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Dissociating Memory Processes in the Developing Brain: The Role of Hippocampal Volume and Cortical Thickness in Recall after Minutes versus Days

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Retention of information over extended time periods places special demands on the brain. The neural correlates of memory performance after a short delay of 30 min and a long delay of 1 week are likely partly different, but we do not know how structural maturation of the brain contributes to the differential development of these functions. This question was investigated in a sample of 107 children and adolescents aged 8–19 years. Measures used were structural magnetic resonance imaging and the Rey Complex Figure Test copy, organizational strategy, and 30-min and 1-week recall. While the amount of details copied and later recalled after both 30 min and 1 week increased with age, the relative saving over 1 week (1-week/30-min ratio score) did not increase with age. Thirty minutes recall performance was related to thinner left orbitofrontal cortex independently of age and organizational strategy measured during copy, possibly reflecting executive components of retrieval or encoding processes. In contrast, the 1-week/30-min ratio, likely reflecting consolidation of memory traces, was related to larger bilateral hippocampal volume. This indicates that differential developmental effects on memory for short and long periods of time are related to differentially developing brain structures.

Keywords: cerebral cortex, development, hippocampus, MRI, RCFT

Introduction

During late childhood and adolescence, great demands are placed on the ability to retain and consolidate information learned at school and in one's life. During the same period, marked changes in the structural organization of the brain take place (Giedd et al. 1999; Sowell et al. 2002; Thompson et al. 2005; Shaw et al. 2008; Ostby et al. 2009; Tamnes et al. 2010), but little is yet known about the importance of these brain maturational events for memory development. There is consensus that after initial acquisition, memories are solidified in long-term stores over an extended period—of days, months, or even years (Moscovitch et al. 2006; Squire and Bayley 2007). In development, no study has so far investigated the neural correlates of consolidation of learned material beyond the typical 30-min interval employed in standardized neuropsychological test settings. Do children lose more of what is initially learned, compared with older adolescents, over extended periods of time? This question has great importance for education but also for the theoretical understanding of the neural organization of memory as seen during development.

Evidence suggests that the different neural structures subserving episodic memory, especially frontal and medial temporal areas, follow diverse developmental paths. As the frontal lobes mature relatively slowly (Shaw et al. 2008; Tamnes et al. 2010), they are thought to be responsible for delays in children's ability to take advantage of organizational strategies during encoding and retrieval (Sowell et al. 2001), which is typically reflected in recall scores on memory tests. The hippocampus differs from other brain regions in its developmental trajectory. While most cortical and subcortical gray matter (GM) regions decrease during development (Sowell et al. 2002; Giedd 2004; Ostby et al. 2009), the hippocampus shows a slight increase (Giedd et al. 1996; Ostby et al. 2009; but see Gogtay et al. 2006). It is, however, not clear what this volume increase means in terms of memory development. While functional magnetic resonance imaging (fMRI) studies find evidence for an early maturation of hippocampal engagement during memory encoding (Menon et al. 2005; Ofen et al. 2007), evidence of continued neurogenesis in the dentate gyrus in adulthood may point to a prolonged development (Leuner and Gould 2010).

The Rey–Osterrieth Complex Figure Test (RCFT) (Meyers JE and Meyers KR 1995) is a way of testing visuoconstructive memory performance, using a novel, complex design which participants are asked to copy and then reproduce from memory after 30-min. Performance on this test has been related to neurological conditions affecting both temporal and frontal brain regions (Shin et al. 2006). A unique feature of this task is that one can also obtain a measure of organizational ability during copy, and memory performance can be seen in the light of organization. Two previous developmental structural MRI studies have used the RCFT as the to-be-remembered material, showing a relationship between GM reduction in frontal regions and memory performance at recall but little or no relationship with temporal lobe structures (Sowell et al. 2001; Antshel et al. 2008). Thus, hippocampal development appears to play a smaller role in memory development after late childhood. However, development in retention of learned material over long-term intervals exceeding 30-min has never been investigated in relation to hippocampal and cortical development. In adults, the relationship between hippocampal volume and memory has been shown to be stronger over extended time periods of weeks between learning and testing than over the usually employed retention interval of 30-min (Walhovd et al. 2004).

Specific subregions of the prefrontal lobes involved in performance of the RCFT have not been identified in previous MRI studies, as regions of interests (ROIs) encompassing the whole of the frontal lobe have been employed, at least in the developmental studies (Sowell et al. 2001; Antshel et al. 2008). However, findings from fMRI studies using various memory approaches have suggested a role for both the ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal

cortex (DLPFC) in retrieval and encoding of both visual and verbal material (Spaniol et al. 2009). Orbitofrontal cortex has also been implicated in encoding and retrieval in long-term memory (Petrides 2007). The role of organizational strategies, seen as an executive component of memory of the RCFT (Savage et al. 2000; Shin et al. 2006), in modulating prefrontal involvement, also needs further investigation, as no MRI studies to date have looked specifically at structural correlates of organizational abilities.

In the present study, development of visual memory and the relationship with structural brain development were investigated. More specifically, the objectives were

1. To investigate the development of long-term memory processes as measured after short (30-min) and long (1-week) periods of time. Measures of recall of the elements of a geometrical figure (RCFT; Meyers JE and Meyers KR 1995) were employed both after 30-min of copying the figure and 1 week later. Of particular interest was to investigate whether there is development in the ability to keep what has been learned over an extended period of time. The proportion of what was recalled after 1 week relative to what was recalled after 30-min, was used as a measure of long-term retention, presumed to be related to consolidation of memories. The RCFT was chosen because it has been established as a validated method within neuropsychology, yielding interindividual variability, and the standard measures (copy and 30-min recall) have previously shown age effects (Meyers JE and Meyers KR 1995). A measure of organization of the gross elements of the figure was employed during the initial copying of the figure (Deckersbach et al. 2000). We hypothesized 1) that age would be positively related to performance on both 30-min and 1-week recall and 2) that performance on these recall trials would be partly explained by organizational ability. We did not have any a priori hypothesis about the effect of age on long-term retention, as this has never been investigated in a developmental sample before.
2. To relate the development of long-term memory to structural brain development. We hypothesized that 30-min recall performance, and possibly also 1-week recall performance, would be related to structural properties of the lateral prefrontal cortex or orbitofrontal cortex, while 1-week retentional abilities (1-week/30-min ratio score) would be related to different regions, possibly the volume of the hippocampi. Based on maturational changes in the form of cortical thinning and hippocampal increase in the relevant age span, we expected negative relationships between memory indices and cortical thickness and positive relationships between memory indices and hippocampal volume. Furthermore, we hypothesized that organizational ability would partly account for a possible relationship between recall and prefrontal cortex, as has been suggested previously (Sowell et al. 2001). The investigation of structure–memory relationships in development was based both on studying age-independent relationships and on relating cross-sectionally estimated developmental trajectories of brain structure to cognitive performance level. Previous studies (Shaw et al. 2006; Tamnes et al. 2010a) have found evidence for both age-independent relationships and for differential timing and rate of development based on level of cognitive functioning.

Materials and Methods

Sample

One hundred and seven children and adolescents (55 males) aged 8–19 years participated in the study (M = 13.90, standard deviation [SD] = 3.42). The distribution of sex and age in 3 age groups is shown in Table 1. The sample was recruited through newspaper advertisements and local schools and workplaces and constitutes the first part of an ongoing longitudinal research project at the Center for the Study of Human Cognition at the University of Oslo (Neurocognitive Development). The study was approved by the Regional Ethical Committee of South Norway. Written informed consent was obtained from all participants older than 12 years of age and from a parent/guardian of volunteers under 18 years of age. Oral informed consent was obtained from all participants under 12 years of age. Participants had no self- or parent-reported history of neurological or psychiatric disorders, chronic illness, premature birth, learning disabilities, or use of medicines known to affect nervous system functioning. They were further required to be right handed, speak Norwegian fluently, and have normal or corrected to normal hearing and vision. Among the initially 116 children and adolescents who met the inclusion criteria, 4 had no useable MRI scans. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant. Of the 111 remaining participants, 4 participants did not complete all memory tests at all trials, leaving the sample with 107 children and adolescents. There was no correlation between sex and age in the current sample (r = –0.08, P = 0.405, females coded as 1, males as 2). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999), and all participants scored above 80 on full-scale IQ (M = 109.11, SD = 10.92, range: 82–141). The distribution of WASI full-scale IQ in 3 age groups is shown in Table 1. There was no difference in IQ between males (M = 110.34, SD = 11.88) and females (M = 107.85, SD = 9.787; t_{109} = –1.201, P = 0.232).

Memory Assessment

Participants were given the RCFT as part of a larger battery of cognitive tests. Examples of copy, 30-min recall and 1-week recall are given in Figure 1. For copy and recall, the administration procedure was standard (Meyers JE and Meyers KR 1995), with a few exceptions. *Copy*: The participants were presented with a picture of a geometrical figure on an A4 sheet of paper and were asked to draw the figure as similar as possible. They were allowed to see the figure the whole time and were given a maximum of 5 min to complete the task. *Thirty minutes recall*: After approximately 30-min, during which time the participants completed other tasks with mainly verbal material, the participants were asked to draw the figure again without the original picture in front of them. *One week recall*: After approximately 1 week (6–9 days) upon returning to the laboratory for further testing, the participants were again asked to draw the figure from memory. Nineteen participants were asked over the telephone to draw the figure at home and to bring it with them for the next testing session or to mail. The participants were not told about the delayed recall condition in advance, in order to limit the possibility of training effects. *Copy and recall scoring*: Each drawing was scored using standard scoring criteria (Meyers JE and Meyers KR 1995). The scoring system divides the figure into18 subunits and awards 2 points for each correct and correctly placed unit, 1 point for an inaccurately drawn or incorrectly placed unit, and a 1/2 point for a unit that is recognizable but both inaccurate and inaccurately placed in the drawing. This results in a maximum score of 36 points for each drawing. A retention score was calculated for the 1 week delayed recall condition, with "retention" defined as the ratio between the 1 week recall score and the 30-min recall score. This score was thought to be related to memory consolidation, independently of copy and retrieval at the 30-min free recall trial. Organization during copy: While the participant was copying the figure, organization of the drawing was scored by the examiner, based on a scoring system developed by Savage et al. (1999) (Deckersbach et al. 2000). Following this scoring system, points were given when the participant completed each of 5 structural units consecutively, that is, without proceeding to draw other units in between. Two points were given when the participant completed the

Table 1
Characteristics of 3 age groups in terms of sex, WASI IQ scores, and Rey Complex Figure Test scores

	Age groups					
	8–11		12–15		16–19	
N	36		36		35	
Males/females	21/15		17/19		17/18	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Full-scale IQ (WASI)	107.67 (10.98)	82–127	107.89 (10.72)	91–141	112.69 (10.42)	91–132
Copy	29.82 (4.10)	17–35	32.47 (2.48)	26–36	32.97 (2.18)	27.5–36
Organization	1.81 (1.35)	0–6	3.39 (1.61)	1–6	4.34 (1.63)	0–6
30-min recall	15.38 (5.33)	3.5–26	21.00 (5.67)	8.5–31	23.36 (4.65)	11.5–31
1-week recall	13.11 (5.09)	3–24	16.86 (6.11)	7–30	18.91 (5.65)	8–29
1-week retention	87.55 (24.16)	30.0–153.85	80.88 (18.52)	43.40–109.52	80.26 (15.50)	40.0–108.33

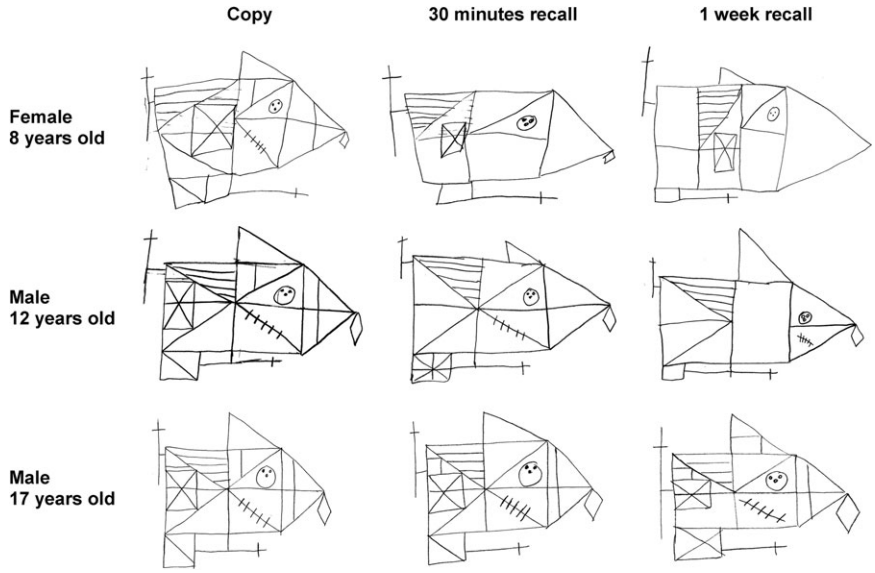

Figure 1. Examples of drawings of the Rey–Osterrieth Complex Figure at copy, 30-min recall and 1-week delayed recall, by 3 subjects of varying age. The 8-year-old received scores (in order of appearance above) of 26.5, 12, and 10.5 points, the 12-year-old was given 35, 24, and 19.5 points, and the 17-year-old's drawings were scored with 34, 31, and 25 points.

large rectangle in 1 piece and 1 point was given for each of the units: horizontal line through the rectangle, vertical line through the rectangle, diagonal cross inside the rectangle, and triangle attached to the right of the rectangle, yielding a maximum score of 6 points. Interrater reliability of this scoring system has been reported to be high ($r = 0.94$ between 2 raters for the total score) (Deckersbach et al. 2000).

MRI Acquisition and Analysis

Imaging data were collected using a 12-channel head coil on a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The pulse sequences used for the morphometric analyses were two 3D T_1-weighted (magnetization prepared rapid gradient echo [MP-RAGE]) scans, with the following parameters: time repetition/time echo/time to inversion/Flip Angle = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 192. Each scan took 7 min 42 s. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.20 mm. Each MP-RAGE was visually inspected, and only scans deemed to have no or minimal movement artifacts were included in analyses. The 2 MP-RAGEs were averaged to increase the signal-to-noise ratio. Where there were problems achieving 2 high quality scans due to motion artifacts, etc., only one scan was used in the analysis. This was the case for 15.2% of the participants, of whom most (73%) were below 12 years of age.

All data sets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with additional use of computing resources from the Titan High Performance Computing facilities (http://hpc.uio.no/index.php/Titan) at the University of Oslo. Volumes of the caudate, putamen, pallidum, accumbens, thalamus, hippocampus, amygdala, cerebellum cortex, cerebellum WM, ventricles, and total cerebral WM, were calculated using FreeSurfer 4.0.5. (http://surfer.nmr.mgh.harvard.edu/fswiki). The automated segmentation procedure (Fischl et al. 2002) assigns a neuroanatomical label to each voxel in an MR volume based on probabilistic information automatically estimated from a manually labeled training set. The segmentation puts constraints on allowable locations of structures in relation to each other based on the training set (e.g., hippocampus is never anterior to amygdala). The automated segmentations have been found to be statistically indistinguishable from manual labeling (Fischl et al. 2002), and correlations between FreeSurfer segmentation and manual labeling of hippocampal volume reached 0.85 in a study by Tae et al. (2008). The segmentations were visually inspected for accuracy and none were discarded. No editing was performed on subcortical structures. Bilateral hippocampal volume was used as a dependent measure in the present paper. The segmented hippocampal formation in FreeSurfer encompasses the CA fields, subiculum, and dentate gyrus (Makris et al. 1999; Tae et al. 2008). The segmentation does not differentiate gray and white matter within the hippocampi. Three-dimensional renderings of the segmented hippocampi are shown in Supplementary Figure 1*a*. Preliminary analyses using left and right hippocampi separately revealed largely similar results, and the 2 hippocampi were therefore combined in further analyses. Total brain volume (TBV) was calculated based on all gray and white matter volumes and ventricular volumes, for inclusion in volumetric analyses.

Cortical thickness was estimated using FreeSurfer 4.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) by means of an automated surface reconstruction procedure (Dale et al. 1999; Fischl, Sereno, and Dale 1999; Fischl, Sereno, Tootell, et al. 1999; Fischl and Dale 2000; Fischl et al. 2001; Segonne et al. 2004). Briefly, a representation of the gray/white matter boundary was reconstructed (Dale et al. 1999), using intensity and continuity information from the entire MR volume in segmentation and deformation procedures. Minor manual editing of vessels and dura was routinely performed, according to FreeSurfer guidelines. The cortical maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups (Fischl and Dale 2000). The measurement technique has been validated via histological (Rosas et al. 2002) as well as manual measurements (Kuperberg et al. 2003). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of approximately 15 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl, Sereno, Tootell, et al. 1999). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Statistical comparisons of surface maps were generated by computing a general linear model (GLM) of the effects of each variable on thickness at each vertex, which were mapped on the semi-inflated surface of the average brain of the sample (Dale et al. 1999; Fischl, Sereno, and Dal 1999).

Statistical Analyses

In order to investigate the development of the various memory components, as measured by RCFT, regression analyses were performed using RCFT measures of copy accuracy, organization, 30-min free recall, 1-week free recall, and 1-week retention (1-week/30-min ratio) as dependent variables and age and sex as predictor variables. Before proceeding to the main analyses, sex differences in the RCFT scores were investigated using analysis of covariance with age as covariate and sex as between-subjects factor. Because the effect of age on recall performance could be brought about by the developmental increase in copy and organization scores, regression analyses were also performed with copy and organization scores as predictor variables in addition to age and sex and the 2 recall scores (after 30-min and after 1-week) as dependent variables. These analyses were also done in order to test the effect of organizational abilities on recall performance.

Next, the memory scores were related to brain morphometry. In order to be able to interpret these relationships, the effect of age on cortical thickness and hippocampal volume was also calculated. Analyses of age effects on brain structures in partly overlapping samples have been reported previously (Ostby et al. 2009; Tamnes et al. 2010, 2010b) and are included here as background information. Relationships between memory scores (RCFT copy, organization, 30-min recall, 1-week recall, and 1-week retention [1-week/30-min ratio] score) and hippocampal volume were investigated using regression analyses with RCFT scores as dependent variables and sex and hippocampal volume as independent variables. Combined bilateral hippocampal volume was used in the analyses after preliminary analyses had revealed no lateralization, and a combined measure would yield better statistical power and reduce the number of analyses. Hippocampal volume was corrected for TBV to account for interindividual variability in brain size. Because any relationship between brain structure and function could be driven by the common effect of age, analyses were then performed with age included among the predictor variables. In order to test whether any of the observed relationships between hippocampal volume and memory scores could be due to nonspecific effects, regression analyses were then performed with the memory scores that showed a relationship with hippocampus as dependent variable and sex, age, TBV-corrected hippocampal volume, and WASI IQ as predictor variables.

In order to investigate the relationships between cortical thickness and memory, GLMs were performed using cortical thickness at each vertex as dependent variables, and RCFT scores (copy, organizational strategy, 30-min recall, 1-week recall, and 1-week retention [1-week/30-min ratio] score) as independent variables, while controlling for sex. This first step was performed to provide a background for the next step of analyses, in which age was controlled for in addition to sex in order to test for any age-independent effects. As the age-independent effects were considered the main results, the results of analyses of age effects and the age-uncorrected analyses with RCFT measures are presented as supplementary material.

Two methods for correction for multiple comparisons were used in the cortical GLMs, depending on the nature of the analyses. Where widespread effects were expected, a commonly used criterion of false discovery rate (FDR) of 5% was employed (Genovese et al. 2002). Such widespread effects were expected in the analyses of age effects on cortical thickness and the age-uncorrected analyses with RCFT scores. When age was controlled for in the analyses, more localized effects were expected and a cluster-based approach was deemed more appropriate. Cluster size inference was performed using FreeSurfer (Hayasaka and Nichols 2003; Hagler et al. 2006), where cluster size limits were estimated with Z Monte Carlo simulations with 5000 iterations per analysis with a cluster-forming threshold of $P < 0.05$. The simulations are a way to get a measure of the distribution of the maximum cluster size under the null hypothesis and then determine the probability of a certain cluster size under the empirical null. A clusterwise corrected $P < 0.05$ was regarded significant.

Clusters showing significant effects were delineated in FreeSurfer, and the mean thickness across the delineated area for each person was used as a ROI in further analyses. To test the effects found in the GLMs for specificity and to test the hypothesis that organizational ability is partly responsible for any prefrontal effects, regression analyses were performed with RCFT scores as dependent variables and sex, age, mean ROI thickness, and each of the 3 variables copy, organization, and IQ, as dependent variables in 3 sets of analyses.

Finally, to test whether performance is related to differences in estimated brain maturational trajectories, separate age correlations with brain structure was calculated for high-performing and low-performing subgroups for the memory measures that showed a relationship with brain structure in the main analyses. This was done by dividing the sample in 2 halves based on each participant's level of performance relative to the median within age groups spanning 2 years. The Pearson correlations between age and brain structure for each of the performance-based groups were then compared statistically, using t-tests of Fisher's z-transformed correlations.

Results

Memory Development

Descriptive statistics of the performance of 3 age groups (8–11 years, 12–15 years, and 16–19 years) on the RCFT copy, organization, 30-min recall, 1-week recall, and 1-week retention (1-week/30-min ratio) measures are shown in Table 1. Sex differences on the 5 RCFT variables were investigated using multivariate analysis of variance, which showed no overall significant difference between males and females, although a trend was seen ($F = 2.124$, $P = 0.069$). However, univariate tests revealed statistically significant differences between males and females on organization (males: $M = 2.73$, SD = 0.22; females: $M = 3.63$, SD = 0.27; $F = 6.82$, $P = 0.010$) and 1-week recall (males: $M = 18.85$, SD = 0.84, females: $M = 20.97$, SD = 0.83; $F = 6.64$, $P = 0.011$). Therefore, sex was included in further analyses. The effects of sex and age on copy, organization, 30-min recall, 1-week delayed recall, and retention (1-week/30-min ratio) are shown in Table 2. In these analyses, the effect of age was moderate to large (R^2 ranging from 0.21 to 0.38, all Ps < 0.05) for all variables except the retention (1-week/30-min ratio) score, which showed no statistically significant relationship with age. The results are plotted in graphs in Figure 2. Regression analyses were then repeated for the 30-min and

1-week recall scores with copy score and organizational strategy score included as additional regressors. The results of these analyses are shown in Table 3. The effect of age remained significant only for the 30-min recall score, when copy and organization scores were accounted for.

Structural Brain Maturation

Regression analysis with TBV-corrected bilateral hippocampal volume as the dependent variable and age as predictor variable, revealed a statistically significant volume increase from 8 to 19 years ($F_{1,107} = 11.531$, $P = 0.001$, $\beta = 0.32$, $R^2 = 0.099$). There was no significant contribution of age^2, when this was included in the regression ($P = 0.924$). A scatter plot showing the effect of age on bilateral hippocampal volume is shown in Supplementary Figure 1*b*.

GLMs with cortical thickness as dependent variable and age as independent variable were performed while controlling for the effects of sex. The results are shown in Supplementary Figure 1*c*,*d*. There were widespread effects of age on cortical thickness across most of the surface of both hemispheres. When a more conservative statistical threshold than FDR < 0.05 was used ($P < 0.01$, uncorrected), the effects were mostly seen in posterior regions but also in temporal and frontal regions.

Effects of Hippocampal Volume on Memory Performance

The contribution of hippocampal volume to memory performance was investigated in regression analyses with RCFT measures as dependent variables and sex and TBV-corrected hippocampal volume as predictor variables. The results are shown in Supplementary Table 1 and indicate a statistically significant relationship between TBV-corrected hippocampal volume and organizational ability, 1-week recall, and 1-week retention when the effect of age is not controlled for. As these relationships may be due to the common effect of age on both measures, in the next step of analyses, the regression analyses were repeated with age as an additional predictor variable. These analyses revealed no effect of TBV-corrected hippocampal volume on copy, organization, 30-min recall, or 1-week recall, as shown in Table 4. The 1-week retention (1-week/30-min ratio) score, on the other hand, was significantly predicted by hippocampal volume ($F_{3,106} = 5.164$, $P = 0.002$; β hippocampus $= 0.31$, $P = 0.002$), when sex and age was included in the regression. The relationship between hippocampal volume and 1-week retention (1-week/30-min ratio) is displayed in Figure 3*A*. To test the specificity of this result, a regression analysis was performed with 1-week retention (1-week/30-min ratio) as dependent variable and sex, age, TBV-corrected hippocampal volume, and IQ as predictor variables. This analysis revealed a statistically significant contribution of IQ

Table 2

Effects of sex and age on Rey Complex Figure Test copy, organization, 30-min recall, 1-week recall, and 1-week retention scores

	F	β sex	β age	*P* sex	*P* age	R^2
Copy	13.479	−0.05	0.45	0.588	1.60×10^{-6}	0.21
Organizational strategy	31.492	−0.19	0.57	0.014	7.05×10^{-11}	0.38
30-min recall	25.786	−0.12	0.55	0.137	5.32×10^{-10}	0.33
1-week recall	16.651	−0.20	0.43	0.019	2.21×10^{-6}	0.24
1-week retention score	2.422	−0.17	−0.14	0.083	0.139	0.05

Table 3

Effects of age, sex, copy performance, and organization score on 30-min and 1-week recall performances

	F	*P*	R^2	β age	*P* age	β sex	*P* sex	β copy	*P* copy	β org	*P* org
30-min recall	23.703	7.07×10^{-14}	0.48	0.26	0.007	−0.06	0.434	0.36	1.90×10^{-5}	0.24	0.011
1-week recall	17.205	8.17×10^{-11}	0.40	0.13	0.200	−0.14	0.079	0.38	2.82×10^{-5}	0.23	0.018

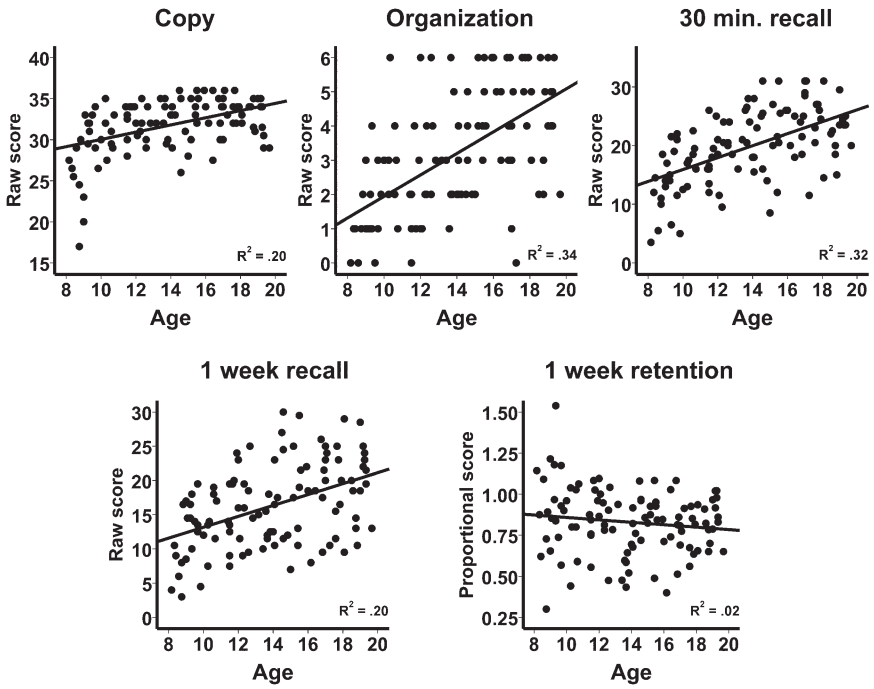

Figure 2. Scatter plots showing the effects of age on Rey Complex Figure Test scores, with age on the *x*-axes, and raw scores (0–36 for copy, 30-min recall, and 1-week recall; 0–6 for organization) and proportional scores (retention [1-week/30-min ratio]) on the *y*-axes.

Table 4

Results of regression analyses with sex, age, and TBV-corrected hippocampal volume as predictor variables and RCFT scores as dependent variables

	F	*P*	R^2	β sex	*P* sex	β age	*P* age	β hippocampus	*P* hippocampus
Copy	8.927	2.60×10^{-5}	0.18	−0.05	0.594	0.45	3.74×10^{-6}	−0.02	0.796
Organization	21.212	8.89×10^{-11}	0.38	−0.20	0.013	0.54	1.75×10^{-9}	0.07	0.378
30-min recall	17.211	3.92×10^{-9}	0.33	−0.12	0.142	0.57	1.29×10^{-9}	−0.05	0.544
1-week recall	11.746	1.11×10^{-6}	0.26	−0.21	0.017	0.39	3.09×10^{-5}	0.12	0.194
1-week retention	5.164	0.002	0.13	−0.18	0.058	−0.24	0.015	0.31	0.002

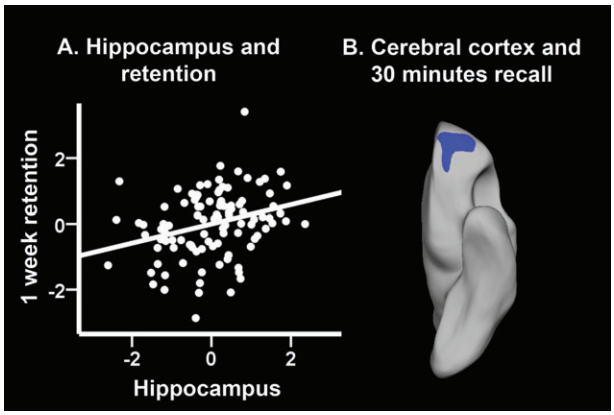

Figure 3. Relationships between brain structure and memory scores. (*A*) Scatter plot showing the relationship between bilateral hippocampal volume (corrected for TBV) on the *x*-axis and 1-week retention (1-week/30-min ratio) score on the *y*-axis, shown as standardized residuals after correcting for the effect of age. (*B*) GLM with 30-min recall score, while controlling for sex and age, here shown only for the left hemisphere in a ventral view, were a cluster (shown in blue) corresponding mainly to orbitofrontal cortex survived a Monte Carlo simulation correcting for multiple comparisons at $P < 0.05$.

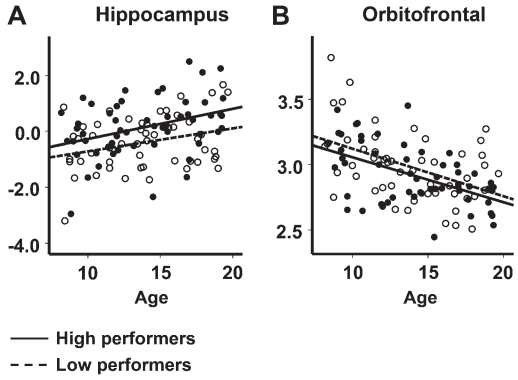

Figure 4. Relationships between memory measures and brain structure according to performance level. (*A*) Scatter plot showing TBV-corrected hippocampal volume on the *y*-axis and age on the *x*-axis. Open circles and dashed line represent the participants who performed below the age-stratified median on retention (1-week/30-min proportion), while black circles and solid line represent the participants scoring above the median. (*B*) Scatter plot showing orbitofrontal thickness, based on the ROI shown in Figure 3A, on the *y*-axis and age on the *x*-axis. Open circles and dashed line represent the participants who performed below the age-stratified median on 30-min recall, while black circles and solid line represent the participants scoring above the median.

(β = 0.35, $P = 0.004$), while the contribution of TBV-corrected hippocampal volume remained statistically significant ($F_{4,106} = 8.330$, $P = 7.44 \times 10^{-6}$; β hippocampus = 0.27, $P = 0.004$). In order to test whether the maturational trajectories of hippocampal volume vary as a function of memory performance, the Pearson correlations between age and hippocampal volume for each of 2 subgroups, a high-performing and a low-performing group, were statistically compared. The 2 correlations (low-performing group: $r = 0.29$, $P = 0.036$; high-performing group: $r = 0.36$, $P = 0.007$) were not significantly different (*z*-score of difference = 0.39, $P > 0.05$). The maturational trajectories of TBV-corrected hippocampus for the 2 groups are displayed in a graph in Figure 4*A*, showing that the hippocampal volume of the high performers is larger than for the low performers throughout the age span, but that the estimated age trajectories do not differ.

Relationships between Cortical Thickness and RCFT Scores

Before proceeding to test for age-independent relationships with brain structure, GLMs were performed testing for the effects of various RCFT measures on cortical thickness without correcting for age. Controlling for the effects of sex, widespread negative effects of copy, organization, 30-min recall, and 1-week recall were found on cortical thickness, with a statistical significance threshold of $P < 0.01$. These results are shown in Supplementary Figure 2.

Because the effect of age on both memory performance and cortical thickness could explain the widespread effects, the unique effects of memory performance on cortical thickness independently of age were investigated in GLMs controlling for both sex and age. The results of these analyses are shown in Figure 3*B* and Supplementary Figure 3 and are briefly described below. Scattered negative relationships between cortical thickness and memory performance were seen, but most were too small to survive corrections for multiple comparisons. However, 30-min recall performance was related to cortical thickness in a left orbitofrontal cluster at a significance threshold of $P < 0.01$, which survived Monte Carlo simulations to control for multiple comparisons ($P = 0.02$) (see Fig. 3*B*). The mean thickness across vertices in the ROI based on the Monte Carlo–corrected relationship between recall and left orbitofrontal thickness was then used as a predictor variable in regression analyses with 30-min recall as the dependent variable. First, a regression analysis was performed, showing that the relationship between 30-min recall and left orbitofrontal thickness remained after controlling for the effect of IQ. Second, a regression analysis showed that left orbitofrontal thickness predicted recall performance independently of sex, age, and copy score. Lastly, a similar regression analysis revealed that left orbitofrontal thickness predicted recall performance independently of sex, age, and organizational ability. The results of the ROI analyses are displayed in Table 5. In order to test whether the maturational trajectories of orbitofrontal cortex vary as a function of 30-min recall performance, the Pearson correlations between age and orbitofrontal thickness in the ROI for each of 2 subgroups, a high-performing and a low-performing groups based on 30-min recall, were statistically compared, and the 2 correlations

Table 5
Results of regression analyses with 30-min recall as dependent variable and sex, age, left orbitofrontal cortical thickness (OFC), and copy/organization (org)/IQ as predictor variables.

	F	*P*	R^2	β sex	*P* sex	β age	*P* age	β test score	*P* test score	β OFC	*P* OFC
Copy	25.443	1.25×10^{-14}	0.50	−0.11	0.118	0.27	0.003	0.35	2.39×10^{-5}	−0.26	0.002
Organization	20.497	2.04×10^{-12}	0.45	−0.08	0.308	0.26	0.010	0.26	0.006	−0.30	0.001
IQ	23.692	7.15×10^{-14}	0.48	−0.16	0.032	0.36	3.59×10^{-5}	0.29	1.56×10^{-4}	−0.26	0.003

(low-performing group: $r = -0.46$, $P = 0.001$; high-performing group: $r = -0.53$, $P = 0.00003$) were not significantly different (z-score of difference = 0.47, $P > 0.05$). The maturational trajectories of left orbitofrontal thickness for the 2 groups are displayed in a graph in Figure 4*B*. Thinner cortex is seen in the high performers, but the estimated age trajectories are similar.

Discussion

Distinct developmental trajectories for different aspects of declarative memory were revealed in the current study. There were marked effects of age on the ability to copy and organize complex visuospatial information, as well as on the ability to recall information after 30-min and 1-week. In contrast, 1 week retention (1-week/30-min ratio)—the relative amount of material that was kept in memory between 30-min recall test and 1-week recall test—did not improve with age. This indicates that the ability to consolidate information in the brain matures relatively early and that improvements in the ability to remember information over longer time periods must be ascribed to encoding or retrieval-related processes. Interestingly, 30-min recall performance was related to thinner cortex in the left orbitofrontal region, while long-term retention (1-week/30-min ratio) was related to bigger hippocampal volume, both with and without correction for age effects. This will be discussed further below.

Memory Development

The developmental effects on copy and recall scores on the RCFT were in accordance with previously published age effects (Meyers JE and Meyers KR 1995; Nakano et al. 2006; Antshel et al. 2008). Memory performance over an extended delay has to our knowledge not been examined previously in children. In the 1 week recall condition, free recall performance showed a similar developmental pattern as recall after the standard 30-min. One-week retention (1-week/30-min ratio), on the other hand, showed no effect of age, indicating that consolidation of episodic memory is relatively early matured and that age-related improvement in recall can be attributed to further development of encoding and/or retrieval abilities. In coherence with the present results, Nakano et al. (2006) found no differences between age groups ranging from 6 to 16 years in the amount of details kept in memory between immediate and 30-min delayed recall. Our results extend this to longer time delays.

Memory–Brain Relationships

Interestingly, different aspects of memory were related to different neuroanatomical structures, when the effect of age was controlled for. Long-term retention (1-week/30-min ratio) was predicted from hippocampal volume, while 30-min recall was related to cortical thickness in left orbitofrontal cortex. The long-term retention (1-week/30-min ratio) score reflects the keeping of memories between the 2 recall conditions. As differences in processes related to encoding and retrieval are embedded in the regular recall scores, the measure of retention reflects consolidation of the acquired information. The long retention interval places high demands on the consolidation processes and makes it likely that the information that is kept across this week is more fully consolidated than information retrieved after only 30-min. The hippocampus is important in the process of solidifying memories, whether this is by transferring them to more enduring cortical networks (Squire and Bayley 2007) or by the making of multiple hippocampal–cortical memory traces (Moscovitch et al. 2006). Our results demonstrate that normal variation in hippocampal volume affects the ability to consolidate memories during development. Previous morphometric studies have not found any relationship between the standard RCFT 30-min recall score and hippocampus or medial temporal lobes (Sowell et al. 2001; Antshel et al. 2008). As our results largely support their conclusions, showing no relationship between 30-min recall and hippocampus, it seems that consolidation processes that are dependent upon macrostructural hippocampal characteristics are better captured at long retention spans. This was also the case in a morphometric study by our group performed with adults and aging participants (Walhovd et al. 2004).

Based on previous morphometric studies of development (Sowell et al. 2001; Antshel et al. 2008), the effect of frontal cortical thickness on recall performance was expected. Orbitofrontal cortex has been implicated in both encoding and retrieval processes (Petrides 2007), through connections with motivational processes and allocation of attention at encoding or monitoring relevance during retrieval. It is unfortunately not possible to know which of the processes, encoding or retrieval, is responsible for the relationship with orbitofrontal cortex, as both are inherently captured in the memory measures used here. The effect was only present in the left hemisphere. The Rey–Osterrieth Complex Figure has elements that are easy to verbalize, and so this may not be interpreted as a purely visual test. Another explanation is that some of the memory functions in the frontal lobes are less modality specific and more task-specific (Gabrieli et al. 1998; Spaniol et al. 2009). While VLPFC and DLPFC have been identified as possible sites for encoding and retrieval of episodic information in fMRI studies (Spaniol et al. 2009), this was not shown in our results. This particular task has, however, not been related to specific subregions of prefrontal cortex before, and the fact that subprocesses are not identified with this task might be the reason for the lack of findings. The RCFT is not suitable for fMRI research in its current form and comparisons with fMRI studies must therefore be done with caution. Results from regional cortical thickness analyses in a larger sample overlapping the present suggest that lateral prefrontal cortex and orbitofrontal cortex show largely similar developmental trajectories (Tamnes et al. 2010).

The involvement of frontal cortical regions in the performance of the RCFT has been hypothesized to be related to the ability to organize the figure, that is, the ability to see the figure as meaningful, larger units rather than an assembly of details, and

to use this overarching structure as a guide to copying the figure (Sowell et al. 2001; Shin et al. 2006). The ability to encode information as organized and meaningful has profound impact on the amount of information later recalled (Chase and Simon 1973). In line with this, our results showed that organization of the figure predicted recall performance, even when controlling for age. However, when controlling for organizational score in the cortical thickness analysis, the relationship between 30-min recall and left orbitofrontal cortex was only marginally affected. Taken together with the connections between orbitofrontal cortex and encoding/retrieval processes discussed above, this leads us to conclude that other executive aspects of encoding, for example, allocation of attention as suggested by Petrides (2007), is responsible for the frontal effects seen. Alternatively, executive aspects of retrieval could also be a factor.

Brain–behavior relationships revealed by correlational methods need not necessarily be specific to the task in question. In the present results, however, different memory processes could be differentiated by brain–behavior relationships, thus showing the specificity of the results. In addition, the relationship between orbitofrontal thickness and recall and the relationship between hippocampal volume and retention were independent of the effects of general intellectual abilities. In a sample overlapping the present, we found relationships between measures of executive functions and cortical thickness in areas not overlapping the orbitofrontal region (Tamnes et al. 2010b). Thus, we believe that the effects observed are less likely to be caused by unspecific maturation changes alone.

Neurobiological Processes and Brain Developmental Trajectories in Memory

The age effects on brain structures were not completely similar to the results that have been published previously based on an overlapping but bigger and on average older sample (Ostby et al. 2009; Tamnes et al. 2010), as no nonlinear component of hippocampal development could be identified in the present sample. This is most likely caused by differences in the sample size and age span between the present study and the previous studies. Nevertheless, it is clear from our results and supported by others (Giedd et al. 1996, 1999; Sowell and Jernigan 1998; Guo et al. 2007), that cortical thickness and hippocampal volume follow distinctly different developmental trajectories. While cortical thickness decreases from an early age, hippocampal volume increases. The neurobiological processes underlying these differing processes are not fully understood. Cortical thinning may be related to pruning of synapses and/or myelination of axons in underlying white matter, shifting the observed border between gray and white matter seen on MRI scans (Gogtay et al. 2004; Shaw et al. 2008; Tamnes et al. 2010). Our results—even when corrected for age—show that thinner cortex in this young group is related to better recall performance, which is in accordance with the findings of Sowell et al. (2001). In the hippocampus, on the other hand, other processes must cause the volume increase; the plasticity of hippocampal connections throughout life might be what makes its contribution to memory consolidation possible (Leuner and Gould 2010). The volume increase could be explained by processes such as myelination (Benes et al. 1994) and neurogenesis (Leuner and Gould 2010). Other processes related to vascular changes or proliferation of glia cells cannot be ruled out either.

The maturational trajectories of brain structures have been found to be different in children at different performance levels (Shaw et al. 2006; Tamnes et al. 2010a). A similar pattern of results was not detected in the present study, where memory performance level did not impact the maturational trajectories of the tested brain structures. This needs to be investigated further in a longitudinal design, as there is a growing need for an increased understanding of the unfolding plasticity of the developing brain and its relationship with functional outcome.

Limitations

This study is part of an ongoing longitudinal project, and the current results are cross-sectional. One problem with a cross-sectional design is that there may be recruitment biases in the different cohorts. However, the sample age groups were well matched with respect to gender and IQ. The genuine effects of development are, however, better captured in a longitudinal design. Future studies are needed to confirm the results using different tasks, for instance of differing difficulty levels or verbal material. Another limitation with the material used, is the difficulty in ascertaining which memory processes are involved in each condition, especially in the recall conditions. Although the RCFT is a validated and well-described measure of visuospatial memory, it lacks the opportunity to separate various memory processes like encoding and retrieval.

Conclusion

In conclusion, the relationship between brain structures and memory abilities during development was shown to vary according to the sort of process (recall vs. retention) and the time interval (30-min vs. 1-week recall) used. Early maturation of long-term retention (1-week/30-min ratio) of visual material, interpreted as an index of memory consolidation, was related to the volume of hippocampus. In contrast, development of recall was accompanied by a relationship with thickness of left orbitofrontal cortex. The results demonstrate the usefulness of assessing memory over different time intervals, extending beyond the commonly employed interval of around 30-min.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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