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Longitudinal development of hippocampal subregions from childhood to adulthood

Christian K. Tamnes[a,*], Marieke G.N. Bos[b,c], Ferdi C. van de Kamp[b], Sabine Peters[b,c], Eveline A. Crone[b,c]

[a] Department of Psychology, University of Oslo, Oslo, Norway
[b] Institute of Psychology, Leiden University, Leiden, The Netherlands
[c] Leiden Institute for Brain and Cognition, Leiden, The Netherlands

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ABSTRACT

Detailed descriptions of the development of the hippocampus promise to shed light on the neural foundation of development of memory and other cognitive functions, as well as the emergence of major mental disorders. Hippocampus is a heterogeneous structure with a well characterized internal complexity, but development of its distinct subregions in humans has remained poorly described. We analyzed magnetic resonance imaging (MRI) data from a large longitudinal sample (270 participants, 678 scans) using an automated segmentation tool and mixed models to delineate the development of hippocampal subregion volumes from childhood to adulthood. We also examined sex differences in subregion volumes and their development, and associations between hippocampal subregions and general cognitive ability. Nonlinear developmental trajectories with early volume increases were observed for subiculum, cornu ammonis (CA) 1, molecular layer (ML) and fimbria. In contrast, parasubiculum, presubiculum, CA2/3, CA4 and the granule cell layer of the dentate gyrus (GC-DG) showed linear volume decreases. No sex differences were found in hippocampal subregion development. Finally, general cognitive ability was positively associated with CA2/3 and CA4 volumes, as well as with ML development. In conclusion, hippocampal subregions appear to develop in diversified ways across adolescence, and specific subregions may link to general cognitive level.

1. Introduction

Knowledge of the development of the hippocampus from childhood to adulthood is important for understanding the neural foundation of development of cognitive functions, including episodic memory (Ghetti and Bunge, 2012; Østby et al., 2012). Moreover, it may offer insight into the origin and ontogeny of major mental disorders including schizophrenia and depression, which frequently emerge in adolescence (Lee et al., 2014a; Whiteford et al., 2013), and for which the hippocampus appears to be a key node in the underlying distributed brain networks (Schmaal et al., 2016; van Erp et al., 2016). Magnetic resonance imaging (MRI) studies have investigated age-related differences or longitudinal changes in hippocampal volume in children and adolescents. The hippocampus is however not a uniform structure, but contains anatomically and functionally distinct regions (Amaral and Lavenex, 2007). It is thus possible that different subregions develop differently.

Hippocampal volume increases during childhood (Brown et al., 2012; Gilmore et al., 2012; Hu et al., 2013; Swagerman et al., 2014; Uematsu et al., 2012), but results for the adolescent period have been more variable. Several cross-sectional studies (Koolschijn and Crone, 2013; Muftuler et al., 2011; Yurgelun-Todd et al., 2003; Østby et al., 2009) and some longitudinal studies (Mattai et al., 2011; Sullivan et al., 2011) found no significant age effects. More recent longitudinal studies have found volume increase (Dennison et al., 2013), decrease (Tamnes et al., 2013), or a quadratic inverted U-shaped trajectory (Narvacan et al., 2017; Wierenga et al., 2014). The latter finding is supported by a recent multisite longitudinal developmental study (Herting et al., 2018) and a large cross-sectional lifespan study (Coupe et al., 2017).

Estimating whole hippocampal volume may however mask regional developmental differences. Anatomically, the hippocampus is a unique structure consisting of cytoarchitectonically distinct subregions, including the cornu ammonis (CA) subfields, the dentate gyrus (DG) and the subicular complex (Insausti and Amaralx, 2012). The hippocampal formation also has a unique set of largely unidirectional, excitatory pathways along the transverse plane (Amaral and Lavenex, 2007).

* Corresponding author at: Department of Psychology, University of Oslo, P.O. Box 1094, Blindern, 0317 Oslo, Norway.
E-mail address: c.k.tamnes@psykologi.uio.no (C.K. Tamnes).

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Despite this well characterized internal complexity, researchers studying the human hippocampus *in vivo* have traditionally modelled and measured it as a whole (but see (Insausti et al., 2010)). Novel protocols to segment the hippocampal subregions in MRI images have however been developed. Analysis of subregion within the hippocampus may unravel heterogeneous developmental patterns with differential functional relevance.

A pioneer study indicated different developmental changes in subareas of the hippocampus, mainly with increases in posterior areas and decreases in anterior areas (Gogtay et al., 2006). This was partly supported by a study investigating age-related differences in the head, body and tail of the hippocampus, finding an increase in the volume of the body and decreases in the right head and tail (DeMaster et al., 2014). Other studies have investigating the development of more clearly defined hippocampal subregions, including its subfields. Krogsrud et al. (2014) found that most subregions showed age-related volume increases from early childhood until approximately 13–15 years, followed by little differences. For a subsample of these participants, Tamnes et al. (2014) performed a longitudinal follow-up and found that change rates were different across subregions, but that nearly all showed small volume decreases in the teenage years. Combined, these results fit with the observed inverted U-shaped trajectory for whole hippocampal volume. Based on manual segmentation of subfields in the hippocampus body, Lee et al. (2014b) found age-related increases in the right CA1 and CA3/DG volumes into early adolescence. Finally, in a lifespan sample, Daugherty et al. (2016) performed manual tracing on slices in the anterior hippocampus body and found negative relationships with age during development for CA1/2 and CA3/DG volumes.

Together, these results suggest that hippocampal subregions continue to change in subtle and diverse ways through childhood and adolescence, but the available studies have major limitations. First, several of the studies had relatively small samples. Second, only two of the studies had longitudinal data (Gogtay et al., 2006; Tamnes et al., 2014) and could investigate growth trajectories. Third, two of the previous studies (Krogsrud et al., 2014; Tamnes et al., 2014) used an automated segmentation procedure (Van Leemput et al., 2009) for which the reliability and validity has later been challenged (de Flores et al., 2015; Wisse et al., 2014), and these results have to be interpreted with caution. The other two studies of specific subregions (Daugherty et al., 2016; Lee et al., 2014b) used manual tracing protocols (Ekstrom et al., 2009; Mueller et al., 2007) which yield estimates of a smaller number regions measured only in the hippocampal body. Moreover, manual segmentation is laborious and can be infeasible for large longitudinal studies, and also requires some subjectivity and is thus vulnerable to bias (Schlichting et al., 2017b). The manual methods are thus not optimal in the context of the increasing focus on larger samples to obtain adequate statistical power (Button et al., 2013) and open science and reproducibility (Nichols et al., 2017). On the other hand, however, automated methods have potential limitations related to validity, e.g., the segmentation tool can be biased towards a different age group or a different type of sample (see Limitations section).

We aimed to partially address some of the shortcomings of the previous studies by analyzing data from a large longitudinal sample of 270 participants with 678 MRI scans in the age-range 8–28 years using a novel automated segmentation tool. Specifically, we aimed to characterize the development of hippocampal subregion volumes from childhood to adulthood. Second, previous studies of sex differences in hippocampal development have been inconsistent (Herting et al., 2018), so we aimed to investigate whether hippocampal subregion volumes and development differs between girls and boys. Finally, we aimed to investigate how hippocampal subregions related to general cognitive ability, which previous studies have found to be related to cortical and white matter structure and development (Shaw et al., 2006; Tamnes et al., 2010; Walhovd et al., 2016).

2. Materials and methods

2.1. Procedure and participants

The current study was part of the accelerated longitudinal research project *Braintime* (Becht et al., in press; Bos et al., in press; Peters and Crone, 2017; Schreuders et al., in press) performed in Leiden, the Netherlands, and approved by the Institutional Review Board at Leiden University Medical Center. Hippocampal subregions have not previously been analyzed in this project. At each time-point (TP), informed consent was obtained from each participant or from a parent in case of minors. Participants received presents and parents received financial reimbursement for travel costs. The participants were recruited through local schools and advertisements across Leiden, The Netherlands. All included participants were required to be fluent in Dutch, right-handed, have normal or corrected-to-normal vision, and to not report neurological or mental health problems or use of psychotropic medication. An initial sample of 299 participants (153 females, 146 males) in the age range 8–26 years old was recruited. All participants were invited to participate in three consecutive waves of data collection approximately two years apart. General cognitive ability was estimated at TP1 and TP2 using different subtests from age-appropriate Wechsler Intelligence Scales (WISC and WAIS) to avoid practice effects; TP1: Similarities and Block Design; TP2: Picture Completion and Vocabulary; TP3: no measurement. All included participants had an estimated IQ ≥ 80.

The final sample for the current study consisted of participants who had at least one structural MRI scan that was successfully processed through both the standard and hippocampal subfield segmentation longitudinal pipelines of FreeSurfer and which passed our quality control (QC) procedure (see below). This yielded a dataset consisting of 270 participants (145, females, 125 males) with 678 scans (Table 1); 169 participants had scans from 3 TP s, 70 participants had scans from two TPs, and 31 participants had one scan. The mean number of scans per participants was 2.51 (SD = 0.69). The mean interval for longitudinal follow-up scans in the final dataset was 2.11 years (SD = 0.46, range = 1.55–4.43).

2.2. Image acquisition

All scanning was performed on a single 3-T Philips Achieve whole body scanner, using a 6 element SENSE receiver head coil (Philips, Best, The Netherlands) at Leiden University Medical Centre. T1-weighted anatomical scans with the following parameters were obtained at each TP: TR = 9.8 ms, TE = 4.6 ms, flip angel = 8°, 140 slices, 0.875 mm × 0.875 mm × 1.2 mm, and FOV = 224 × 177 × 168 mm. Scan time for this sequence was 4 min 56 s. There were no major scanner hardware or software upgrades during the MRI data collection period. A radiologist reviewed all scans at TP1 and no anomalous findings were reported.

2.3. Image analysis

Image processing was performed on the computer network at Leiden University Medical Center. Whole-brain volumetric segmentation and

Table 1
Sample characteristics for each time-point (TP).

	TP1	TP2	TP3
n	237	224	217
n females/males	128/109	118/106	119/98
Age, mean (SD)	14.5 (3.7)	16.4 (3.6)	18.4 (3.7)
Age, range	8.0–26.0	9.9–26.6	11.9–28.7
Estimated IQ, mean (SD)	110.0 (10.2)	108.5 (10.1)[a]	–
Estimated IQ, range	80–138	80–148[a]	–

[a] Data missing for 1 participant.