 4 as “post-puberty” (Petersen et al., 1988). The TANN reports development based on pubic hair and gonadal development in males and females. Participants were asked to determine their pubertal status for each characteristic with the help of pictures that corresponded to different TANN stages: pre-puberty (Stage 1), puberty (Stages 2-4) and post-puberty (Stage 5). A mean total score of 1 was categorized as “pre-puberty”, 2-4 as “puberty”

and 5 as "post-puberty". This allowed us to classify data from the PDS and TANN scales into three pubertal categories: pre-puberty, puberty, and post-puberty.

MRI acquisition

Neuroimaging data were acquired from three sites: Staten Island, Rutgers, and Citigroup Biomedical Imaging Centre (CBIC) (see Supplementary Figure 1). At the Staten Island site, participants were scanned with a 1.5T Siemens Avanto scanner using a 32-channel head coil. The T1-weighted anatomical scan was acquired with the following parameters: sagittal acquisition, echo time/repetition time (TE/TR)=1.64/2730 ms; inversion time = 1000 ms; 176 slices; flip angle = 7˚; matrix = 256 x 256; field-of-view (FOV) = 256 x 256 mm; 1mm isotropic voxels. The Rutgers site used a Siemens 3T Tim Trio scanner with a 32-channel head coil. The T1-weighted anatomical scan was acquired with the following parameters: sagittal acquisition, TE/TR=3.15/2500 ms; inversion time = 1060 ms; 224 slices; flip angle = 8˚; matrix = 320 x 320; FOV = 256 x 256 mm; 0.8 mm isotropic voxels. The CBIC site used a Siemens 3T Prisma Fit scanner with a 32-channel head coil. The T1-weighted anatomical scan was acquired with the following parameters: sagittal acquisition, TE/TR=3.15/2500 ms; inversion time = 1060 ms; 224 slices; flip angle = 8˚; matrix = 320 x 320; FOV = 256 x 256 mm; 0.8 mm isotropic voxels.

Volumetric segmentation

Volumetric segmentation of the hippocampus was performed in FreeSurfer v7.0 (http://surfer.nmr.mgh.harvard.edu/). Each individual's T1-weighted anatomical scan underwent volumetric segmentation using the standard "recon-all" pipeline (for further detail, please see: Fischl et al., 2002). The hippocampus was further segmented using the hippocampal module (Iglesias et al., 2015). This allowed the labelling of the hippocampal regions of the head, body, and tail, which correspond to the antHC (head), and postHC (body and tail). Briefly, this algorithm uses Bayesian inference using priors from a probabilistic atlas and the scan's observed image intensities. The probabilistic atlas used for priors is based on manual segmentations of high-resolution *ex vivo* (0.1mm isotropic resolution) scans and *in vivo* MRI scans. The reliability of this method was established in

children and young adults (Brown et al., 2020; Schoemaker et al., 2016). We further adopted a rigorous manual quality check of the overall reconstruction from FreeSurfer which allowed us to apply objective general guidelines described in (Klapwijk, van de Kamp, van der Meulen, Peters, & Wierenga, 2019). Each scan was rated with a final score between 1 to 4 (1 as "excellent" and 4 as "failed"). Scans rated as 4 were excluded from the study. Then, we checked our subcortical segmentations based on published recommendations (Sankar et al., 2017): if the segmentations were over- or under-estimated by ≥10 voxels on 3 or more slices, the subject was excluded from the analysis (examined by K.P.) (see Supplementary Table 1.3). Inter-rater reliability between two raters (K.P. & L.J.A.) was assessed on 20% of the total scans (50 scans) for overall scan quality and hippocampal segmentations. We quantified the percentage of agreement as 92%, and kappa coefficient (k ± SE) = 0.73 ± 0.13, indicating substantial agreement (Landis & Koch, 1977). For each subject that passed these quality checks, we exported the head, body, and tail volumes of the hippocampus (in mm^3) bilaterally, and the estimated intracranial volume (eICV) (see Supplementary Figure 2 for raw eICV volume distribution). We then labelled the head of the hippocampus as the antHC and added the body and tail volumes to represent the postHC.

Statistics

All statistical tests were performed with RStudio (Team, 2021).

Volume corrections

We first evaluated whether the raw hippocampal volumes varied across sites using Kruskal-Wallis test with Dunn's test (p values adjusted with Bonferroni correction), with significance set at $p<0.05$ (see Supplementary Table 3). We then adjusted the raw hippocampal volumes for the confounding effect of scanner sites given the statistical differences between sites (Staten Island-Rutgers, and Staten Island-CBIC). In addition, we adjusted hippocampal volumes using the eICV correction method in Jack and colleagues (Jack et al., 1989) and previously used by Decker and colleagues (Decker, Duncan, Finn, & Mabbott, 2020). We applied this correction method to hippocampal volumes across age and sex, because we found no statistically significant interactions between age, sex and eICV in our sample (see

Supplementary Table 4). The correction method was applied as follows: $Vol_{adjusted\ (i)} = Vol_{(i)} - b^{*}\ (eICV_{(i)} - mean\ eICV)$. $Vol_{adjusted(i)}$ and $Vol_{(i)}$ represent the adjusted and hippocampal volumes, respectively, of each participant. The beta (b) value was found for each subregion by computing the slope of the regression of the hippocampal volumes ($Vol_{(i)}$ on eICV). The $eICV_{(i)}$ is the individual's eICV and the mean eICV is the mean value of all eICV in our sample. Given that the left and right hippocampal subregions were highly correlated with their contralateral counterpart (Spearman's rank test; antHC: rho=0.79, p<2.2e-16 and postHC: rho=0.86, p<2.2e-16), we used the mean of the left and right subregions for the analysis as previously done (Goddings et al., 2014). We have included supplementary material for the visualization of these corrections (see Supplementary Figure 3 and Supplementary Table 5).

Models for age-related effects

For each hippocampal subregion, we sought to identify the best-fitting model to map the age-effect in our sample. Given previous literature on the influence of sex and puberty on hippocampal volumes, we tested three different model families: 1) age, 2) age and puberty, and 3) age and sex. Linear and polynomial equations (quadratic and cubic), were also compared, given the nature of the trajectories evaluated previously for hippocampal volumes (Goddings et al., 2014). Age was centralized to the minimum age in our sample (age=6 years of age), as previously done (Goddings et al., 2014), and standardized to improve numerical accuracy of polynomial age terms (quadratic and cubic). Puberty was coded as a categorical ordinal variable. We fitted the data into the following equations:

Model Family 1: Age

M1, linear function: Adjusted Volume = Intercept + β_1(Age)*

M2, quadratic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2)*

M3, cubic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2) + β_3*(Age^3)*

Model Family 2: Age and puberty

M4, linear function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Puberty) + β_3*(Age*Puberty)*

M5, quadratic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2) + β_3*(Puberty) + β_4*(Age*Puberty) + β_5*(Age^2*Puberty)*

M6, cubic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2) + β_3*(Age^3) + β_4*(Puberty) + β_5*(Age*Puberty) + β_6*(Age^2*Puberty) + β_7*(Age^3*Puberty)*

Model Family 3: Age and sex

M7, linear function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Sex) + β_3*(Age*Sex)*

M8, quadratic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2) + β_3*(Sex) + β_4*(Age*Sex) + β_5*(Age^2*Sex)*

M9, cubic function: Adjusted Volume = Intercept + β_1(Age) + β_2*(Age^2) + β_3*(Age^3) + β_4*(Sex) + β_5*(Age*Sex) + β_6*(Age^2*Sex) + β_7*(Age^3*Sex)*

We used the second-order Akaike information criterion (AICc) to compare all models (linear and nonlinear) for each hippocampal subregion and select the best-fitting model (K. Burnham & Anderson, 2002; Hurvich & Tsai, 1989). We used AICc because a second-order bias adjustment is required when the ratio between the sample size and the number of parameters (n/K) is small (≤ 40) (K. P. Burnham & Anderson, 2004). We selected the best-fitting model based on the lowest AICc value (K. P. Burnham & Anderson, 2004). We finally report the F test result of the best model, with the alpha level set at $p<0.05$.

RESULTS

Participants

There were 247 typically developing participants eligible for our study with T1-weighted images and pubertal scores. We excluded 64 participants with failed segmentations; therefore, 183 participants were included in our analysis (95 F, 88 M, age range: 6-21 years, mean ± SD age: 12.19 ± 3.63 years). The age distribution for each sex and puberty category are presented in Figure 1 and Supplementary Tables 1.2 and 2. The age distribution by sex for each scanner site is provided in Supplementary Figure 1.

Age-only model selection for the antHC and postHC volumes

The adjusted antHC and postHC volumes show disparate age-related effects from childhood to early adulthood (Figure 2). For all subregions, the best-fitting models were the age-only models, suggesting that neither sex nor puberty contributed to a significantly better model than age alone (see Supplementary Tables 6.1, 7 and 8). Although a linear function best represented the relationship between the antHC volume and age, this association was not statistically significant ($F_{(1,181)}$=2.772, Adjusted R^2=0.01, p= 0.098). Conversely, the postHC showed a significant non-linear relationship with age. The postHC volume is best represented with a cubic function across age ($F_{(3,179)}$=4.574, Adjusted R^2=0.06, p=0.004). In addition, age improves a model that first began with pubertal status (see Supplementary Table 10). Thus, we observed distinct age-related effects for the antHC and postHC volumes during development.

Volumetric distribution for each subregion by sex and puberty

We plotted the adjusted volumes for each hippocampal subregion by sex and pubertal stage for visualization purposes to ensure that sex and puberty in our analyses were not masking more subtle effects (Figure 3). We observed similar distributions in females and males for each subregion, as well as similar distributions across pubertal stages. We further evaluated regression models for each subregion using the main effects of puberty and sex with age without the interaction terms and found that neither puberty nor sex were significant in our sample (see Supplementary Table 11).

DISCUSSION

Given emerging evidence of distinct functional contributions of the antHC and postHC in memory processes and representations, their age-related effects on volume and whether these are influenced by sex or puberty during this time-period requires characterization to provide a more complete picture of hippocampal development. Here, we used model selection to evaluate the influence of sex and pubertal state on the volumes of the hippocampal subregions defined along its longitudinal axis in 6-21 year olds. We anticipated a non-linear age-effect for both subregions, but only the postHC had a significant cubic relationship between volume and age. Specifically, the postHC shows age-related volume increases

during this period, but the rate of change decreases during adolescence. Furthermore, sex and pubertal status did not significantly improve model performance either for the antHC or postHC volumes. Thus, our findings confirm distinct age-related effects for the antHC and postHC.

The antHC volume showed a linear relationship with age, but this relationship was not significant in our sample, indicating volumetric stability from age 6 to 21 years. Our finding is in line with previous evidence of a non-significant relationship between antHC volume and age from age 8 to 25 years (Daugherty et al., 2017). However, our finding also diverges from other previous studies. The first study to explore the structural development of the hippocampal long axis for individuals aged 4-25 years reported non-linear (quadratic) volume decrease within regions of the antHC and increase within regions the postHC with age (Gogtay et al., 2006). Schlichting and colleagues observed an inverted quadratic trajectory (5-30 years) of the antHC over time, with an initial rapid increase during childhood, reaching peak volume during adolescence, and volume decrease during late adolescence and adulthood (Schlichting et al., 2017). It is possible that volume decline in the antHC is more pronounced well into late adolescence and adulthood, and therefore the reason we did not observe such a pattern here may be due to our sample's more restricted upper age limit of 21 years. AntHC volume growth has only recently been characterized in childhood (4-8 years old) (Canada, Botdorf, & Riggins, 2020), and specifically in the CA1 subfield in children aged between 4-5 years only, suggesting that the antHC grows before age 6 and at the level of subfields (Canada, Hancock, & Riggins, 2021).

The postHC volume shows a significant cubic relationship with age. This trajectory indicates three periods of development: an initial age-related volume increase in childhood, followed by a decline during adolescence and a further increase in early adulthood. Compared to previous studies, we have captured the volume of the entire postHC. For example, Gogtay and colleagues compared linear, quadratic, and cubic functions and observed a U-shaped quadratic volumetric trajectory within specific regions of the postHC (Gogtay et al., 2006). When evaluating the hippocampal body (part of the postHC), others fitted a quadratic U-shaped trajectory, defining a low point in adolescence, with

increased volume in early adulthood (Daugherty et al., 2017; Schlichting et al., 2017). Our results are thus indicative of an overall cubic relationship between postHC volume and age, characterized by initial and later volume increase with a decrease during adolescence.

The underlying neurological basis of such remodeling during maturation has not been characterized, as it is still not possible to identify the correlates of such age-related effects on the hippocampus with volumetry. Some possibilities identified in rodent and non-human primate histological studies include cell proliferation, increased synaptogenesis, dendritic arborization, pruning and/or glial changes (for a review, see: Brenhouse & Andersen, 2011). A previous high-field neuroimaging study characterized subfield composition differences between antHC and postHC in adults, and found that the postHC hosts a larger portion of the dentate gyrus, the site for neurogenesis, compared to antHC (Malykhin, Lebel, Coupland, Wilman, & Carter, 2010). It is thus possible that our structural observations are related to differences in their cellular and molecular substrates and how they influence normal development.

How might regional differences in the development of hippocampal volume relate to memory function? Changes in structural development have been observed concurrently with changes in memory abilities, attributing childhood amnesia (typically until 3 years old, but may extend to 6 years) to immaturity of the hippocampus (Bouyeure & Noulhiane, 2020; Lavenex & Banta Lavenex, 2013) and improvement of episodic memory to the maturation of hippocampal subregions (D. DeMaster, Pathman, Lee, & Ghetti, 2014; Keresztes et al., 2017; Lee, Ekstrom, & Ghetti, 2014; Lee et al., 2020) and the cortex (Ofen et al., 2007). The first longitudinal study to evaluate concurrent volumetric changes of hippocampal subregions with relational memory from middle childhood to adolescence found distinct associations between volumetry and memory processes (Lee et al., 2020). Relational memory improvements (item-item memory) were associated with hippocampal head (antHC) and body (part of the postHC) growth in older children, while right tail growth was associated with item-space memory. In young adults, better recollection memory was associated with smaller antHC and larger postHC volumes

from four different datasets (Poppenk & Moscovitch, 2011). When comparing adults (aged 18-25 years) and children (aged 8-11 years), adults had larger hippocampal bodies than children (D. DeMaster et al., 2014). In adults, increased volume was related to better episodic recollection. Furthermore, volume increases in the postHC have been associated with improvements in memory and navigation in adult taxi drivers (Woollett & Maguire, 2011). As such, postHC volume increases, such as those which we observed in our sample, may correlate with memory capacity or fidelity. From a network perspective, the functional connectivity gradient of the postHC and antHC was previously mapped with cortical structures (e.g., perirhinal and parahippocampal gyrus) (Libby, Ekstrom, Ragland, & Ranganath, 2012), but whether they develop concurrently with structural changes remains to be determined. Such information at the network level could enhance our understanding of not only the heterogeneity of hippocampal development along its longitudinal axis, but the development of relevant conceptual and episodic memory processes during this time-period.

Models including sex did not significantly improve the fit of our data for the antHC and postHC volumes, and visual inspection confirms that there is little discernable impact of this variable (see Supplementary Figure 3 for eICV correction). One previous study in a sample of 8-30 year-old participants found no sex by age interaction for whole hippocampal volumes, but the antHC and postHC volumes were not assessed separately (Koolschijn & Crone, 2013). Similar findings were observed in children (aged 4-9 years), where age and sex together were not associated with volume change of the antHC and hippocampal body (excluding tail) (Riggins et al., 2018). On the other hand, we had anticipated sexual dimorphism for hippocampal subregions given recent neuroimaging evidence in individuals between 5 and 25 years of age (Fish et al., 2020). Differences in hippocampal volume trajectories for females and males were more accentuated in late adolescence and early adulthood, such that a pronounced growth was observed in males compared to females. Given that previous studies did not evaluate the effects of age with sex for the antHC and postHC volumes separately using model

selection, our findings add to a growing neuroimaging literature exploring the effect of age and sex in normative development in hippocampal subregions.

Contrary to hypotheses, pubertal status did not improve the performance of the antHC and postHC volume developmental trajectory models. The rise in sex hormones during puberty may be expected to directly influence hippocampal structure, given the high concentration of androgen and estrogen receptors on pyramidal neurons (Clark, MacLusky, & Goldman-Rakic, 1988; Morse, Scheff, & DeKosky, 1986). Histological studies in rodents and non-primates show an increase in dendritic spine number and density in pyramidal cells of the hippocampus in response to increased concentration of gonadal hormones (Cooke & Woolley, 2005; Cunningham, Claiborne, & McGinnis, 2007; Hao et al., 2003; Leranth, Petnehazy, & MacLusky, 2003; Woolley & McEwen, 1992). However, such histological changes have not been directly correlated in neuroimaging studies given the paucity of post-mortem evidence. One neuroimaging study investigated the effect of puberty on whole hippocampal volume while controlling for age and found a puberty-by-sex interaction, such that post-pubertal females had larger volumes than males, particularly in the postHC, but no differences were identified between pre-pubertal females and males (Satterthwaite et al., 2014). When evaluating hippocampal volume in function of age and pubertal development, most structural studies have assessed the effect of puberty within each sex separately. For example, Goddings and colleagues found that hippocampal growth in females was influenced by both age and puberty, while an age-only model best accounted for the variance in males (Goddings et al., 2014). Wierenga and colleagues did not find age-by-puberty effects in hippocampal volume changes in 8-26-year-olds, but did not investigate subregions, which have differential trajectories (Wierenga et al., 2018). Thus, we propose that puberty did not significantly improve model performance in the development of the antHC and postHC volumes from childhood to adulthood.

Our cross-sectional study design limits us to identify age-related effects rather than developmental trajectories as has been done in other work (Fish et al., 2020; Goddings et al., 2014;

Gogtay et al., 2006; Herting et al., 2018). Given that puberty and sex did not significantly improve the performance of our age models, it is important to continue evaluating their effects in sufficiently powered longitudinal designs. Drawing comparisons with the literature can be challenging, because of differences in (1) age ranges sampled, which may account for differences in model fit in non-linear trajectories (Fjell et al., 2010); and (2) in methodology [e.g., segmentation protocols, inability of volumetry to detect subtle differences, pubertal measurements (hormone concentration, qualitative scores), nature of pubertal scores (continuous or categorical)]. As others have documented, it is possible that anatomical changes are also occurring at the finer-grain level of subfields within the antHC and postHC (Riggins et al., 2018). Such analyses require different scan acquisition parameters to capture a better resolution for mapping hippocampal subfields (Wisse et al., 2021). Thus, investigations of subfields within the antHC and postHC could further our understanding of structural and memory development from childhood to adulthood.

In conclusion, hippocampal development is heterogenous, with distinct age-related effects in the antHC and postHC. Our findings align with other studies reporting non-linear age effects on postHC volumes and further indicate that the age-only model best represented this relationship in 6–21 year olds. Whether such changes are facilitators or consequences of memory development, and how structural and functional changes relate to one another, are topics for future research.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The neuroimaging data that support the findings of this study are publicly available on the Child Mind Institute Healthy Brain Network database (Alexander et al., 2017).

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FIGURES

Figure 1. Age distribution of participants included in the analysis for each pubertal category by sex.

Figure 2. Age-related effects on the anterior and posterior hippocampal volumes. The segmentation of the hippocampal subregions is represented by best-fitted age-only models. Volumes of the anterior hippocampus (antHC) are represented in red and the posterior hippocampus (postHC) in green and purple. The grey area represents the 95% confidence interval.

Figure 3. Visualization of anterior and posterior hippocampal volumes by sex (A) and pubertal stage (B). The volumetric distribution (median and interquartile range) of each hippocampal subregion is displayed separately for females (F) and males (M) in panel A, and for each pubertal stage (pre-puberty, puberty, and post-puberty) in panel B.