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Regional Hippocampal Volumes and Development Predict Learning and Memory

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Key Words
Adolescence · Brain maturation · Hippocampal subfields · Longitudinal study · Magnetic resonance imaging · Recall · Retention

Abstract
The hippocampus is an anatomically and functionally heterogeneous structure, but longitudinal studies of its regional development are scarce and it is not known whether protracted maturation of the hippocampus in adolescence is related to memory development. First, we investigated hippocampal subfield development using 170 longitudinally acquired brain magnetic resonance imaging scans from 85 participants aged 8–21 years. Hippocampal subfield volumes were estimated by the use of automated segmentation of 7 subfields, including the cornu ammonis (CA) sectors and the dentate gyrus (DG), while longitudinal subfield volumetric change was quantified using a nonlinear registration procedure. Second, associations between subfield volumes and change and verbal learning/memory across multiple retention intervals (5 min, 30 min and 1 week) were tested. It was hypothesized that short and intermediate memory would be more closely related to CA2-3/CA4-DG and extended, remote memory to CA1. Change rates were significantly different across hippocampal subfields, but nearly all subfields showed significant volume decreases over time throughout adolescence. Several subfield volumes were larger in the right hemisphere and in males, while for change rates there were no hemisphere or sex differences. Partly in support of the hypotheses, greater volume of CA1 and CA2-3 was related to recall and retention after an extended delay, while longitudinal reduction of CA2-3 and CA4-DG was related to learning. This suggests continued regional development of the hippocampus across adolescence and that volume and volume change in specific subfields differentially predict verbal learning and memory over different retention intervals, but future high-resolution studies are called for.

Introduction

The hippocampus is a brain structure of particular interest due to its essential role in learning and memory [1, 2] and in certain developmental [3, 4] and neurodegen-

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erative disorders [5, 6]. Longitudinal studies of the regional structural development of the hippocampus from childhood to adulthood are, however, scarce, and it is not known how this development relates to increasing capacity and efficiency in cognitive functioning. To explore both hippocampal development and its role in memory, we performed a longitudinal study of hippocampal subfields and how these relate to learning and memory performance across multiple time intervals.

Brain development generally involves early increases followed by decreases in cortical and subcortical volumes and monotonically increasing white matter volumes [7–11]. Several magnetic resonance imaging (MRI) studies have investigated age-related differences or longitudinal changes in hippocampal volumes specifically (table 1). It is clear that the hippocampus undergoes growth in childhood [12–14], but studies have given varying results concerning the second decade of life: the majority have not found significant effects [13–17], while others have found volume decreases [18] or increases [19]. Importantly, the hippocampus is anatomically and functionally heterogeneous [20], and insufficient spatial resolution may mask regional developmental patterns. Anatomically, the hippocampus is a unique structure consisting of distinct regions including the cornu ammonis (CA) sectors and the dentate gyrus (DG) [21]. Gogtay et al. [22] found no changes in total hippocampal volumes but found heterogeneous changes in different subareas. Regional differences are also indicated by two recent cross-sectional studies [23; Krogsrud et al., unpubl. data].

Functional MRI studies disagree on whether maturation of the medial temporal lobe in adolescence is relevant for episodic memory development [24] or whether prefrontal areas are more important [25]. Further, functional imaging studies of healthy adults and patients with amnestic mild cognitive impairment and rodent studies have suggested that hippocampal subfields may have different involvement in memory over different time scales. One suggestion is that CA3 and DG are especially important in memory encoding and early retrieval [26, 27], while CA1 plays a more central role in consolidation and late retrieval [28].

Here, we combined an automated hippocampal subfield segmentation procedure [29] and a sensitive method for quantification of change [30]. First, we aimed to provide the first longitudinal characterization of the development of specific hippocampal subfields (n = 85, age range 8–21 years, 170 scans). Second, to investigate how hippocampal subfields in development relate to memory, we tested whether subfield volumes and/or volumetric changes correlate with verbal learning and recall across multiple retention intervals. Based on previous functional MRI and rodent studies [26–28], we tentatively hypothesized that CA2-3 and CA4-DG would be more related to learning and recall over shorter time intervals, and CA1 more to extended memory.

Materials and Methods

Participants

The included subjects were from the longitudinal research project 'Neurocognitive Development' [18, 31] run by the Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo. Children and adolescents aged 8–19 years were recruited though newspaper advertisements and local schools. Written informed consent was obtained from all participants older than 12 years of age and from a parent of participants under 16 years of age, while participants under 12 years of age gave oral informed consent. At both time points, parents and participants aged 16 years or older completed screening for each participant with separate standardized health interviews to ascertain eligibility. Participants were required to be right-handed, be fluent Norwegian speakers, have normal or corrected-to-normal vision and hearing, not have a history of injury or disease known to affect central nervous system (CNS) function, including neurological or psychiatric illness or serious head trauma, not be under psychiatric treatment, not use psychoactive drugs known to affect CNS functioning, not have had complicated or premature birth, and not have MRI contraindications. A senior neuroradiologist evaluated all scans, and participants were required to be deemed free of significant injuries or conditions. The Regional Committee for Medical and Health Research Ethics approved the study.

At time point 1 (TP_1), 111 participants satisfied the inclusion criteria and had adequate processed and quality-checked MRI data. At time point 2 (TP_2), 18 participants did not want to or were unable to participate, 2 were not located, 3 had dental braces and 3 had acquired a neurological or psychiatric condition. The sample for the current study thus included 85 children and adolescents (38 females) who at TP_1 were 8.2–19.4 years old (mean = 13.7, SD = 3.4) and had a mean IQ of 109.0 (SD = 11.4, range = 82–141), as estimated by the Wechsler Abbreviated Scale of Intelligence [32]. At TP_2, the participants were 10.8–21.9 years old (mean = 16.3 years, SD = 3.4) and their mean IQ score was 112.5 (SD = 10.5, range = 87–136). The mean interval between the 2 time points was 2.6 years (SD = 0.2, range = 2.4–3.2). The interval was not correlated with age ($r = -0.03$, $p = 0.772$), and was not different for females and males ($t = 0.42$, $p = 0.675$).

MRI Acquisition

MRI data were collected at 2 time points using a 12-channel head coil on the same 1.5-tesla Siemens Avanto scanner (Siemens Medical Solutions). The pulse sequence used for morphometric analyses was a 3D T1-weighted MPRAGE with the following parameters: TR/TE/TI/FA = 2,400 ms/3.61 ms/1,000 ms/8°, matrix 192 × 192, field of view = 240, 160 sagittal slices, voxel size 1.25 × 1.25 × 1.20 mm. The sequence was repeated at minimum twice in

Table 1. Summary of studies of hippocampal volume development in children and adolescents

Study	Method	Subjects, n	Age range, years	Developmental finding on raw hippocampal volumes	Other findings related to hippocampus
Brown et al. [12], 2012	Cross-sectional, multisite 3 T, FreeSurfer	885	3 – 20	Age-related increase until 14.2 years, followed by slight age-related decrease (spline-fit curve)	
DeMaster et al. [23], Epub ahead of print	Cross-sectional, 3 T, FreeSurfer and manual tracing	62	8 – 11/18 – 26	Not reported	Age-related increases in ICV-adjusted left hippocampus and hippocampal body and decreases in right hippocampal head and tail
Dennison et al. [19], 2013	Longitudinal, multisite 3 T, FreeSurfer	60 (120 scans)	11 – 17	Significant increases	Greater increase in the right hemisphere. Similar results for TBV corrected estimates
Giedd et al. [48], 1996	Cross-sectional, 1.5 T, manual tracing	99	4 – 17	Age-related increase only in right hippocampus in females	Rightward volume asymmetry
Gogtay et al. [22], 2006	Longitudinal, 1.5 T, manual tracing	31 (100 scans)	4 – 25	No significant changes in total hippocampal volumes	Heterogeneous changes in hippocampal subregions
Hu et al. [13], 2013	Cross-sectional, multisite 1.5 T, automatic segmentation	306	4 – 18	Age-related increases before puberty, but no relationships during puberty	During puberty: sex- and hemisphere-specific relationships between normalized hippocampus volumes and puberty score
Koolschijn and Crone [82], 2013	Cross-sectional, 3 T, FreeSurfer	442	8 – 29	Not reported	No association with age after correcting for ICV
Krogsrud et al. [unpubl. data]	Cross-sectional, 1.5 T, FreeSurfer subfield segmentation	244	4 – 22	Age-related volume increase in childhood, followed by little age-related change in adolescence	Age-related increases in most hippocampal subfields in group of children, but no significant relationships for adolescents
Mattai et al. [15], 2011	Longitudinal, 1.5 T, FreeSurfer	79 (198 scans)	10 – 29	Nonsignificant linear decreases over time	Fixed reduction in hippocampal volumes in childhood-onset schizophrenia patients (n = 89) relative to healthy siblings (n = 78) and healthy controls (n = 79)
Muftuler et al. [83], 2011	Cross-sectional, 3 T, FreeSurfer	126	6 – 10	Not reported	No association with age or sex when controlling for ICV
Sullivan et al. [16], 2011	Longitudinal, 3 T, FSL	28 (56 scans)	10 – 13	Nonsignificant increase in combined hippocampus and amygdala volume	
Suzuki et al. [50], 2005	Cross-sectional, 1.5 T, manual tracing	23/30	13 – 14/19 – 21	Not reported	Larger volumes in older than in younger male adolescents when controlling for ICV; no difference in females
Tamnes et al. [18], 2013	Longitudinal, 1.5 T, FreeSurfer and QUARC	85 (170 scans)	8 – 21	Significant decreases	No hemisphere or sex differences in change rates
Uematsu et al. [14], 2012	Cross-sectional, 1.5 T, manual tracing	109	0 – 25	Age-related increases until 9 – 11 years	Rightward volume asymmetry; larger volumes in males than females after peak age, but not before; similar age-related differences after adjustment for ICV
Yurgelun-Todd et al. [84], 2003	Cross-sectional, 1.5 T, manual tracing	37	12 – 17	Not reported	No associations with age after correcting for TBV
Østby et al. [17], 2009	Cross-sectional, 1.5 T, FreeSurfer	171	8 – 30	Nonsignificant age-related increase	Significant age-related increase after correcting for TBV

ICV = Intracranial volume; TBV = total brain volume.

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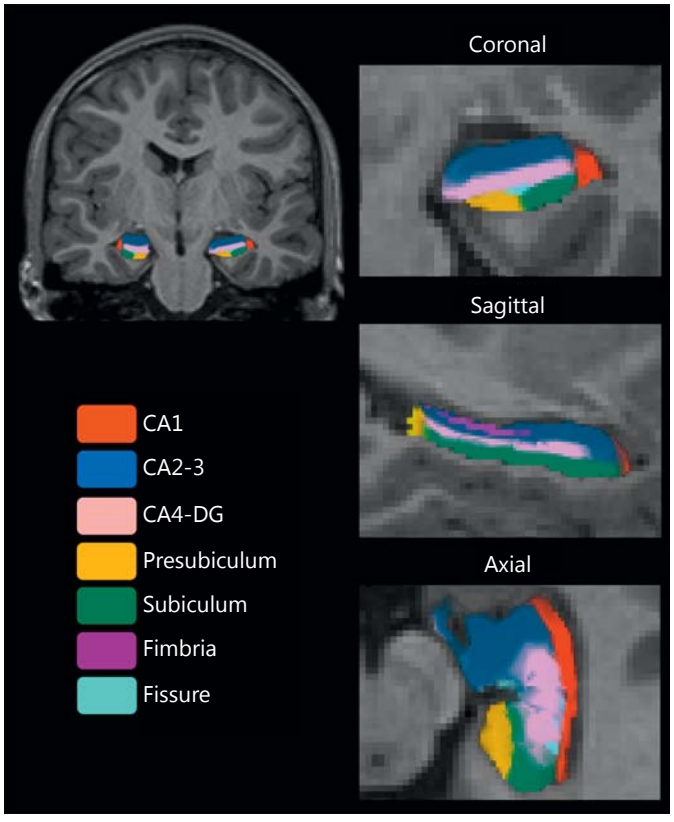

Fig. 1. Hippocampal subfield segmentation. The results of the automated subfield segmentation for 1 subject, a 13-year-old female, superimposed on the subject's T1-weighted scan in coronal, sagittal and axial views. The bright yellow posterior section seen in the sagittal slice is the tail of the hippocampus where the delineation no longer discerns between the different subfields. Fissure = Hippocampal fissure.

each session. Each scan took 7 min 42 s. The protocol also included a 176-slice sagittal 3D T2-weighted turbo spin-echo sequence (TR/TE = 3,390/388 ms) and a 25-slice coronal FLAIR sequence (TR/TE = 7,000–9,000/109 ms) to aid the radiological examination.

MRI Processing and Analysis

All scans were reviewed for quality and automatically corrected for spatial distortion due to gradient nonlinearity [33] and B1 field inhomogeneity [34]. The volumes were coregistered, averaged to increase the signal-to-noise ratio and resampled to isotropic 1-mm voxels. Three scans were used from 21 of the 170 sessions, 4 scans were included from 3 sessions and 2 from the rest. Volumetric segmentation [35, 36] and cortical reconstruction [37–39] were performed with FreeSurfer 5.1 (https://surfer.nmr.mgh.harvard.edu). The procedures were run automatically but required supervision of the accuracy of spatial registration and tissue segmentation. All volumes were inspected for accuracy and minor manual edits were performed on most subjects.

Next, we performed hippocampal subfield segmentation using a new automated technique within the FreeSurfer suite [29, 40]. The procedure uses Bayesian inference and a probabilistic atlas of the hippocampal formation based on manual delineations of subfields in ultra-high-resolution MRI scans [29]. A total of 7 subfield volumes were estimated for each hemisphere: CA1, CA2-3, CA4-DG, presubiculum, subiculum, fimbria and hippocampal fissure. The automated volume measurements of the larger subfields CA2-3, CA4-DG and, to a lesser degree, the subiculum, have been shown to correlate well with manual volume estimates and, unlike manual segmentations, the technique is fully reproducible and fast enough for use in large studies [29]. See figure 1 for an example of the subfield segmentation results in 1 of the participants.

Longitudinal change was quantified using QUARC (quantitative anatomical regional change) [30, 41], as described in detail elsewhere [18]. In brief, the percentage volume outcome measure of change was calculated by registering the TP_1 scan to the TP_2 scan. The processing scheme uses an explicitly inverse-consistent registration approach [30]; QUARC essentially eliminates longitudinal image processing bias by combining forward and reverse image registrations and provides a powerful volumetric change biomarker compared with other state-of-the-art processing schemes [41]. Finally, the hippocampal subfield segmentation [29] was used to obtain percentage volume change estimates in each of the specific subfields. Labels from the TP_2 images were used to extract the average change for each region and the annual percentage volume change from TP_1 was calculated for each participant prior to statistical analyses.

Hippocampal Subfield Segmentation across 1.5 and 3 T

In the present study we used scans obtained at 1.5 T (1.25 × 1.25 × 1.20 mm resolution) compared with the 3-tesla scans (380-μm in-plane resolution; 0.8-mm slice thickness) used for the development of the hippocampal subfield segmentation procedure [29]. Although we have previous good experience with using the procedure on 1.5-tesla scans [42], it is unknown which effects the differences in field strength and image resolution have on the segmentation results. For reliability purposes, 7 children (5 male) aged 6–10 years (mean = 8.4) were therefore scanned on both the 1.5-tesla Siemens Avanto scanner used in the main study and a 3-tesla Siemens Skyra scanner [Krogsrud et al., unpubl. data]. On the 3-tesla scanner, a 16-channel head coil was used and the pulse sequence was a 3D T1-weighted MPRAGE with the following parameters: TR/TE/TI/FA = 2,300 ms/2.98 ms/850 ms/8°, 176 sagittal slices, voxel size 1 × 1 × 1 mm, scan duration 5 min 30 s. Since this validation study included children, we used a parallel imaging technique (iPAT) on both scanners, acquiring multiple T1 scans within a short scan time, enabling us to discard scans with residual movement and average the scans with sufficient quality.

To test for effects of field strength and image resolution differences, hippocampal subfield segmentation results from the 1.5- and 3-tesla scans were correlated (Pearson's correlation coefficients). The results showed strong significant ($p < 0.05$) positive correlations for 6 of the 7 subfields: CA1 ($r = 0.83$), CA2-3 ($r = 0.97$), CA4-DG ($r = 0.96$), presubiculum ($r = 0.85$), subiculum ($r = 0.81$) and hippocampal fissure ($r = 0.80$). The correlation for fimbria was weak and not significant ($r = 0.34$, $p = 0.458$), and this subfield was therefore excluded from all further analyses. The results of the reliability analysis are further discussed in Limitations.

Memory Assessment

Verbal learning and memory was assessed for 84 of the 85 participants at TP_2 using the California Verbal Learning Test (CVLT-II) [43]. We followed the division of episodic memory, suggested by Kesner and Hunsaker [28], in 3 critical time intervals: short-term episodic memory with a duration of seconds, medium or intermediate episodic memory with a duration of minutes to hours, and long or remote episodic memory with a duration of days or more. A list of 16 words from 4 semantic categories was read 5 times consecutively, and each time the participant was immediately instructed to repeat all items she or he could recall. After these 5 trials, a list of 16 new words was read once, with instructions to recall as many of the items as possible. Next, the participant was asked to again freely recall the items from the first list, followed by a cued recall test. After about a 30-min delay during which other tasks were performed, the participant was asked, without having been forewarned, to recall the first list again, followed by cued recall, recognition and forced recognition tests. The final procedure was repeated by telephone after a mean of 7.3 days (SD = 0.7, range = 6–10). To avoid rehearsal effects, the participants were not forewarned about this; therefore, appointments could not be made and 20 of the 84 participants could not be reached within the decided time interval of 6–10 days. For the 64 remaining participants (age range 10.8–21.8 years, mean = 16.2, SD = 3.5, 31 females), the extended retention interval was not different for females and males ($t = 0.12$, $p = 0.906$) and not correlated with age ($r = -0.09$, $p = 0.467$) or number of correctly recalled items ($r = 0.12$, $p = 0.344$). For the current study, we used the total number of words recalled across the 5 learning trials ('learning'), the number of words freely recalled at the 5-min delay trial ('short-delay recall'), the number of words recalled after 30 min ('medium-delay recall') and the number of words recalled after 1 week ('long-delay recall') as the measures of interest.

Statistical Analyses

For each of the hippocampal subfields, we estimated the volume at both time points and the annual percentage volume change. One-sample t tests were performed to test whether mean annual changes were different from zero. General linear models (GLMs) on annual change in all subfields per hemisphere with subfield 6 as within-subject factor were used to test for regional differences in change. Correlation analyses between annual change and age were used to test whether change rates varied across the age range. To illustrate longitudinal changes without any assumption about the form of the curve, we plotted annual change in each hippocampal subfield against age at TP_1 and fitted a nonparametric local smoothing model, the smoothing spline, implemented in MATLAB. We used an algorithm that optimizes smoothing level based on a version of Bayesian information criterion, which provides a way of obviating the need for arbitrarily chosen smoothing levels [44]. To further evaluate changes within individuals across the age span, annual change within each hippocampal subfield was binarized, so that change greater than or equal to zero was counted as increase and negative change was counted as decrease, and displayed as a moving average across age. The participants were divided into 6 age groups: 8–12 years (n = 16, initially aged 8–9 years), 10–14 years (n = 14, initially 10–11 years), 12–16 years (n = 15, initially 12–13 years), 14–18 years (n = 14, initially 14–15 years), 16–20 years (n = 16, initially 16–17 years) and 18–21 years (n = 10, initially 18–19 years) and the percentage of participants showing an increase or a decrease in each subfield in each group was illustrated with stacked bar charts. Next, paired-samples t tests were performed to compare both volume at TP_1 and annual change in the left- and right-hemisphere subfields, and independent-samples t tests were performed to compare volumes and annual changes in males and females.

Behavioral performance on the test of verbal learning and memory (CVLT-II) completed at TP_2 was characterized with descriptive statistics, sex differences were tested with independent-samples t tests and age-related differences were investigated with partial correlations, controlled for sex. Before exploring the relationships between hippocampal subfield volumes and annual change and test performance, we performed a series of GLMs on each of the subfield measures, with hemisphere (left, right) as within-subject factor, each of the test measures as between-subject factor and age and sex as covariates. As none of the hemisphere × test performance interactions were significant ($p > 0.05$), we averaged measures across hemispheres prior to the following analyses. First, we performed partial correlations between both hippocampal subfield volumes at TP_2 and annual changes and learning scores, controlling for age and sex. Second, we performed a series of GLMs on the 3 recall scores, with time (short-delay, medium-delay, long-delay recall) as within-subject factor and age, sex and each of the subfield volumes and annual change rates as covariates. If there was no significant time × subfield measure interaction ($p > 0.05$), the available recall scores for each participant were averaged before we performed partial correlations between both hippocampal subfield volumes at TP_2 and annual change and recall, controlling for age and sex. To additionally control for differences in general cognitive abilities, analyses showing significant relationships between learning/recall performance and subfield volumes or change were repeated with concurrently measured IQ as an additional covariate. Finally, in those cases where there was a significant effect of time and significant relationships were found between subfield measures and recall at selected delays, we computed retention scores (in all cases: long-delay/medium-delay recall) and repeated the partial correlations with these. This was done to get an approximate measure of memory consolidation and maintenance, controlled for effects of encoding and earlier retrieval.

Results

Hippocampal Subfield Volumes and Development

CA2-3 had the largest volume, followed by subiculum, CA4-DG, presubiculum and CA1, while the hippocampal fissure was the smallest subfield (table 2), which is consistent with previous studies employing the same subfield segmentation procedure [45, 46]. Mean annual percentage change was negative in all regions and significant ($p < 0.05$) volume decreases over time were found bilaterally for CA2-3, CA4-DG, the presubiculum, subiculum and hippocampal fissure, as well as in the left CA1 (table 2). Mean annual change in the right CA1 was not significant. Change rates were significantly different across subfields in both the left ($F = 3.33$, $p = 0.028$) and right

Table 2. Hippocampal subfield volumes and developmental change

	Left hemisphere						Right hemisphere					
	volume at TP_1	mean annual change			correlation change and age		volume at TP_1	mean annual change			correlation change and age	
	mean ± SD	%	t	p	r	p	mean ± SD	%	t	p	r	p
CA1	333.3 ± 36.2	–0.14	*–2.07*	0.041	–0.01	0.911	341.1 ± 40.4	–0.09	–1.21	0.229	0.09	0.404
CA2-3	1,051.6 ± 139.1	–0.17	*–4.42*	$<10^{-4}$	–0.17	0.124	1,108.3 ± 129.4	–0.11	*–2.90*	0.005	–0.16	0.144
CA4-DG	570.4 ± 72.5	–0.23	*–5.80*	$<10^{-6}$	–0.10	0.369	595.8 ± 69.6	–0.25	*–5.98*	$<10^{-7}$	0.09	0.425
Presubiculum	521.9 ± 51.6	–0.23	*–5.47*	$<10^{-6}$	–0.11	0.339	511.5 ± 63.2	–0.20	*–4.76*	$<10^{-5}$	0.03	0.797
Subiculum	678.4 ± 63.9	–0.09	*–2.22*	0.029	*–0.24*	0.028	677.7 ± 69.8	–0.11	*–2.75*	0.007	–0.17	0.132
Hippocampal fissure	38.5 ± 14.3	–0.32	*–3.78*	$<10^{-3}$	0.13	0.223	43.3 ± 14.0	–0.33	*–4.33*	$<10^{-4}$	*0.29*	0.007

Mean volumes are in millimeters cubed. The significance of annual change in each subfield was tested with one-sample t tests. Pearson's correlations were performed to test the associations between annual change and age. Significant changes ($p < 0.05$) and correlations with age are shown in italics (n = 85, age range 8–21 years).

($F = 4.91$, $p = 0.003$) hemisphere. Of the subfields, the hippocampal fissure showed the largest annual percentage decreases in both the left and right hemisphere (–0.32 and –0.33%, respectively), followed by CA4-DG (–0.23 and –0.25%) and the presubiculum (–0.23 and –0.20%).

Annual percentage change in the left subiculum was negatively correlated with age, indicating an accelerating volume reduction with higher age. In contrast, annual change in the right hippocampal fissure was positively correlated with age, indicating a decelerating volume reduction. To illustrate volumetric change within individuals in each hippocampal subfield we created plots of the annual percentage volume change by age and bar charts of the percentage of subjects showing the volume increase or decrease within different age categories (fig. 2). Variability in change rates was high for all subfields. Further, for many subfields, for example the presubiculum and the left CA4-DG and CA2-3, volume reductions were greatest in the middle of the age span, before leveling off in late adolescence. The highest percentages of subjects showing volume reductions were also typically seen in the middle age categories. Finally, slight volume increases among the youngest participants were indicated in some subfields, particularly the left subiculum.

Hemisphere and Sex Differences

To test for hemisphere and sex differences in both hippocampal subfield volumes and annual percentage changes, we performed paired- and independent-samples t tests, respectively (table 3). Significantly larger right-hemisphere volumes were seen for CA2-3, CA4-DG and the hippocampal fissure, while no hemisphere differences were seen in the mean annual percentage volume change in any of the subfields ($p > 0.05$). The majority of the subfield volumes were significantly larger in males than in females, specifically bilateral CA1, CA2-3, CA4-DG and the subiculum, and also the left presubiculum. There were, however, no significant sex differences in mean annual percentage volume change in any of the subfields ($p > 0.10$).

Verbal Learning and Memory Performance

On average, females performed better on short- and medium-delay recall, and there were also trend effects in the same direction for learning and long-delay recall (table 4). Age-related improvements were seen on learning and short- and long-delay recall, and there was also a trend effect for medium-delay recall (table 4). Long-delay recall showed the strongest age-related improvement ($r = 0.35$).

Relationships between Verbal Learning and Memory and Hippocampal Subfields

Associations between verbal learning and both hippocampal subfield volumes at TP_2 and annual percent-

Fig. 2. Hippocampal subfield development. The scatter plots show annual percentage volume change in each hippocampal subfield against age, with local smoothing models. The stacked bar charts illustrate the percentage of subjects showing volume increase (green) or decrease (red) in each subfield within 6 age categories.

(For figure see next page.)

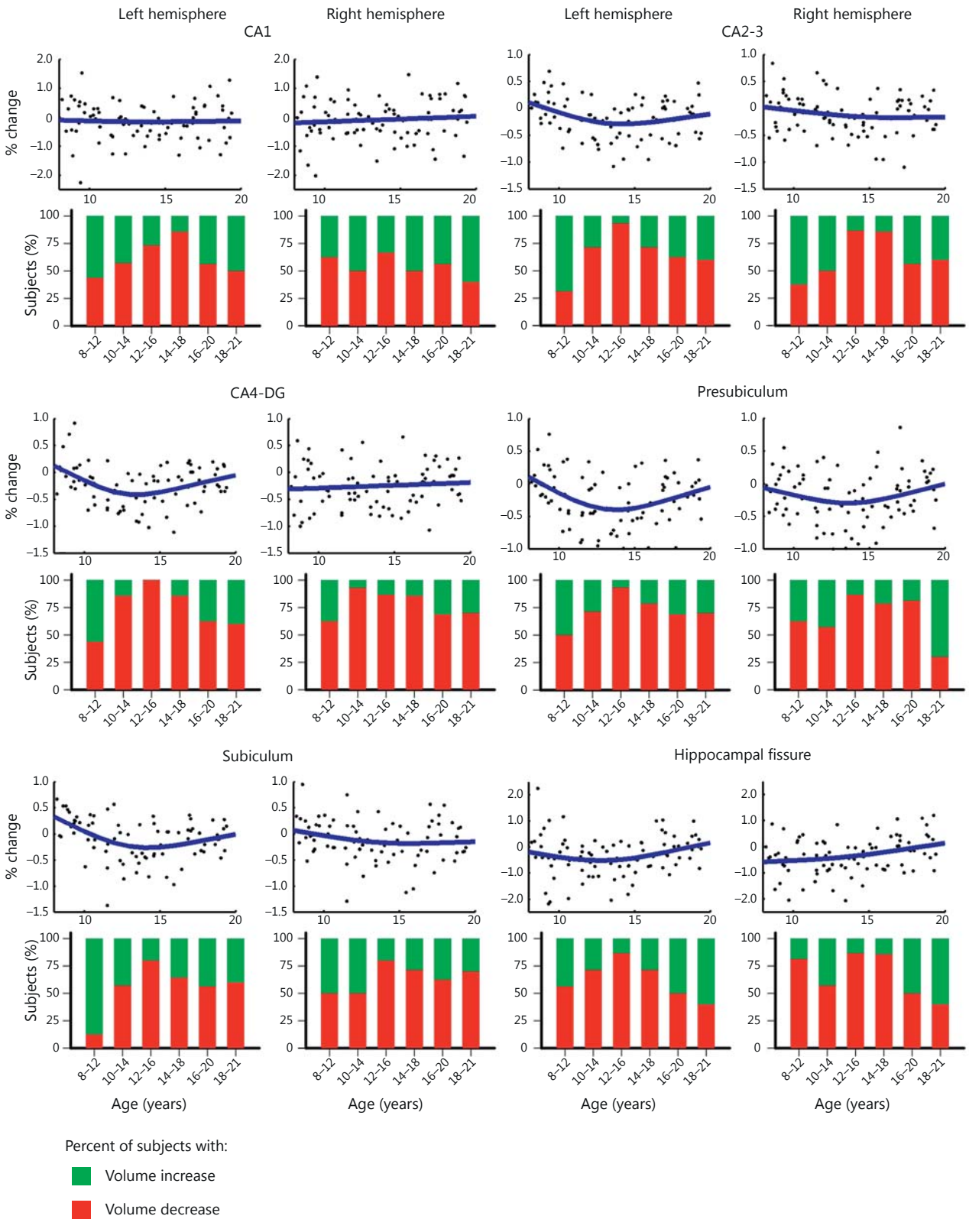

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Table 3. Hemisphere and sex differences in hippocampal subfield volumes and change

	Hemisphere difference				Sex difference LH				Sex difference RH			
	volume at TP_1 (LH-RH)		mean annual change (LH-RH)		volume at TP_1 (M-F)		mean annual change (M-F)		volume at TP_1 (M-F)		mean annual change (M-F)	
	t	p	t	p	t	p	t	p	t	p	t	p
CA1	–1.98	0.051	–0.81	0.419	*4.15*	*<10^{-4}*	1.02	0.311	*3.23*	0.002	0.26	0.793
CA2-3	*–5.36*	*<10^{-6}*	–1.86	0.066	*4.41*	*<10^{-4}*	–0.96	0.341	*4.47*	*<10^{-4}*	–0.77	0.444
CA4-DG	*–4.72*	*<10^{-5}*	0.47	0.638	*4.43*	*<10^{-4}*	–0.92	0.363	*3.93*	*<10^{-3}*	–1.32	0.190
Presubiculum	1.71	0.091	–1.11	0.271	*2.39*	0.019	0.00	0.999	1.81	0.074	–1.49	0.140
Subiculum	0.11	0.909	0.58	0.564	*3.70*	*<10^{-3}*	–1.44	0.154	*3.92*	*<10^{-3}*	–0.54	0.957
Hippocampal fissure	*–3.05*	0.003	0.04	0.966	–0.45	0.657	0.99	0.328	–0.71	0.482	–0.75	0.454

The significance of hemisphere differences in subfield volumes and annual percentage change were tested with paired-samples t tests. Sex differences were tested with independent-samples t tests. Significant differences ($p < 0.05$) are shown in italics (n = 85, age range 8–21 years). LH = Left hemisphere; RH = right hemisphere.

Table 4. Verbal learning and memory performance

	Total sample		Females		Males		Sex difference		Correlation performance and age	
	mean ± SD	range	mean ± SD	range	mean ± SD	range	t	p	r	p
Learning	61.3±7.5	37–79	63.0±6.3	48–74	60.0±8.2	37–79	1.88	0.063	*0.22*	0.041
Short-delay recall	13.5±2.3	7–16	14.1±1.9	8–16	13.1±2.6	7–16	*2.01*	0.048	*0.22*	0.043
Medium-delay recall	14.0±2.2	7–16	14.6±1.8	8–16	13.5±2.4	7–16	*2.37*	0.020	0.21	0.064
Long-delay recall	10.3±3.6	2–16	11.0±3.0	3–16	9.7±4.0	2–16	1.52	0.134	*0.35*	0.005

Verbal learning and memory were assessed at TP_2 using the CVLT-II and the following variables: total number of words recalled across the 5 learning trials (learning), free recall after 5 min (short-delay recall), free recall after 30 min (medium-delay recall) and free recall after approximately 1 week (long-delay recall). The significance of sex differences in performance were tested with independent-samples t tests and associations with age were examined with partial correlations, controlling for sex. Significant effects ($p < 0.05$) are shown in italics (n = 84, n = 64 at long-delay recall).

age volume change were investigated with partial correlations, controlling for age and sex. Negative associations were found between learning and change in CA2-3 ($r = –0.23$, $p = 0.039$) and CA4-DG ($r = –0.28$, $p = 0.011$; fig. 3), while there were no significant associations between learning and hippocampal subfield volumes. To test whether the observed relationships between learning and change in CA2-3 and CA4-DG were influenced by differences in general cognitive abilities, these analyses were repeated with IQ as an additional covariate. In both cases the relationships remained virtually identical ($r = –0.24$, $p = 0.031$ and $r = –0.29$, $p = 0.008$, respectively).

Before testing the associations between verbal recall and hippocampal subfields, we performed GLMs to test the effect of retention interval time. The results showed significant effects of test interval (short-, medium- and long-delay recall) on the relationship between memory score and subfield measure only for volume of CA1 ($F = 3.99$, $p = 0.039$) and CA2-3 ($F = 3.96$, $p = 0.040$). For these measures we performed follow-up analyses on the 3 recall measures separately, while for the other measures we combined the available recall scores across all test intervals for each participant (see Statistical Analyses). Associations between verbal recall and both hippocampal subfield volumes and annual percentage volume change were then investigated with partial correlations, controlling for age and sex. Positive associations were found between long-delay recall and volume of CA1 ($r = 0.27$, $p = 0.034$) and CA2-3 ($r = 0.28$, $p = 0.030$; fig. 3), while

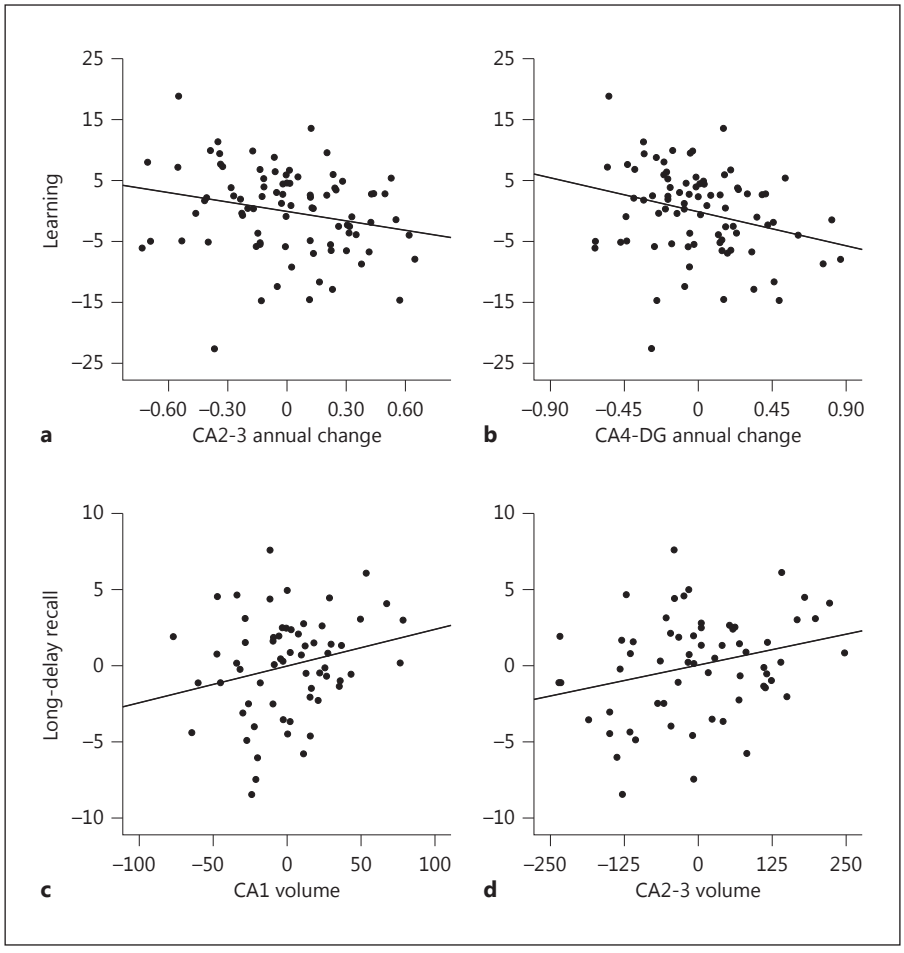

Fig. 3. Relationships between learning/memory and hippocampal subfields. The plots show residuals of each variable after controlling for age and sex and the associations between learning performance and annual percentage volume change in CA2-3 (**a**) and CA4-DG (**b**) and long-delay recall performance and volume of CA1 (**c**) and CA2-3 (**d**). The fit lines correspond to the partial correlations.

there were no significant associations between short- or medium-delay recall and these volumes. Further, there were no significant associations between the averaged recall score and volume of the other hippocampal subfields or change in any of the subfields. To test whether the observed relationships were influenced by general cognitive abilities, the partial correlation analyses between long-delay recall and volumes of CA1 and CA2-3 were repeated with IQ as an additional covariate. In both cases, the relationships were only slightly weaker, but not significant ($r = 0.24$, $p = 0.061$ and $r = 0.23$, $p = 0.075$, respectively). Last, we performed partial correlations between long-delay retention (long-delay/medium-delay recall) and volume of CA1 and CA2-3, controlling for age and sex, and both of the associations remained significant ($r = 0.29$, $p = 0.025$ and $r = 0.28$, $p = 0.030$, respectively).

Discussion

The present research provides the first longitudinal delineation of the development of hippocampal subfield volumes in adolescence, and examines associations with verbal learning and memory across multiple retention intervals. Most subfields showed significant volume decreases over time, indicating continued development across adolescence. Moreover, volume and volumetric change in specific subfields differentially predict verbal learning and memory performance. Below, we first discuss the developmental subfield changes, before turning to the relationship to memory.

Hippocampal Subfield Development

Several MRI studies have investigated age-related differences in hippocampal volumes (table 1), but cross-sectional designs may not be sufficiently sensitive since medial temporal lobe structures show relatively small changes

during adolescence [18]. Longitudinal studies investigating global hippocampal development across adolescence have, however, also yielded inconsistent results. We have previously found volume decreases [18], and Mattai et al. [15] observed trend decreases in patients with childhood-onset schizophrenia, healthy siblings and healthy controls. In contrast, Dennison et al. [19] found hippocampal volume increases, although different scanners were used across time points. There are several probable sources of this disparity, including differences in age span, image processing and statistical models used [44]. Moreover, results from Gogtay et al. [22] indicated that selected posterior hippocampal subregions increase over time, while selected anterior subregions decrease, suggesting that the above inconsistency may partly be due to assessing the hippocampus as a whole. Regionally specific developmental patterns are also indicated by a cross-sectional study by DeMaster et al. [23], where young adults had a larger hippocampal body bilaterally and smaller right hippocampal head and tail compared to older children.

The hippocampus formation comprises cytoarchitectonically distinct subfields along largely unidirectional transverse pathways [21], and procedures for reproducible automated subfield segmentation are now available [29, 47]. Our recent cross-sectional results based on 244 participants (aged 4–22 years) indicate that most hippocampal subfields show substantial volume increases until early adolescence [Krogsrud et al., unpubl. data]. The current longitudinal results extend these findings by showing that volumes of CA2-3, CA4-DG, the presubiculum, subiculum, hippocampal fissure and the left CA1 decrease over time throughout adolescence. The variability in change rates was high, but for several subfields the volume reductions appeared to be greatest in mid-adolescence. Early increases in hippocampal subfields volumes thus appear to be followed by small volume reductions in adolescence, which are detectable with sensitive longitudinal methods.

The present results showed larger right-hemisphere CA1, CA2-3 and CA4-DG subfields, which are consistent with studies on total hippocampal volume in children and adolescents [14, 48], as well as with findings in adults [49]. Recently, it has been indicated that the hippocampal hemispheric asymmetry emerges during adolescence [19]. In the current subfield results, however, none of the subfields showed hemisphere differences in change rates. Further, while earlier cross-sectional studies have found conflicting sex-specific hippocampal age-related differences [48, 50], the present results showed that although the majority of the hippocampal subfields were larger in males, there were no sex differences in change rates.

Relationship to Memory

Developmental changes within brain systems partly parallel behavioral changes [51], and it has even been suggested that the shape of brain developmental trajectories may be more strongly related to functional characteristics than absolute measures at any given point. We tested this 'journey as well as the destination' tenet [52, p. 733], by investigating whether concurrent volumes and/or preceding developmental changes in hippocampal subfields predicted verbal learning and memory. Moreover, functional MRI, patient and rodent studies have indicated that hippocampal subfields have partly different involvement in memory over different time scales [26–28, 53], and we therefore tested memory performance after 3 different intervals. Greater volume of CA1 and CA2-3 predicted better recall and retention after an extended interval of 1 week, although these relationships were partly explained by differences in general cognitive abilities. Additionally, a longitudinal decrease in CA2-3 and CA4-DG predicted learning. The results indicate that volume and volumetric change in specific subfields differentially predict verbal learning and memory, and that the relation to memory depends on the time interval prior to retrieval.

Developmental improvements in learning and memory emerge from the concerted effort of a network of relevant brain structures [54], but several active lines of research have investigated the particular role of the hippocampus. Developmental changes in the functional organization of the medial temporal lobe have been indicated by studies showing, for example, that adolescents and young adults, in contrast to children, engage regions of the hippocampus and parahippocampal gyrus selectively for subsequent recollection [24]. Further, consistent with the present findings, positive relationships between memory performance over extended time periods and hippocampal volume have been shown for visuospatial material in children and adolescents [55] and for both visuospatial and verbal information in adults [56, 57].

These studies, however, did not distinguish between hippocampal regions or subfields. There is a rich tradition of investigating functional differentiation along the longitudinal axis of the hippocampus [23, 58–66]. Less is known about how specific sectors in the transverse plane of the hippocampus are associated with the development of learning and memory [67]. Although disruption of learning following selective damage to each of the major subfields appears similar to a total lesion, this does not imply functional homogeneity [62]. In fact, a recent func-

tional MRI study found that it is possible to detect representations of autobiographical memories in individual subfields [68].

A few studies have investigated relationships between hippocampal subfield volumes and memory performance in adult or elderly participants. A positive association between verbal associative recognition and the combined volume of CA3 and CA4-DG has been found in healthy older adults [69], and verbal recall has been shown to relate to volumes of the CA2-3, CA4-DG and subiculum in patients with amnestic mild cognitive impairment [46]. Moreover, preliminary findings in a mixed group of cognitively intact and impaired subjects indicate that verbal short-term memory is associated with CA3 and DG, while intermediate memory is associated with CA1 [70]. Volumes of CA2-3 and CA4-DG were also positively related to memory improvements after training in a study of older adults [42]. A recent study also indicates that the associations between hippocampal subfield volumes and memory performance vary along the longitudinal axis and differ for verbal and visuospatial tasks [71]. To our knowledge, however, the present study is the first to document relationships between hippocampal subfields and learning and memory in development.

Limitations

The present findings should be considered in light of the following limitations. First, the longitudinal hippocampal results stem from only 2 time points, which constrain any inferences about nonlinear developmental trajectories. Moreover, verbal learning and memory was assessed using the CVLT only at the second time point, preventing analysis of change in behavioral performance. Second, some considerations relate to the hippocampal subfield segmentation procedure employed. In the original validation study of the technique, the larger subfields scored better than the smaller ones on a number of segmentation evaluation metrics, and automated segmentation of the smallest subfields, the fimbria and the hippocampal fissure, showed somewhat less reliability [29]. Thus, different subfield segmentation reliability may have contributed to the current results. Further, direct comparison with manually delineated subfields has only been performed in adult subjects [29]. Also, our scans were obtained at 1.5 T (1.25 × 1.25 × 1.20 mm), while high-resolution scans at 3 T (380-μm in-plane resolution, slice thickness 0.8 mm) were used for the development of the procedure. Our reliability analysis on 7 subjects scanned at both 1.5 and 3 T (1 × 1 × 1 mm), however, showed strong correlations across these field strengths and image resolutions for all hippocampal subfield volumes except the fimbria, which we therefore excluded from all further analyses. Nevertheless, future reliability and validation studies on children and adolescents and across standard and submillimeter image resolution are surely awaited. Additionally, results obtained with the segmentation procedure used in the current study [29] should be compared with other available protocols [72–74], as a great deal of variability exists in both nomenclature and boundary rules. Third, as previous studies disagree with respect to whether adolescent memory development is associated with hippocampal or prefrontal cortical maturation [24, 25], future studies should also analyze prefrontal cortical regions. Finally, biological interpretation of hippocampal subfield volumetric changes is complicated due to the myriad of possible contributing factors [75]. Postmortem data have demonstrated myelination in the DG and the subicular and presubicular regions throughout adolescence [76–78] and long-lasting neurogenesis in the DG [79–81], but it is not known how these and other processes affect MRI volumetry.

Conclusions

The present results showed that most hippocampal subfield volumes, including CA2-3, CA4-DG, the presubiculum, subiculum, hippocampal fissure and the left CA1, decreased over time in adolescents, but also that there were regional differences in subfield development. Interestingly, volume and change in specific subfields differentially predicted verbal learning and memory. Specifically, volumes of CA1 and CA2-3 were related to memory after an extended interval, while a developmental decrease in CA2-3 and CA4-DG predicted learning. This underscores the heterogeneity of structural hippocampal subfield development, as well as the differential role of subfields in cognitive performance in late childhood and adolescence. Future longitudinal studies with multiple time points and high-resolution imaging are, however, needed to further inform us on the nonlinear and regional hippocampal developmental trajectories underlying the development of memory functions.

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Disclosure Statement

A.M.D. is a founder and holds equity in CorTechs Labs Inc. and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California San Diego, in accordance with its conflict of interest policies.

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