

2 **Changes in Anterior and Posterior Hippocampus Differentially Predict Item-Space, Item-
3 Time, and Item-Item Memory Improvement**

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24

25

Abstract

26 Relational memory requires the hippocampus, but whether distinct hippocampal mechanisms
27 along the anterior-posterior axis are required for different types of relations is debated. We
28 investigated the contribution of structural changes in hippocampal head, body, and tail
29 subregions to the capacity to remember item-space, item-time, and item-item relations. Memory
30 for each relation and volumes of hippocampal subregions were assessed longitudinally in 171
31 participants across 3 time points (M_{age} at T1= 9.45 years; M_{age} at T2= 10.86 years, M_{age} at T3=
32 12.12 years; comprising 393 behavioral assessments and 362 structural scans). Among older
33 children, volumetric growth in: (a) head and body predicted improvements in item-time memory,
34 (b) head predicted improvements in item-item memory; and (c) right tail predicted improvements
35 in item-space memory. The present research establishes that volumetric changes in hippocampal
36 subregions differentially predict changes in different aspects of relational memory, underscoring
37 a division of labor along the hippocampal anterior-posterior axis.

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48 Without the ability to retain relational information about life events our memories would
49 be fragmentary, difficult to retrieve, and ultimately of little value. Relational memory depends on
50 mechanisms that bind features of experiences into integrated event representations ¹; these
51 features include where an event happened (item-space)², when it happened (item-time)³, and with
52 what other events it co-occurred (item-item)⁴. The hippocampus is critical for learning and
53 recalling these arbitrary memory relations ^{5,6}, but whether all types of memory relations are
54 supported by the same or different hippocampal mechanisms is debated ⁷⁻⁹.

55 On the one hand, there is substantial evidence that the hippocampus is necessary to learn
56 all arbitrary relations. For example, Konkel and colleagues found that adults with hippocampal
57 lesions were equally impaired in their ability to remember spatial, temporal, or item-item
58 relations ⁶. On the other hand, at least some degree of segregation within the hippocampus has
59 been reported ¹⁰. Item-item relations may be supported by more anterior regions ¹¹, whereas
60 item-space relations may be supported more strongly by right-lateralized posterior hippocampal
61 regions ¹². Here, we adopt a developmental approach to address the question of whether
62 developmental improvements in these three forms of relational memory rely on structural
63 changes in the hippocampus and, if so, whether they depend on the same or different subregions.

64 Recent research has highlighted age-related differences in hippocampal structure and
65 function in children and adolescents and evidence of cross-sectional associations between
66 volume and memory ¹³⁻¹⁶. However, longitudinal evidence linking changes in hippocampal
67 structure to memory development is lacking. We shed new light on these issues by capitalizing
68 on a longitudinal design in which we assessed both structural changes in hippocampal head,
69 body, and tail subregions and behavioral changes in an experimental task assessing item-space,
70 item-time and item-item memory.

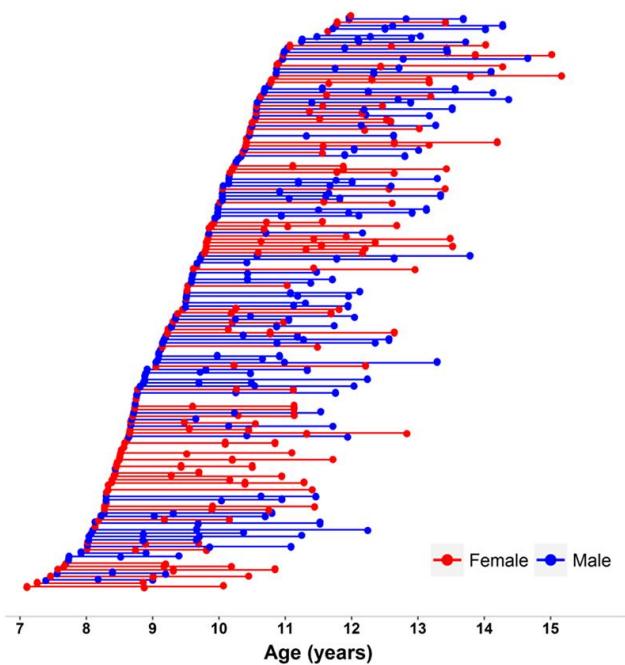
71 There are at least two lines of evidence suggesting that this approach may be particularly
72 informative. First, initial cross-sectional findings suggested heterogeneous development of the
73 hippocampus along the anterior-posterior axis with distinct relations with memory^{14,16-18}.
74 Second, heterogeneities in age-related differences in memory for spatial, temporal and
75 associative information have been documented in cross-sectional studies against a backdrop of
76 general memory improvement during childhood^{15,19-21}. This body of research indicates that
77 memory for spatial relations may be more robust at a younger age compared to memory for
78 temporal relations²⁰⁻²² and item-item associative relations²². Overall, these two lines of
79 evidence suggest a co-occurrence of distinct structural changes in the anterior and posterior
80 hippocampus and distinct behavioral changes in relational memory, consistent with a functional
81 segregation in the hippocampus during development. However, an important limitation of these
82 cross-sectional studies is that it was not possible to examine whether developmental changes in
83 hippocampal structures predicted developmental improvements in memory over time within the
84 same individuals.

85 In the present study, we used a combination of experimental and longitudinal approaches
86 to examine a cohort of 172 children between 7 and 15 years of age who underwent structural
87 magnetic resonance imaging (MRI) and relational memory assessment on up to three
88 measurement occasions (T1, T2, T3) (Fig. 1A; 362 longitudinal scans; 393 longitudinal
89 behavioral assessments). The advantage of a longitudinal approach combining behavior and
90 brain assessment is its potential to reveal how structural changes predict behavioral development,
91 accounting for concurrent associations. Participants encoded triplets of novel visual objects, each
92 appearing one at a time in one of three locations on the screen (Figure 1B, Top). Memory was
93 tested immediately after study with a probe signaling whether participants were required to

94 retrieve item-space, item-time, or item-item associations (Figure 1B, Bottom).

95 The central hypothesis guiding the present research is that changes in hippocampal
96 structure contribute to developmental improvements in relational memory. Specifically, we
97 predicted that relational memory developed differentially as a function of type of relation, with
98 the ability to remember item-space relations developing earlier than the other relations. We also
99 predicted distinct developmental trajectories of hippocampal volume as a function of subregion,
100 with the hippocampal head decreasing and the hippocampal body increasing in volume at least
101 prior to age 10¹⁵. Finally, we hypothesized that volumetric changes in hippocampal subregions
102 would predict behavioral changes differently as a function of type of relation. For example,
103 changes in more posterior subregions (i.e., tail) were expected to relate to the development of
104 memory for item-space relations¹⁰.

A



B

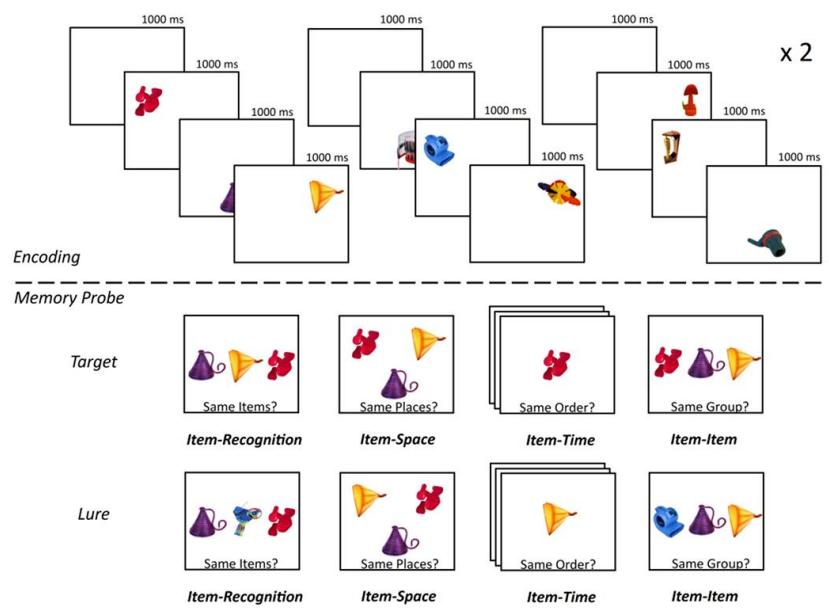


Figure 1. **A.** Longitudinal cohort of 172 children providing MRI structural images and relational memory assessments on up to three occasions (362 longitudinal scans, 393 longitudinal behavioral assessments). **B.** Triplet Binding Task (TBT). Encoding: Item-Recognition, Item-Space, Item-Time, and Item-Item relation conditions shared identical encoding procedures. Memory probe: Target and lure test trials for item-recognition, item-space, item-time, and item-item relation conditions, from left to right, respectively.

105 To briefly summarize our key and novel findings, we report that memory for item-space
106 relations matured earlier than memory for item-time and item-item relations, and that the
107 hippocampal head declined in volume throughout most of middle childhood, whereas
108 hippocampal body increased in volume until approximately age 10 before declining. Finally, we
109 report that volumetric increases in head and body predicted better item-time and item-time
110 memory, whereas increases in tail volume predicted better item-space memory.

111 Results

112 We conducted longitudinal analyses using mixed effect models ²³. Memory for each
113 relation was calculated as the difference between hit and false-alarm rates. Total hippocampal
114 volumes were first extracted using the semi-automated procedure described in the Methods
115 section, and were then manually segmented into head, body and tail based on established
116 guidelines ¹⁴. This segmentation had excellent inter-rater reliability (Head/Body Division:
117 ICC=.98; Body/Tail Division: ICC=.99). Volumes were adjusted for intracranial volume (ICV)
118 using regression methods ²⁴. In all models, the effect of age was separated into a time-varying
119 within-subject effect (i.e., change in age since T1) and a time-invariant between-subject effect
120 (i.e., age at T1) (25, 27; see Methods). In brain-behavior models, the effects of head, body, and
121 tail volumes were similarly separated into a time-varying within-subject effect (i.e., changes in
122 volume since T1) and a time-invariant between-subject effect (i.e., volume at T1).

123 In each longitudinal analysis, model comparisons were conducted to test whether the
124 inclusion of key variables of interest increased model fit over baseline models, beginning with
125 testing for main effects, and then systematically adding higher order interaction effects with
126 these key variables. The full longitudinal models are described in Table 1. The key variables of
127 interest in the behavioral models included the effect of age at T1 and change in age, as well as

128 the two-way interactions between these variables and three-way interactions with type of
129 memory relation. The key variables of interest in the hippocampal models were also age at T1
130 and change in age, as well as their interaction, and three-way interactions with hippocampal
131 subregion. Finally, in the brain–behavior models, the key variables of interest were volume of
132 head, body, and tail at T1 and changes in these volumes since T1, as well as their interactions
133 with age at T1 and change in age.

Table 1. Fixed and Random Effect Models

Behavioral: $\text{Memory} = \text{Sex} + \text{Item-recognition}_{T1} + \text{Age}_{T1} * \Delta\text{Age} * \text{Relation} + (1 + \Delta\text{Age} | \text{Participant})$

Hippocampal: $\text{Volume} = \text{Sex} + \text{Hemisphere} + \text{Age}_{T1} * \Delta\text{Age} * \text{Subregion} + (1 + \Delta\text{Age} | \text{Participant})$

Brain–Behavior: $\text{Memory} = \text{Sex} + \text{Item-recognition}_{T1} + \text{Head}_{T1} + \text{Body}_{T1} + \text{Tail}_{T1} + \text{Age}_{T1} * \Delta\text{Age} * \Delta\text{Head} + \text{Age}_{T1} * \Delta\text{Age} * \Delta\text{Body} + \text{Age}_{T1} * \Delta\text{Age} * \Delta\text{Tail} + (1 + \Delta\text{Age} | \text{Participant})$

Note: '*' denotes inclusion of main and interactive effects between operands. '(1 + Δ Age | Subject)' indicates a random intercept and slope model. Female gender, item-item relations, and hippocampal head served as reference categories. Brain-Behavior models examined each relation separately. T1 subscript denotes value at Time 1.

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135 **Distinct Developmental Trajectories of Relational Memory**

136 We first conducted the longitudinal analysis of relational memory (See Table 1). Overall,
137 relational memory was greater in children who were older at T1 ($\chi^2 = 17.8, df = 1, p < .0001$;
138 $\beta = .18, b = .04, t(170) = 4.4, p < .0001$), capturing cross-sectional differences, and it increased
139 more as more time passed, as indicated by a positive association with change in age ($\chi^2 = 25.5, df$
140 $= 1, p < .0001; \beta = .17, b = .04, t(121) = 5.19, p < .0001$). Improvements in relational memory over
141 time were greater for children who were younger at T1 (age at T1 x change in age in years
142 interaction; $\chi^2 = 7.90, df = 1, p = .005; \beta = .18, b = -.02, t(140) = -2.88, p = .004$). We also found a
143 significant effect of type of relation ($\chi^2 = 368.5, df = 2, p < .0001$), such that the highest
144 performance was observed for item-space memory ($M = .45, SE = .01$), which was greater than item-
145 item-time ($M = .36, SE = .01; t(864) = 7.1, p < .0001$). Item-time was, in turn, greater than item-

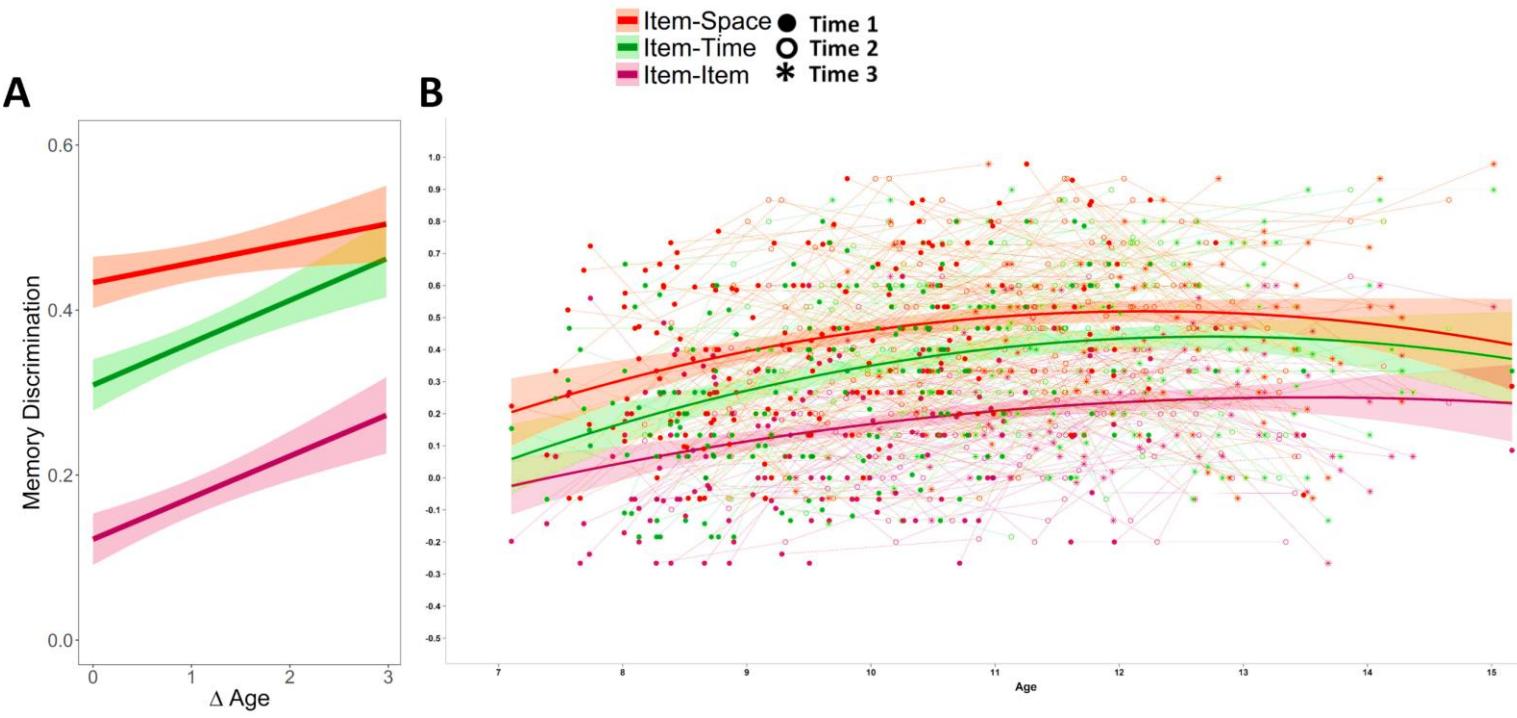


Figure 2. Developmental changes in memory for item-space, item-time, and item-item relations. Error bands represent 95% confidence intervals. **A.** Depicting the three-way interaction between memory relation, within-subject changes in age since Time 1 (Δ Age), and cross-sectional differences in the starting age at Time 1 (here at 8- and 11-years of age). **B.** A descriptive spaghetti plot of item-space, item-time, and item-item memory performance by years in age, with quadratic lines fitted. Note that the use of age conflates between-person cross-sectional differences with within-person changes, and thus these fit lines do not reflect true longitudinal change.

146 item memory ($M=.17$, $SE .01$; $t (864) = 10.03$, $p < .0001$). Consistent with our primary
147 hypothesis, the magnitude of memory improvement over time depended on the type of relation,
148 as indicated by a significant interaction between change in age and type of relation ($\chi^2 = 6.21$ df
149 = 2, $p = .04$) (Figure 2). See Table 2 for parameter estimates for each type of relation separately,
150 and Table S1 for parameter estimates testing the interaction with type of relation. The positive
151 association between change in age and change in memory was stronger for item-time and item-
152 item than for item-space (item-space: $\beta=.09$, $b = .02$, $t (374) = 2.17$, $p = .03$; item-time relative to

153 item-space, $\beta=.08$, $b = .03$, $t (867) = 2.18$, $p = .03$; item-item relative to item-space, $\beta=.08$, $b =$
154 $.03$, $t (867) = 2.11$, $p = .04$). Associations between change in age and performance did not differ
155 between item-time and item-item relations ($p = .94$). Model parameters predicted that item-space
156 memory plateaued around 10.4 years, item-time memory around 12.2 years of age, and item-item
157 around 12.5 years. Thus, consistent with prior work, item-space memory matured earlier than
158 both item-item and item-time relations.

Table 2. Parameter Estimates for Item-Time, Item-Item and Item-Space Models

Effect	Beta	b	SE	t	p
Item-Time					
(Intercept)	–	.323	.023	14.3	<.001
Item-Recognition	.310	.353	.066	5.39	<.001
Male	-.048	-.025	.029	-.861	.390
Start-Age	.213	.044	.013	3.29	.001
Δ Age	.212	.051	.011	4.61	<.001
Start-Age x Δ Age	-.125	-.019	.009	-2.05	.043
Item-Item					
(Intercept)	–	.133	.019	6.93	<.001
Item-Recognition	.162	.151	.053	2.87	.005
Male	-.033	-.014	.023	-.605	.546
Start-Age	.204	.035	.012	2.95	.004
Δ Age	.244	.048	.009	5.27	<.001
Start-Age x Δ Age	-.128	-.016	.008	-2.07	.041
Item-Space					
(Intercept)	–	.457	.023	20.2	<.001
Item-Recognition	.328	.357	.065	5.49	<.001
Male	-.076	-.038	.029	-1.31	.191
Start-Age	.180	.036	.014	2.66	.009
Δ Age	.083	.019	.011	1.73	.086
Start-Age x Δ Age	-.139	-.020	.009	-2.18	.031

Notes: Model Fits: Item-Time: $\chi^2 = 68.7$, $df = 5$, $p < 1.85e-13$; Item-Space: $\chi^2 = 48.2$, $df=5$, $p = 3.3e-9$; Item-Item: $\chi^2 = 48.0$, $df=5$, $p = 3.6e-9$; Interactions with sex were not significant ($\chi^2s \leq 4.6$, $dfs=3$, $ps \geq .20$). Note: Δ Age is defined at time in years since Time 1. Item-recognition and Start-Age are centered at the mean at Time 1. Left hemisphere and female are reference categories.

159 **Distinct Developmental Trajectories of Hippocampal Subregions**

160 We assessed developmental changes in hippocampal head, body, and tail (See Table 1).

161 We found a significant interaction between change in age and hippocampal subregion ($\chi^2 = 8.83$

162 $df = 2, p = .012$), which was further moderated by age at T1 ($\chi^2 = 9.80, df = 3, p = .020$). As

163 predicted, we found distinct within-subject trajectories for the three subregions (Figure 3). See

164 Table S2 for parameter estimates of this full model. For completion, we also estimated

165 longitudinal models using total hippocampal volume, the results of which are reported in Table

166 S3. Given the differences in volumetric change as a function of subregion, we examined the

167 trajectory of each subregion separately.

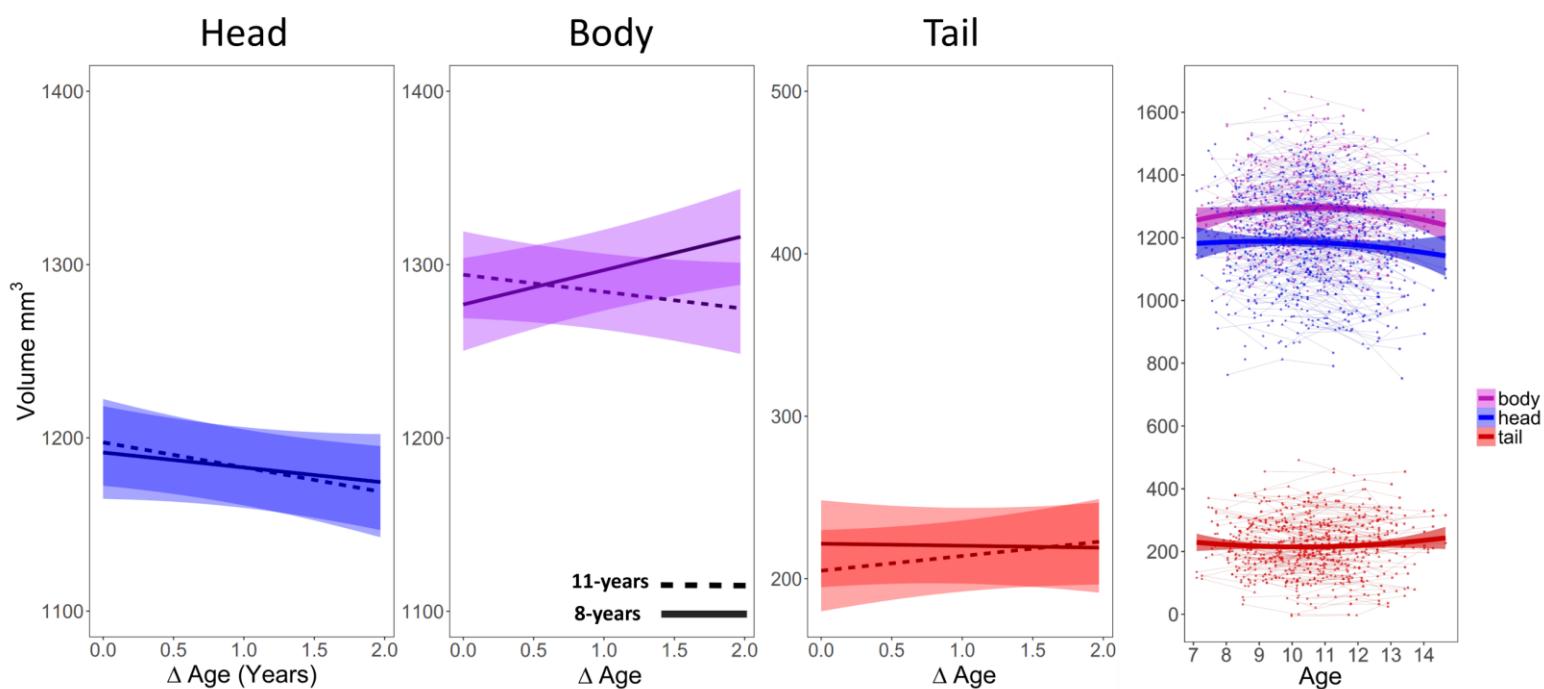


Figure 3. Developmental changes in head, body, and tail ICV-corrected volume. Error bands represent 95% confidence intervals. **A.** Depicting the three-way interaction between hippocampal sub-region, within-subject change in age since Time 1 (Δ Age), and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age. **B.** Spaghetti plots of head, body, and tail ICV-corrected volume over time with quadratic lines fitted.

Table 3. Parameter Estimates for Models of Hippocampal Head, Body, and Tail Change

Sub-Region	Effect	Beta	b	SE	t	p
Head	(Intercept)	–	1128	16.4	68.8	<.001
	Male	.030	11.7	22.3	.525	.600
	Hemisphere [Right]	.313	106	5.23	20.2	<.001
	Start-Age (Mean-Centered)	.011	3.02	10.2	.298	.770
	ΔAge	-.060	-7.07	2.70	-2.62	.009
	Start-Age x ΔAge	-.056	-5.51	2.56	-2.16	.033
Body	(Intercept)	–	1314	13.4	98.1	<.001
	Male	-.133	-26.1	18.1	-1.44	.150
	Hemisphere [Right]	-.104	-33.5	4.93	-6.80	<.001
	Start-Age (Mean-Centered)	.015	1.40	8.35	.167	.873
	ΔAge	.012	1.68	2.53	.661	.514
	Start-Age x ΔAge	-.061	-4.86	2.39	-2.03	.042
Tail	(Intercept)	–	208	9.38	22.1	<.001
	Male	.067	11.5	12.6	.912	.363
	Hemisphere [Right]	.024	4.10	2.92	1.40	.164
	Start-Age (Mean-Centered)	-.042	-3.30	5.86	-.564	.572
	ΔAge	.022	1.76	1.50	1.17	.240
	Start-Age x ΔAge	.010	.538	1.42	.377	.712

Model Fits: Hippocampal Head: $\chi^2 = 312$, $df = 5$, $p < 2.2e-1$; Hippocampal Body: $\chi^2 = 51.4$, $df = 5$, $p = 7.2e-10$; Hippocampal Tail: $\chi^2 = 4.44$, $df = 5$, $p = .49$. Note: ΔAge is defined as time in years since Time 1; Left hemisphere and female are reference categories; Volumes are in cubic mm.

169 **Hippocampal Head.** As predicted, hippocampal head volumes declined over time, as
 170 indicated by the negative effect of change in age ($\chi^2 = 5.63$, $df = 1$, $p = .02$; $b = -7.07$, $t(449) = -2.62$, $p = 9.2e-3$). This effect was moderated by age at T1 ($\chi^2 = 4.65$, $df = 1$, $p = .03$; $\beta = -.06$, $b = -5.51$, $t(457) = -2.16$, $p = .03$), such that greater volumetric declines were observed in children
 171 the older you were at T1. Associations with change in age did not significantly differ between
 172 hemispheres ($\chi^2 = .60$, $df = 1$, $p = .44$) or sex ($\chi^2 = 2.58$, $df = 1$, $p = .11$) (Table 3). A descriptive
 173 examination of the partial derivatives of model parameters suggests that peak volume of
 174 hippocampal head occurred at 8.17 years of age before declining during late childhood.
 175

177 ***Hippocampal Body.*** As predicted, hippocampal body exhibited a non-linear trajectory.

178 Change in age significantly interacted with age at T1 ($\chi^2 = 4.10, df = 1, p = .04; \beta = -.06, b = -$

179 $4.86, t(496) = -2.03, p = .04$): The volume of the hippocampal body increased over time for

180 younger children, but it declined for older children. Association with changes in age did not

181 significantly differ by hemisphere ($\chi^2 = .60, df = 1, p = .44$) or sex ($\chi^2 = 3.4e-3, df = 1, p = .95$)

182 (Table 3). A descriptive examination of the partial derivatives of model parameters suggests that

183 peak volume of hippocampal body occurred at 9.79 years before declining in late childhood.

184 ***Hippocampal Tail.*** No significant developmental changes were observed for either left or
185 right tail (Table 3).

186 **Linking Hippocampal and Relational Memory Development**

187 We examined whether and how volumetric changes along the anterior-posterior axis
188 predicted the development of each type of memory relation (See Table 1). All models included
189 volume at T1, changes in volume since T1, age at T1, and changes in age since T1, as well as
190 their interactions. Volume and volume changes were in cubic millimeters for unstandardized
191 betas. The primary longitudinal effects of interest were the two- and three-way interactions
192 between age at T1, change in age, and change in volume. These interactions allow us to link
193 developmental changes in volume to behavioral development, with the additional consideration
194 that longitudinal relations may depend on the age at the start of the study. We started by
195 examining item-time and item-item memory, because they showed the most robust behavioral
196 change, and ended with item-space memory, which we established develops relatively earlier
197 (see Methods for detailed description of the models). For these, left and right hippocampal
198 volumes were summed because no hemispheric differences were observed.

199 **Item-Time.** Consistent with predictions, changes in hippocampal head, body, and tail
200 predicted item-time memory. Specifically, we observed a significant three-way interaction
201 between change in hippocampal subregion volumes, age at T1 and change in age ($\chi^2 = 12.1, df$
202 =3, $p = .007$) (See Table 4). Increase in head and body volumes, but not tail, significantly
203 predicted greater memory performance after longer delays (e.g., a 3-year change is depicted in
204 Figure 4A), but not shorter delays (e.g., a 1-year change in age is depicted in Figure S1A),
205 indicating that several years were necessary for these brain-behavior relations to manifest.
206 Furthermore, this result depended on age at T1. When the model was evaluated for children who

Table 4. Hippocampal Volume Predicting the Development of Item-Time Memory.

Effect	Left and Right Hippocampal Sum				
	Beta	b	SE	t	p
(Intercept)	-	3.2e-1	2.5e-2	13	<.0001
Item-Recognition	0.28	3.2e-1	7.4e-2	4.4	<.0001
Sex [Male]	-0.053	-2.8e-2	3.2e-2	-0.86	0.39
Start-Volume Head	-0.049	-4.5e-5	5.6e-5	-0.79	0.43
Start-Volume Body	-0.065	-7.0e-5	6.6e-5	-1.1	0.29
Start-Volume Tail	0.062	9.8e-5	9.9e-5	0.99	0.32
Start-Age	0.25	5.8e-2	1.7e-2	3.4	0.001
Δ Age	0.26	6.2e-2	1.3e-2	4.7	<.0001
Δ Head	-0.063	-1.9e-4	4.1e-4	-0.47	0.64
Δ Body	-0.056	-1.6e-4	3.8e-4	-0.43	0.67
Δ Tail	-0.2	-1.4e-3	9.5e-4	-1.5	0.14
Start-Age x Δ Age	-0.13	-2.1e-2	1.2e-2	-1.7	0.095
Start-Age x Δ Head	-0.26	-6.4e-4	3.2e-4	-2	0.048
Start-Age x Δ Body	-0.22	-6.3e-4	3.7e-4	-1.7	0.096
Start-Age x Δ Tail	-0.037	-2.6e-4	1.0e-3	-0.25	0.8
Δ Age x Δ Head	0.072	1.1e-4	2.2e-4	0.5	0.62
Δ Age x Δ Body	0.14	2.0e-4	1.9e-4	1.1	0.29
Δ Age x Δ Tail	0.11	4.0e-4	5.0e-4	0.8	0.42
Start-Age x Δ Age x Δ Head	0.33	4.1e-4	1.9e-4	2.2	0.027
Start-Age x Δ Age x Δ Body	0.29	4.2e-4	1.9e-4	2.2	0.032
Start-Age x Δ Age x Δ Tail	0.12	4.2e-4	5.5e-4	0.77	0.44

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

207 were older at T1 (e.g., 11 years, as depicted in Figure 4A), volumetric increases in head and body
208 volume predicted better item-time memory (Body: $\beta=.47$, $b=.001$, $SE = 4.9e-4$, $t=2.59$, $p=.01$;
209 Head: $\beta=.35$, $b=.001$, $SE = 5.1e-4$, $t=1.87$, $p=.06$), but was not significant for children who were
210 younger at T1 (e.g., 8 years, as depicted in Figure 4A), despite the appearance of a negative
211 relation ($ps \geq .17$). Change in the tail was not associated with item-time performance ($ps \geq .18$).
212 Thus, although the normative pattern of volumetric change in this sample was a linear decrease
213 in the head, and a curvilinear in the body volume over time, protracted increases in head and
214 body volume in older children predicted better item-time memory. Parameter estimates for
215 models separating left and right hippocampal structures are also included in Table S4.

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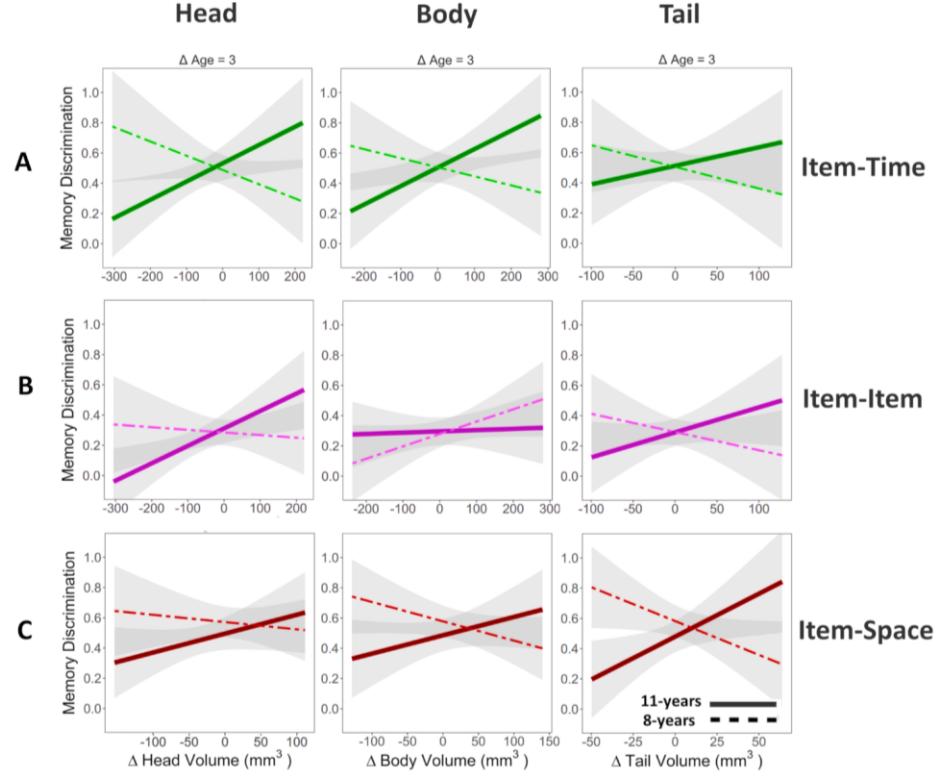


Figure 4. Depicting interaction between change in ICV-corrected volume and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age evaluated at change in age since Time 1 equaling three years ($\Delta\text{Age} = 3$). See Supplemental Figure 1 for depiction of interaction after one year since Time 1; relations between volume changes and memory were stronger at longer delays. Error bands represent 95% confidence intervals. **A.** Item-Time. **B.** Item-Item. **C.** Item-Space.

217 **Item-Item.** Consistent with our prediction, changes in hippocampal structure predicted
218 item-item memory. Specifically, we found a significant interaction between volumetric changes
219 in head, body, and tail (as a block) and age at T1 ($\chi^2 = 8.82, df = 3, p = .03$), but this interaction
220 was not significantly moderated by changes in age ($\chi^2 = 3.2, df = 3, p = .37$) (See Table 5).
221 Examining the volumetric change and age at T1 interaction, we found that among children who
222 were young at T1 (i.e., 8 years), increases in body volume predicted greater item-item memory
223 ($\beta = .27, b = .0007, SE = 2.5\text{e-}4, t = 2.93, p = .004$). In contrast, among children who were older at T1
224 (i.e., 11 years), increases in head volume predicted better behavioral performance ($\beta = .24,$
225 $b = .0006, SE = 2.3\text{e-}4, t = 2.38, p = .02$) (See Figure 4B and Figure S1B). Parameter estimates for
226 models separating left and right hippocampal structures are also included in Table S5.

227 **Table 5.** Hippocampal Volume Predicting the Development of Item-Item Memory.

228	229	Effect	Left and Right Hippocampal Sum				
			Beta	b	SE	t	p
230	(Intercept)		-	1.2e-1	2.2e-2	5.4	<.0001
231	Item-Recognition	0.16	1.5e-1	6.2e-2	2.5	0.013	
232	Sex [Male]	-0.0048	-2.1e-3	2.7e-2	-0.077	0.94	
233	Start-Volume Head	-0.013	-1.0e-5	4.7e-5	-0.21	0.83	
234	Start-Volume Body	0.025	2.3e-5	5.6e-5	0.41	0.69	
235	Start-Volume Tail	0.018	2.4e-5	8.2e-5	0.29	0.78	
236	Start-Age	0.2	3.9e-2	1.5e-2	2.6	0.012	
237	Δ Age	0.27	5.5e-2	1.1e-2	5	<.0001	
238	Δ Head	-0.048	-1.2e-4	3.5e-4	-0.35	0.73	
	Δ Body	-0.00071	-1.7e-6	3.4e-4	-0.005	>0.99	
	Δ Tail	-0.15	-8.7e-4	8.5e-4	-1	0.31	
	Start-Age x Δ Age	-0.081	-1.1e-2	1.0e-2	-1.1	0.29	
	Start-Age x Δ Head	0.12	2.5e-4	1.2e-4	2.1	0.039	
	Start-Age x Δ Body	-0.13	-3.0e-4	1.4e-4	-2.2	0.028	
	Start-Age x Δ Tail	0.015	8.5e-5	3.3e-4	0.26	0.8	
	Δ Age x Δ Head	0.16	2.1e-4	1.8e-4	1.1	0.26	
	Δ Age x Δ Body	0.1	1.2e-4	1.6e-4	0.76	0.45	
	Δ Age x Δ Tail	0.13	3.8e-4	4.3e-4	0.88	0.38	

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

239 Overall, volumetric changes in hippocampal body appeared to differentially predict item-
240 time and item-item memory. Consistent with this, we found that the age at T1 by change in body
241 volume interaction was significantly different for item-time and item-item memory ($\chi^2 = 8.92, df$
242 $= 1, p = .003$). In younger children, the association between change in body and memory was
243 more positive for item-item than item-time ($\beta = .32, b = .001, SE = 5.2e-4, t = 2.50, p = .014$), but in
244 older children, there was a trend for a more negative relation for item-item than item-time
245 memory ($\beta = -.28, b = -.001, SE = 5.8e-4, t = -1.93, p = .055$). Overall results are consistent with the
246 protracted behavioral trajectory of item-item memory and suggest a transition from body to head
247 in supporting developmental improvements in item-item memory.

248 **Item-Space.** No significant relations between changes in hippocampal structure and item-
249 space memory were found when we used volume changes summed across hemispheres ($\chi^2 s \leq$
250 $4.04, df s = 3, p s \geq .26$) (See Table S6), nor did using overall hippocampal volume perform better
251 than using subregions ($\chi^2 = 3.84, df = 8, p = .87$).

252 Given the suggestion from the literature that associations between change in head, body,
253 and tail volumes and spatial memory could be right-lateralized, we also tested our model in the
254 right hippocampus. This analysis revealed a significant three-way interaction between changes in
255 right hippocampus, changes in age, and starting age at T1 ($\chi^2 = 10.6, df = 3, p = .01$) (See Table
256 6). Volumetric changes significantly more positively predicted memory performance with longer
257 delay (e.g. 3 years; Figure 4C), but not significantly with shorter delays (e.g., 1 year; $p s > .098$;
258 Figure S1C). In other words, in younger children at T1, there was a trend for reduction of tail
259 volume over time predicting better item-space memory ($\beta = -.32, b = -.004, SE = .002, t = -1.86,$
260 $p = .07$), but in older children at T1, volumetric increases in the tail predicted better item-space
261 memory ($\beta = .528, b = .006, SE = .003, t = 2.16, p = .03$). However, neither the body ($p s \geq .11$) nor

262 the head ($p \geq .21$) were significantly associated to item-space memory at those starting ages.

263 Thus, although the hippocampal tail did not seem to show an average pattern of volumetric

264 change based on previous analyses, the present results suggest that individual differences in tail

265 development predict item-space memory performance.

266

267 **Table 6.** Hippocampal Volume Predicting the Development of Item-Space
268 Memory.

269	Effect	Right Hippocampus				
		Beta	b	SE	t	p
270	(Intercept)	-	4.6e-1	0.025	18	<.0001
	Item-Recognition	0.31	3.5e-1	7.2e-2	4.8	<.0001
271	Sex [Male]	-0.083	-4.2e-2	3.2e-2	-1.3	0.19
	Start-Volume Head	-0.027	-4.6e-5	1.0e-4	-0.45	0.66
272	Start-Volume Body	-0.042	-7.6e-5	1.1e-4	-0.68	0.5
	Start-Volume Tail	0.039	1.1e-4	1.8e-4	0.61	0.54
273	Start-Age	0.28	6.3e-2	1.7e-2	3.8	0.0003
	ΔAge	0.12	2.9e-2	1.3e-2	2.2	0.028
274	ΔHead	-0.086	-4.2e-4	6.5e-4	-0.65	0.52
	ΔBody	-0.018	-8.3e-5	6.3e-4	-0.13	0.9
275	ΔTail	-0.14	-1.7e-3	1.7e-3	-0.99	0.32
	Start-Age x ΔAge	-0.21	-3.4e-2	1.2e-2	-2.7	0.0077
276	Start-Age x ΔHead	-0.055	-2.3e-4	5.5e-4	-0.42	0.68
	Start-Age x ΔBody	-0.11	-4.7e-4	5.8e-4	-0.81	0.42
277	Start-Age x ΔTail	-0.33	-4.0e-3	1.8e-3	-2.3	0.025
	ΔAge x ΔHead	0.13	3.2e-4	3.6e-4	0.88	0.38
278	ΔAge x ΔBody	0.025	5.5e-5	3.2e-4	0.17	0.86
	ΔAge x ΔTail	0.16	9.6e-4	9.2e-4	1	0.3
279	Start-Age x ΔAge x ΔHead	0.12	2.4e-4	3.1e-4	0.78	0.44
	Start-Age x ΔAge x ΔBody	0.2	4.4e-4	3.2e-4	1.4	0.18
280	Start-Age x ΔAge x ΔTail	0.41	2.4e-3	9.6e-4	2.5	0.012

281 Note: Female is reference sex. For unstandardized betas, volume is in cubic millim
282 eters and age is in years.

283

284

285

Discussion

286 The ability to remember associations between events and their spatio-temporal context
287 depends on hippocampal mechanisms, which bind contextual features into integrated event
288 representations ¹. Here, we asked whether volumetric changes in hippocampal volume predict
289 longitudinal improvements in relational memory, and whether those developmental associations
290 differed depending on hippocampal subregion or type of memory relation.

291 This is the first report showing that longitudinal improvements in relational memory
292 differed as a function of the type of memory relation, such that item-space memory developed
293 more rapidly than item-time and item-item memory. In the largest longitudinal study of
294 hippocampal subregions to date, this research showed that hippocampal head, body, and tail
295 follow different developmental trajectories from childhood into adolescence. Linking structural
296 and behavioral changes, we report for the first time that volumetric changes in hippocampal
297 head, body, and tail differentially predicted longitudinal improvement in item-space, item-time,
298 and item-item.

299 **Developmental Change in Relational Memory Depends on the Nature of the Relation**

300 In our initial cross-sectional analysis ²², item-space memory reached adults' levels of
301 performance before item-time memory, which in turn preceded item-item memory. In the present
302 research, we examined within-person change while accounting for cross-sectional differences
303 and showed that item-space memory improves until around 10½, whereas item-time and item-
304 item memory followed prolonged trajectories with improvements about 12 and 12½ years of age
305 respectively. This finding is additionally consistent with prior cross-sectional evidence that
306 spatial memory develops earlier than temporal memory ^{20–22}. Although we cannot rule out the
307 possibility that aspects of our tasks might differ across conditions for reasons other than the type

308 of relation manipulated, we argue that the use of novel stimuli and arbitrary associations is an
309 effective way to assess relational memory. The more rapid development of item-space memory
310 compared to the other relations suggests that relational memory processes are not fully unitary.

311 Although item-time memory was generally better than item-item, their developmental
312 trajectories were similar. This may have been due to the dependence of these tasks on shared
313 hippocampal operations. For example, performance on both item-time and item-item memory
314 may have benefitted from some form of temporal processing—the former from processing the
315 precise temporal order of the images and the latter from processing which groups of items were
316 presented together in the same temporal context⁷. On the other hand, there may also be
317 differences in how the hippocampus supports item-time and item-item memory despite the
318 apparent similarity in behavioral trajectory, which may help to explain why item-item is a more
319 challenging task^{26,27}. Disentangling these two possibilities was made possible by the
320 longitudinal design combining assessments of both brain and behavior and was addressed in the
321 brain–behavior analyses. Overall, these behavioral findings provide the first longitudinal
322 evidence of protracted and distinct developmental trajectories of different aspects of relational
323 memory. The examination of these relations within participants and within the same task form,
324 which constrain response demands, offers strong support for a functional distinction in relational
325 memory.

326 **Developmental Change in Hippocampal Volumes Varies Along the Anterior-Posterior Axis**

327 We provided new longitudinal evidence indicating that hippocampal head, body, and tail
328 develop differentially from middle childhood into adolescence. Consistent with the findings of
329 the seminal longitudinal study of 31 individuals that first examined morphometric development
330 along the anterior–posterior axis²⁸, hippocampal head declined in volume from middle

331 childhood to adolescence, while hippocampal body increased in volume until about 10 years of
332 age and declined thereafter. Hippocampal tail volume was stable throughout middle childhood
333 and adolescence, suggesting that its development occurred earliest, consistent with previous
334 reports ^{14,16,28}.

335 Curvilinear trajectories in hippocampal development are frequently observed ^{15,18}.
336 Although not yet definitively linked, volumetric increases may reflect ongoing synaptogenesis
337 and dendritic elaboration, while volumetric declines may reflect synaptic pruning ²⁹. It is not
338 known why the body, unlike the head and the tail, continues to increase in volume into late
339 childhood (i.e. 9 to 10 years of age). However, the body has been postulated to act as a bridge or
340 integrator of anterior and posterior mechanisms ³⁰. We can speculate that continued dendritic
341 elaboration in the body, compared to head and tail, may be important for the body to complete
342 the required connections with head and tail. Whatever the reason, the diverging developmental
343 trajectories of head, body, and tail reported here provide a demonstration that the hippocampus is
344 not a uniform structure and joins the growing body of evidence suggesting functional differences
345 along the anterior-posterior hippocampal axis ¹⁰.

346 **Changes in Hippocampal Volume Predict Developmental Improvements in Relational
347 Memory**

348 We found evidence that increases in hippocampal volumes over time predicted
349 longitudinal improvements in relational memory. We note that these positive relations with
350 behavior are observed even in the context of normative volumetric decreases (e.g., hippocampal
351 head). Previous cross-sectional studies have reported negative associations between hippocampal
352 head volume and behavior ^{14,17}, suggesting the hypothesis that decreases of hippocampal head
353 over time may promote behavioral improvements. Instead, even though we confirmed normative

354 volumetric declines in this region during development, greater memory performance was
355 observed among those with a relative *increase* in volume. These findings may shed light on
356 underlying mechanisms. One possibility is that these positive associations may depend on
357 ongoing synaptogenesis and dendritic elaboration within hippocampal circuitry³¹ and these
358 processes may be particularly important for behavior, even when other mechanisms of structural
359 change, such as pruning, may result in a net loss of volume. Our findings overall support a
360 nascent body of cross-sectional research obtained over the last decade linking the hippocampus
361 to age differences in memory^{13,14}. These findings dispel a long-held, but not adequately tested
362 assumption, that the hippocampus and the associative processes it supports, do not contribute to
363 developmental improvements in memory after early childhood¹⁹.

364 We also assessed, for the first time, whether the longitudinal association between
365 hippocampal structure and memory differed as a function of subregion and type of memory
366 relation. These analyses revealed distinct associations, suggesting that processes supporting
367 memory for item-space, item-time, and item-item relations are not uniform across the anterior-
368 posterior axis of the structure. Bilateral increases in the volume of hippocampal head and body
369 predicted larger improvement in item-time memory in older children. In contrast, increases in
370 body volumes predicted item-item memory in younger children and increases in head volume
371 predicted better item-item memory in older children, suggesting a developmental transition from
372 body to head for this type of relation. Finally, the relation between volumetric changes and the
373 development of item-space memory was right lateralized and restricted to the tail, increases in
374 right hippocampal tail over time predicted greater item-space memory, particularly in older
375 children.

376 Overall, these data suggest that protracted increase in sub-regional volumes are
377 associated with behavioral improvement. It is somewhat surprising that we did not detect reliable
378 relations between hippocampal growth and memory in younger children for item-time and item-
379 space memory. It is possible that memory improvements in younger compared to older children
380 reflect not only change in relational memory, but also increased consistency in children's
381 engagement with the memory task, potentially obscuring relations between memory and
382 volumetric change. However, contrary to this possibility, we found an association between
383 increases in hippocampal body in younger children and item-item memory, the most difficult of
384 the three relational tasks and, potentially, the most likely to produce less consistent data.
385 Nevertheless, we cannot exclude that our *change in age* parameter captured more variance than
386 our *change in volume parameter* because of additional processing demands in young children.
387 Change in age was included to model time and account for any source of development due to
388 extra hippocampal processes, but shared variance with measures of hippocampal development
389 cannot be excluded.

390 Our results are consistent with prior evidence that the hippocampus supports memory for
391 item-space, item-time, and item-item relations ^{6,8}, but also indicate heterogeneity in how each
392 subregion contributes to these memory relations. Memory for temporal order reliably recruits the
393 hippocampus in functional neuroimaging studies ³; however, while we only observed relations
394 with item-time memory for the hippocampal head and body, associations with hippocampal tail
395 have also been reported ³², suggesting that temporal memory may not be strongly localized to
396 any anterior-posterior subregion. Memory for associations between items has been preferentially
397 associated with hippocampal head and body ^{4,11}, and our results are consistent with these
398 findings. It is notable that item-time and item-item memory trajectories were similar

399 behaviorally. Yet, their trajectories were support by different hippocampal subregions
400 underscoring the advantage of a longitudinal design. Finally, spatial memory is frequently
401 associated with posterior hippocampus (i.e. tail and body)¹². We found evidence consistent with
402 this suggestion restricted to the right tail.

403 Many open questions remain about the processes that might underlie these different
404 longitudinal structure-behavior relations. One possibility is that hippocampal head, body, and tail
405 differ in terms of cell types and genetic expression³³, synaptic plasticity³⁴, and relative
406 cytoarchitectural composition (i.e. dentate gyrus, CA 1,3)^{15,16} For example, there is some
407 evidence for a division of time and space in some cytoarchitectural circuits³. Another possibility
408 is that each subregion supports the same set of operations via the tri-synaptic circuit, but on
409 different types of information received through differential connections with extrahippocampal
410 brain regions. More anterior subregions exhibit greater functional connectivity with perirhinal
411 cortex, while more middle and posterior regions of the hippocampus exhibit greater functional
412 connectivity with posterior parahippocampal cortex³⁵. The perirhinal cortex is widely
413 recognized as a region supporting complex item representations, while posterior
414 parahippocampal cortex may support spatial and non-spatial contextual associations⁵. A third
415 possibility is that the differences we observed reflect more general divisions of labor that
416 transcend the type of relation examined^{10,17}. Although we have no reason to suspect that our
417 item-time and item-item tasks required more generalization processes (as suggested by being the
418 only tasks associated with changes in hippocampal head), the current study cannot exclude this
419 possibility directly. Future research is required to disentangle these possibilities.

420 The present research has several limitations. One potential limitation is that we did not
421 differentiate between encoding and retrieval operations, and thus we cannot address hypotheses

422 that anterior and posterior hippocampus preferentially support encoding and retrieval,
423 respectively³⁶. However, it is not clear how differential support for encoding or retrieval
424 operations could explain the structure-behavior relations we observed here, especially given
425 identical encoding procedures, and minimization of retrieval demands using short-term memory
426 delays. Another potential limitation is that we focused exclusively on the development of the
427 hippocampus, while extra-hippocampal changes can additionally account for memory changes.
428 However, the goal of this research was to examine relational memory processes in the
429 hippocampus in a task that manipulated the type of relation. Moreover, our task used materials
430 and procedures designed to ensure that differences in performance across relational conditions
431 depended more strongly on hippocampally mediated associative processes^{6,8} than on pre-
432 frontally mediated strategic or controlled processes³⁷⁻³⁹. These procedures included identical
433 encoding procedures across relational conditions, the use of novel objects, which could not easily
434 be labeled, and arbitrary relations among them. As discussed earlier, retrieval demands were
435 reduced by testing memory over short delays. Finally, this research did not address how
436 cytoarchitectural subfields in the hippocampus (i.e. dentate gyrus, CA 1-3) may account for the
437 relations with head, body, and tail development, which should be the subject of future research
438 and analysis.

439 In conclusion, we present the first evidence to establish distinct links between
440 subregional changes in hippocampal structure to the differential development of relational
441 memory for associations between items and space, time, and other items. These results—beyond
442 their implication to theories of memory development—begin to disentangle the contributions of
443 the hippocampus to three critical dimensions of relational memory.

444

445

446 **Materials and Methods**

447 **Participants**

448 Our sample included 171 participants at T1 (84 females; 143 behavioral assessments; 155
449 structural scans; $M_{age} = 9.45$ years, $SD_{age} = 1.09$, 7.1 – 12.0 years), 140 participants at T2 (66
450 females; 136 behavioral assessments, 118 structural scans; $M_{age} = 10.86$ years, $SD_{age} = 1.22$, 8.2
451 – 13.86 years), and 119 participants at T3 (52 females; 114 behavioral assessments, 88 structural
452 scans; $M_{age} = 12.12$ years, $SD_{age} = 1.31$, 9.0 – 15.16 years). Item-space, item-time, and item-item
453 memory at T1 did not significantly differ between those who returned at T2 compared to those
454 who did not ($\chi^2 = 2.61$, $df = 3$, $p = .46$ uncorrected), or between participants who returned for T3
455 and those who did not ($\chi^2 = 1.31$, $df = 3$, $p = .73$ uncorrected). Head, body, and tail volumes did
456 not differ at T1 in those who returned at T2 than those who did not ($\chi^2 \leq 1.17$, $dfs = 2$, $ps \geq .56$
457 uncorrected), or between participants who returned for T3 and those who did not ($\chi^2 \leq 2.13$, dfs
458 = 2, $ps \geq .34$ uncorrected). Children were ineligible if parents reported a learning disability,
459 neurological or psychological diagnosis requiring medication at the time of enrollment. Children
460 were compensated for their participation. This research was conducted with the approval of the
461 Institutional Review Board at the University of California, Davis.

462 **Materials and Procedures**

463 Behavioral and imaging data were collected over two visits. The Triplet Binding Task
464 (TBT) was administered on the first visit. Magnetic Resonance Imaging (MRI) occurred
465 approximately one week after the behavioral assessment.

466 **Triplet Binding Task.** The TBT is a memory task that assesses item-time, item-space,
467 and item-item relational memory and item-recognition memory using ^{6,22}. To counter fatigue, the

468 TBT was administered over two separate sessions on the same day. In each session, each
469 memory type was assessed in blocks to minimize increased task-switching costs in younger
470 children. Blocks were counterbalanced across participants. Within each assessment block, 5
471 encoding-retrieval phases were administered. TBT stimuli included color images of novel and
472 obscure real-world objects unlikely to be familiar to participants; these stimuli limit the utility of
473 semantic-based organizational memory strategies known to underlie some developmental
474 improvements in memory³⁷.

475 ***Encoding Phase.*** Prior to each testing block, participants were instructed and tested on
476 their understanding of the task, the relation to be encoded, and the triplet trial structure using
477 practice encoding and retrieval phases. The encoding phase format was identical for item-time,
478 item-space, item-item, and item-recognition encoding conditions. Each encoding phase
479 comprised three trials. In each trial, three novel objects (i.e. triplet) were sequentially presented
480 for one second to three locations on a computer screen, one object per location (see Figure 1B
481 Top). A one second inter-trial fixation was then presented before proceeding to the next of the
482 three encoding trials. To aid learning, the encoding phase was repeated a second time.

483 ***Retrieval Phase.*** Retrieval immediately followed each encoding phase. Each retrieval
484 phase, depending on the testing block, assessed memory for item-space, item-time, or item-item
485 relations, or item recognition memory (Figure 1B Bottom). The retrieval phase comprised three
486 target and/or lure probes. Overall, 15 targets and 15 lures were probed in each retrieval
487 condition.

488 ***Item-space.*** In each item-space test probe, three objects from the same encoding trial
489 appeared together on the screen. Participants decided whether all objects appeared at their
490 original positions or not. In target trials all objects maintain their original positions, while in lure

491 trials the spatial positions of two objects are exchanged.

492 *Item-time.* In each item-time retrieval phase, three objects from the same encoding trial
493 were sequentially presented to the center of the screen. No object appeared at their original
494 spatial position. Participants decided whether the sequence of objects in the probe appeared in
495 their original order or not. In target trials all objects maintain their original order, while in lure
496 trials the ordinal position of two objects are switched.

497 *Item-item.* In each item-item test probe, three objects appeared on the screen at three
498 horizontal positions. No object appeared at their original spatial position. Participants decided
499 whether all objects had appeared together in the same trial (i.e. triplet) or not. In target trials all
500 objects came from the same encoding trial, while in lure trials one object was exchanged with an
501 object from another trial from the same encoding phase.

502 *Item recognition.* In each item-recognition test probe, three objects appeared together on
503 the screen at three horizontal positions. No object appeared at their original spatial position.
504 Participants decided whether all objects had previously been studied. In target trials all objects
505 were studied, while in lure trials two of the three objects were new.

506 **Magnetic Resonant Imaging.** Magnetic Resonance Imaging (MRI) was acquired at the
507 University of California, Davis Imaging Research Center in a 3T Siemens Tim Trio scanner with
508 a 32-channel head coil. Two 7½-minute T1-weighted MPRAGE images were acquired (TE: 3.2
509 ms; TR: 2500 ms; in-plane resolution: 640 × 256 matrix, 0.35 mm x 0.70 mm; slice resolution:
510 640, 0.35 mm). Each participant's two structural images were co-registered, averaged, and
511 oriented so that the coronal plane was perpendicular to the long axis of the hippocampus. Each
512 image was cropped into left and right hippocampal regions, after which retrospective bias
513 correction was performed.

514 ***Hippocampal Segmentation.*** Hippocampal segmentation was performed using the
515 Automatic Hippocampal Estimator using Atlas-based Delineation (AHEAD) software which
516 implements a state-of-the-art multi-atlas joint label fusion approach to image segmentation ⁴⁰.
517 Briefly, manually labeled atlases of left and right hippocampus are non-linearly registered to
518 each participant's structural image using Advanced Normalization Tools. This produces
519 candidate segmentations for each target's hippocampus from which a consensus segmentation is
520 computed using joint label fusion, an advanced weighted voting procedure ⁴⁰. The multi-atlas of
521 the hippocampus was produced by expert manual rater (JKL) in 14 children balanced for sex and
522 age using an established protocol ⁴¹, a quantity of atlases sufficient to yield high accuracy
523 segmentation ⁴². Each segmentation was manually reviewed for accuracy.

524 ***Delineation of Hippocampal Sub-Regions.*** Head, body, and tail subregions were
525 delineated by blinded rater PD and JKL under an established protocol ¹⁴. Each subregion volume
526 was adjusted by estimated intracranial volume (ICV) using the analysis of covariance approach
527 ²⁴. ICV estimates were obtained using previously described procedures ¹⁵.

528 **Analytical Approach**

529 All analyses used mixed random effect models capable of accounting for within-subject
530 dependencies in the data ²³. Since accelerated longitudinal designs enroll participants across a
531 range of starting ages, the effects of age comprise both the within-individual effect of age change
532 and the between-subject effect of cross-sectional differences in age. We therefore followed the
533 approach in which the effects of age at each time point are separated into a within-subject time-
534 varying covariate (i.e. change in age since T1) and a between-subject time-invariant covariate
535 (i.e. starting age at T1) ^{23,25}. Given that at most only three measurement occasions were
536 available, we did not estimate non-linear within-subject effects. However, we capitalize on the

537 accelerated longitudinal design to test whether children of different starting ages have different
538 within-subject trajectories. Time invariant covariates (e.g., starting age at T1) were centered at
539 the mean of the measure at the T1. All mixed effect models included a random intercept and
540 random slope for change in age since T1. Estimation of model parameters used restricted
541 maximum likelihood (REML), while model comparisons used maximum likelihood (ML). Data
542 were inspected for univariate and multivariate outliers using distribution-based outlier detection,
543 data and Q-Q plots, Z-scoring, and Cook's distance; outlying volume changes were identified
544 and Winsorized at the 2nd and 98th percentiles. Mixed models were fitted and plotted using the
545 lme4 (ver. 1.1), lmerTest (ver. 2.0) and effects (ver. 3.1) packages in R (ver. 3.3.1). Model
546 comparisons were used to build up each model over baseline models, beginning with first-order
547 effects and systematically testing inclusion of higher order interaction effects.

548 ***Behavioral Model.*** Memory scores were computed at each time point and relation as the
549 difference between hit and false alarm rates. Models include the effects of starting age at T1,
550 change in age, and memory relation, and control for effects of sex and item-recognition at T1.
551 The full behavioral model is described in Table 1.

552 ***Hippocampal Model.*** We tested for main and interactive effects of starting age at T1,
553 change in age, and hippocampal subregion, and control for effects of sex and hemisphere. The
554 hippocampal model is described in Table 1. We also computed partial derivatives to derive the
555 starting age at T1 in which the slope of change in age would be predicted to equal zero (i.e., the
556 apex/base of the trajectories).

557 ***Brain-Behavior Model.*** Brain-behavior analyses examined item-time, item-space, and
558 item-item memory separately. Each model simultaneously tested the effects of changes in
559 hippocampal head, body, and tail on memory performance, while accounting for their volumes at

560 T1. The brain-behavior model is described in Table 1. Model comparisons tested the effect of
561 head, body, and tail changes together as a block, building up the model. We began by testing the
562 change in model fit by simultaneously adding the three volume changes (as a block) over a
563 baseline model, which included age at T1, change in age, item-recognition at T1. We then
564 proceeded by testing the change in fit by adding the two-way interactions between changes head,
565 body, and tail volume and change in age since T1, as a block. Likewise, the two-way interactions
566 changes in head, body, and tail volumes with the age at T1. Lastly, we tested the change in
567 model fit by adding the three-way interactions between changes in head, body, and tail volumes
568 with change in age and age at T1. Finally, primary analyses summed volumes across
569 hemispheres. Additional analyses considering left and right hippocampal structures separately
570 were also conducted.

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575 **Declarations**

576 The authors have no financial or non-financial competing interests to declare.

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Supplementary Information

Figure S1 Related to Figure 4. Depicting interaction between change in ICV-corrected volume and cross-sectional differences in the starting age at Time 1 at 8- and 11-years of age evaluated at a change in age since Time 1 equaling one year ($\Delta\text{Age} = 1$). See Figure 4 for depiction of interaction after three years since Time 1; smaller changes in age corresponded to smaller differences in memory with increased sub-region ICV-corrected volume. **A.** Item-Time. **B.** Item-Item. **C.** Item-Space.

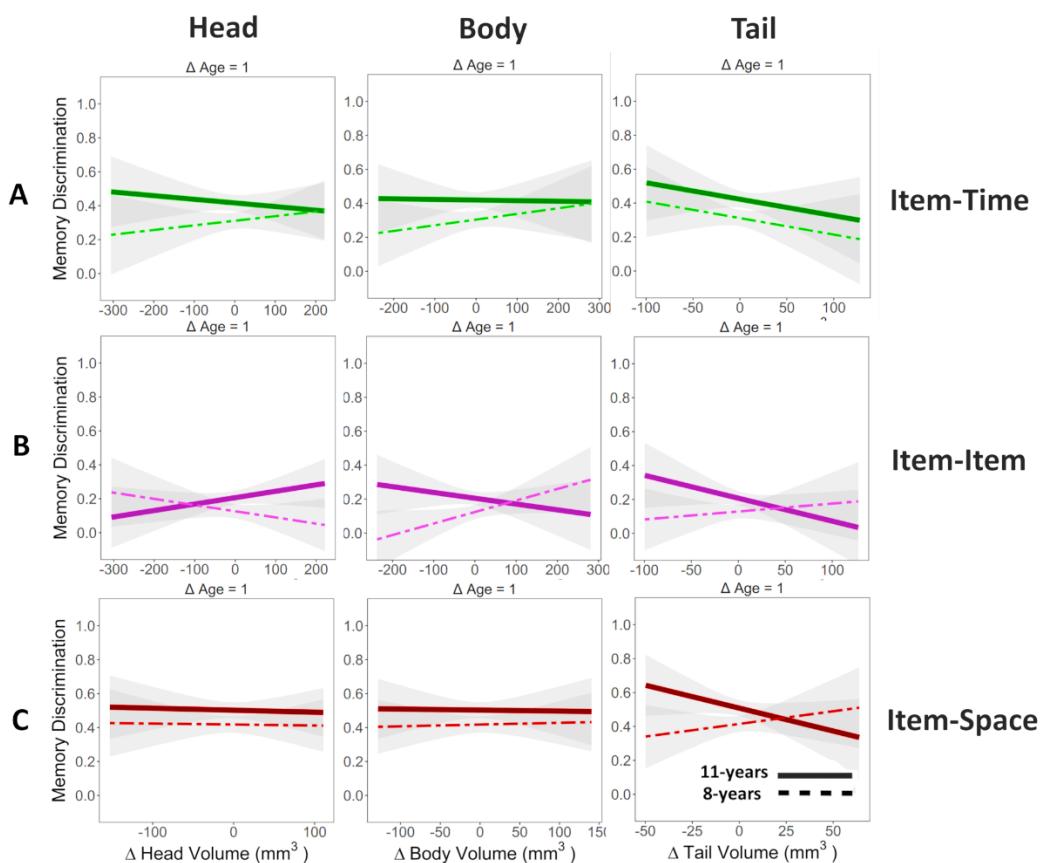


Table S1 Related to Table 2 and Figure 2. Relational Memory Development

Effect	Beta	b	SE	t	p
(Intercept)	–	.453	.020	22.9	<.0001
Item-Recognition (Mean-Centered)	.244	.294	.048	5.98	<.0001
Male	-.049	-.026	.021	-1.24	.223
Start-Age (Mean-Centered)	.183	.039	.013	3.07	.002
ΔAge	.091	.023	.011	2.14	.033
Item-Time	-.218	-.124	.019	-6.62	<.0001
Item-Item	-.548	-.311	.019	-16.7	<.0001
Start-Age x ΔAge	-.124	-.019	.009	-2.20	.029
Start-Age x Item-Time	.021	.008	.014	.540	.590
Start-Age x Item-Item	.027	-.010	.014	-.705	.482
ΔAge x Item-Time	.079	.028	.013	2.19	.029
ΔAge x Item-Item	.081	.027	.013	2.12	.034
Start-Age x ΔAge x Item-Time	.003	.0007	.011	.066	.950
Start-Age x ΔAge x Item-Item	.002	.0006	.011	.061	.951

Model Fit of Fixed Effects: $\chi^2=464.3$, $df=13$, $p < 2.2e-16$; Interactions with sex were not significant, $\chi^2s \leq 4.66$, $dfs=3$, $ps \geq .20$. Item-Space and female are reference categories. Thus, ΔAge and Start-Age x ΔAge represents development of Item-Space.

Table S2 Related to Table 3. Subregional Differences in Hippocampal Development

Effect	Beta	b	SE	t	p
(Intercept)	–	1270	10.0	127	<.0001
Male	.0008	-2.08	11.7	-.178	.862
Right Hemisphere	-.031	24.8	4.62	5.38	<.0001
Start-Age (Mean-Centered)	.013	1.41	6.85	.206	.842
ΔAge	.006	3.20	3.86	.830	.411
Hippocampal Head	-.151	-91.3	7.97	-11.5	<.0001
Hippocampal Tail	-1.02	-1069	7.89	-136	<.0001
Start-Age x ΔAge	-.031	-9.19	3.64	-2.53	.012
Start-Age x Head	-.005	2.66	7.13	.373	.711
Start-Age x Tail	-.014	-7.04	7.06	-.997	.322
ΔAge x Head	-.022	-12.6	5.27	-2.39	.017
ΔAge x Tail	.002	.256	5.23	.049	.960
Start-Age x ΔAge x Head	.012	5.01	4.97	1.01	.312
Start-Age x ΔAge x Tail	.024	12.8	4.94	2.59	.010

Model Fit of Fixed Effects: $\chi^2=6,304$, $df=13$, $p < 2.2e-16$; Interactions with hemisphere not significant: $\chi^2=4.97$, $df=9$, $p=.84$. Note: Female and hippocampal body are reference categories. Thus, ΔAge and Start-Age x ΔAge represents development of the body.

Table S3 Related to Table 3. Development of Total Hippocampal Volume

Effect	Beta	b	SE	t	p
(Intercept)	–	2651	25.5	104	<.001
Male	.013	5.95	34.9	.170	0.86
Right Hemisphere	.167	78.0	6.82	11.4	<.001
Start-Age (Mean-Centered)	.007	1.31	15.8	.083	.932
ΔAge	-.023	-5.50	3.94	-1.40	.174
Start-Age x ΔAge	-.053	-7.69	3.73	-2.06	.042

Model Fit of Fixed Effects: $\chi^2=119.7$, $df=5$, $p<2.2e-16$. Note: Interactions with hemisphere not significant: $\chi^2=6.95$, $df=5$, $p = .22$; Female and left hemisphere are reference categories.

Table S4 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Time Memory.

Effect	Left Hippocampus					Right Hippocampus					Left and Right Hippocampal Sum				
	Beta	b	SE	t	p	Beta	b	SE	t	p	Beta	b	SE	t	p
(Intercept)	-	3.1e-1	2.6e-2	12	<.0001	-	3.2e-1	2.6e-2	12	<.0001	-	3.2e-1	2.5e-2	13	<.0001
Item-Recognition	0.29	3.3e-1	7.3e-2	4.5	<.0001	0.27	3.1e-1	7.4e-2	4.3	<.0001	0.28	3.2e-1	7.4e-2	4.4	<.0001
Sex [Male]	-0.041	-2.1e-2	3.3e-2	-0.65	0.52	-0.061	-3.2e-2	3.2e-2	-0.99	0.33	-0.053	-2.8e-2	3.2e-2	-0.86	0.39
Start-Volume Head	-0.093	-1.5e-4	1.0e-4	-1.5	0.14	-0.018	-3.1e-5	1.1e-4	-0.29	0.77	-0.049	-4.5e-5	5.6e-5	-0.79	0.43
Start-Volume Body	-0.028	-5.6e-5	1.2e-4	-0.45	0.65	-0.097	-1.8e-4	1.1e-4	-1.6	0.12	-0.065	-7.0e-5	6.6e-5	-1.1	0.29
Start-Volume Tail	0.074	2.2e-4	1.8e-4	1.2	0.24	0.044	1.3e-4	1.9e-4	0.69	0.49	0.062	9.8e-5	9.9e-5	0.99	0.32
Start-Age	0.24	5.6e-2	1.7e-2	3.3	0.0014	0.25	6.0e-2	1.7e-2	3.4	0.00076	0.25	5.8e-2	1.7e-2	3.4	0.001
ΔAge	0.25	6.0e-2	1.3e-2	4.7	<.0001	0.27	6.5e-2	1.3e-2	5.2	<.0001	0.26	6.2e-2	1.3e-2	4.7	<.0001
ΔHead	-0.11	-4.9e-4	6.1e-4	-0.81	0.42	-0.12	-6.0e-4	6.5e-4	-0.92	0.36	-0.063	-1.9e-4	4.1e-4	-0.47	0.64
ΔBody	-0.2	-9.6e-4	6.5e-4	-1.5	0.14	0.02	9.5e-5	6.3e-4	0.15	0.88	-0.056	-1.6e-4	3.8e-4	-0.43	0.67
ΔTail	-0.25	-2.9e-3	1.5e-3	-2	0.05	-0.13	-1.6e-3	1.7e-3	-0.95	0.34	-0.2	-1.4e-3	9.5e-4	-1.5	0.14
Start-Age x ΔAge	-0.092	-1.5e-2	1.2e-2	-1.3	0.21	-0.15	-2.4e-2	1.2e-2	-2	0.044	-0.13	-2.1e-2	1.2e-2	-1.7	0.095
Start-Age x ΔHead	-0.34	-1.4e-3	5.5e-4	-2.5	0.014	-0.22	-9.5e-4	5.5e-4	-1.7	0.084	-0.26	-6.4e-4	3.2e-4	-2	0.048
Start-Age x ΔBody	-0.3	-1.4e-3	6.6e-4	-2.1	0.035	-0.22	-9.4e-4	5.8e-4	-1.6	0.11	-0.22	-6.3e-4	3.7e-4	-1.7	0.096
Start-Age x ΔTail	-0.001	-1.1e-5	1.4e-3	-0.008	0.99	-0.078	-9.5e-4	1.8e-3	-0.54	0.59	-0.037	-2.6e-4	1.0e-3	-0.25	0.8
ΔAge x ΔHead	0.12	2.8e-4	3.1e-4	0.89	0.37	0.18	4.6e-4	3.6e-4	1.3	0.2	0.072	1.1e-4	2.2e-4	0.5	0.62
ΔAge x ΔBody	0.31	7.0e-4	3.3e-4	2.1	0.035	0.004	9.1e-6	3.1e-4	0.029	0.98	0.14	2.0e-4	1.9e-4	1.1	0.29
ΔAge x ΔTail	0.15	8.7e-4	7.9e-4	1.1	0.27	0.11	6.4e-4	9.0e-4	0.71	0.48	0.11	4.0e-4	5.0e-4	0.8	0.42
Start-Age x ΔAge x ΔHead	0.4	8.4e-4	2.9e-4	2.9	0.0042	0.29	6.4e-4	3.1e-4	2.1	0.038	0.33	4.1e-4	1.9e-4	2.2	0.027
Start-Age x ΔAge x ΔBody	0.35	8.4e-4	3.5e-4	2.4	0.018	0.31	7.0e-4	3.2e-4	2.2	0.028	0.29	4.2e-4	1.9e-4	2.2	0.032
Start-Age x ΔAge x ΔTail	0.032	1.8e-4	7.3e-4	0.25	0.81	0.22	1.4e-3	9.4e-4	1.5	0.15	0.12	4.2e-4	5.5e-4	0.77	0.44

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

Table S5 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Item Memory.

Effect	Left Hippocampus					Right Hippocampus					Left and Right Hippocampal Sum				
	Beta	b	SE	t	p	Beta	b	SE	t	p	Beta	b	SE	t	p
(Intercept)	-	1.2e-1	2.3e-2	5.3	<.0001	-	1.2e-1	2.3e-2	5.2	<.0001	-	1.2e-1	2.2e-2	5.4	<.0001
Item-Recognition	0.15	1.4e-1	6.1e-2	2.4	0.019	0.15	1.4e-1	6.2e-2	2.3	0.024	0.16	1.5e-1	6.2e-2	2.5	0.013
Sex [Male]	-0.015	-6.6e-3	2.7e-2	-0.24	0.81	-8.2e-05	-3.6e-5	2.7e-2	-0.001	0.99	-0.0048	-2.1e-3	2.7e-2	-0.077	0.94
Start-Volume Head	-0.018	-2.5e-5	8.6e-5	-0.29	0.77	-0.011	-1.6e-5	8.9e-5	-0.18	0.85	-0.013	-1.0e-5	4.7e-5	-0.21	0.83
Start-Volume Body	-0.012	-2.1e-5	1.0e-4	-0.2	0.84	0.025	3.9e-5	9.7e-5	0.4	0.69	0.025	2.3e-5	5.6e-5	0.41	0.69
Start-Volume Tail	0.034	8.3e-5	1.5e-4	0.55	0.59	0.0012	2.9e-6	1.6e-4	0.019	0.99	0.018	2.4e-5	8.2e-5	0.29	0.78
Start-Age	0.21	4.2e-2	1.5e-2	2.7	0.0068	0.2	3.8e-2	1.5e-2	2.5	0.014	0.2	3.9e-2	1.5e-2	2.6	0.012
ΔAge	0.25	5.1e-2	1.1e-2	4.7	<.0001	0.27	5.5e-2	1.1e-2	5.2	<.0001	0.27	5.5e-2	1.1e-2	5	<.0001
ΔHead	0.026	1.0e-4	5.4e-4	0.19	0.85	-0.13	-5.5e-4	5.8e-4	-0.94	0.35	-0.048	-1.2e-4	3.5e-4	-0.35	0.73
ΔBody	-0.19	-7.4e-4	5.8e-4	-1.3	0.2	0.1	4.1e-4	5.5e-4	0.74	0.46	-0.00071	-1.7e-6	3.4e-4	-0.005	1
ΔTail	-0.068	-6.6e-4	1.3e-3	-0.5	0.62	-0.14	-1.4e-3	1.5e-3	-0.95	0.34	-0.15	-8.7e-4	8.5e-4	-1	0.31
Start-Age x ΔAge	-0.11	-1.5e-2	1.0e-2	-1.5	0.15	-0.11	-1.5e-2	1.0e-2	-1.4	0.16	-0.081	-1.1e-2	1.0e-2	-1.1	0.29
Start-Age x ΔHead	0.075	2.5e-4	2.0e-4	1.3	0.2	0.062	2.2e-4	2.0e-4	1.1	0.28	0.12	2.5e-4	1.2e-4	2.1	0.039
Start-Age x ΔBody	-0.12	-4.9e-4	2.2e-4	-2.2	0.029	-0.06	-2.2e-4	2.2e-4	-1	0.32	-0.13	-3.0e-4	1.4e-4	-2.2	0.028
Start-Age x ΔTail	0.01	9.0e-5	5.0e-4	0.18	0.86	0.034	3.5e-4	5.8e-4	0.6	0.55	0.015	8.5e-5	3.3e-4	0.26	0.8
ΔAge x ΔHead	0.1	1.9e-4	2.7e-4	0.71	0.48	0.25	5.2e-4	3.0e-4	1.7	0.087	0.17	2.1e-4	1.8e-4	1.1	0.26
ΔAge x ΔBody	0.34	6.5e-4	2.8e-4	2.3	0.022	-0.027	-5.1e-5	2.6e-4	-0.2	0.85	0.1	1.2e-4	1.6e-4	0.76	0.45
ΔAge x ΔTail	0.068	3.4e-4	6.7e-4	0.51	0.61	0.11	5.4e-4	7.6e-4	0.72	0.48	0.13	3.8e-4	4.3e-4	0.88	0.38

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

Table S6 Related to Figure 4. Hippocampal Volume Predicting the Development of Item-Space Memory.

Effect	Left Hippocampus					Right Hippocampus					Left and Right Hippocampal Sum				
	Beta	b	SE	t	p	Beta	b	SE	t	p	Beta	b	SE	t	p
(Intercept)	-	0.46	0.026	18	<.0001	-	0.46	0.025	18	<.0001	-	0.46	0.025	18	<.0001
Item-Recognition	0.31	3.5e-1	7.1e-2	4.9	<.0001	0.31	3.5e-1	7.2e-2	4.8	<.0001	0.31	3.4e-1	7.2e-2	4.7	<.0001
Sex [Male]	-0.089	-4.5e-2	3.2e-2	-1.4	0.16	-0.083	-4.2e-2	3.2e-2	-1.3	0.19	-0.08	-4.0e-2	3.2e-2	-1.3	0.21
Start-Volume Head	-0.00091	-1.4e-6	1.0e-4	-0.014	0.99	-0.027	-4.6e-5	1.0e-4	-0.45	0.66	-0.012	-1.1e-5	5.6e-5	-0.2	0.84
Start-Volume Body	-0.097	-1.9e-4	1.2e-4	-1.6	0.12	-0.042	-7.6e-5	1.1e-4	-0.68	0.5	-0.068	-7.2e-5	6.5e-5	-1.1	0.27
Start-Volume Tail	0.0045	1.3e-5	1.8e-4	0.071	0.94	0.039	1.1e-4	1.8e-4	0.61	0.54	0.019	2.9e-5	9.8e-5	0.3	0.76
Start-Age	0.27	6.1e-2	1.7e-2	3.6	0.0004	0.28	6.3e-2	1.7e-2	3.8	0.0003	0.27	6.2e-2	1.7e-2	3.7	0.0003
ΔAge	0.1	2.4e-2	1.3e-2	1.8	0.071	0.12	2.9e-2	1.3e-2	2.2	0.028	0.1	2.4e-2	1.4e-2	1.8	0.078
ΔHead	0.055	2.5e-4	6.1e-4	0.41	0.69	-0.086	-4.2e-4	6.5e-4	-0.65	0.52	0.012	3.6e-5	4.1e-4	0.087	0.93
ΔBody	-0.0065	-3.0e-5	6.5e-4	-0.046	0.96	-0.018	-8.3e-5	6.3e-4	-0.13	0.9	0.0087	2.5e-5	3.9e-4	0.065	0.95
ΔTail	-0.1	-1.2e-3	1.5e-3	-0.78	0.44	-0.14	-1.7e-3	1.7e-3	-0.99	0.32	-0.13	-8.7e-4	9.7e-4	-0.9	0.37
Start-Age x ΔAge	-0.17	-2.7e-2	1.2e-2	-2.2	0.027	-0.21	-3.4e-2	1.2e-2	-2.7	0.0077	-0.20	-3.1e-2	1.3e-2	-2.5	0.014
Start-Age x ΔHead	-0.062	-2.4e-4	5.5e-4	-0.44	0.66	-0.055	-2.3e-4	5.5e-4	-0.42	0.68	0.0019	4.6e-6	3.3e-4	0.014	0.99
Start-Age x ΔBody	-0.2	-9.2e-4	6.7e-4	-1.4	0.17	-0.11	-4.7e-4	5.8e-4	-0.81	0.42	-0.13	-3.7e-4	3.8e-4	-0.97	0.33
Start-Age x ΔTail	0.18	1.9e-3	1.4e-3	1.4	0.16	-0.33	-4.0e-3	1.8e-3	-2.3	0.025	-0.012	-8.2e-5	1.0e-3	-0.078	0.94
ΔAge x ΔHead	-0.035	-7.7e-5	3.2e-4	-0.25	0.81	0.13	3.2e-4	3.6e-4	0.88	0.38	-0.015	-2.2e-5	2.3e-4	-0.096	0.92
ΔAge x ΔBody	0.093	2.1e-4	3.3e-4	0.62	0.54	0.025	5.5e-5	3.2e-4	0.17	0.86	0.06	8.3e-5	1.9e-4	0.43	0.67
ΔAge x ΔTail	0.0033	1.9e-5	8.0e-4	0.024	0.98	0.16	9.6e-4	9.2e-4	1	0.3	0.071	2.5e-4	5.1e-4	0.49	0.63
Start-Age x ΔAge x ΔHead	0.091	1.9e-4	2.9e-4	0.63	0.53	0.12	2.4e-4	3.1e-4	0.78	0.44	0.034	4.2e-5	1.9e-4	0.22	0.82
Start-Age x ΔAge x ΔBody	0.17	3.9e-4	3.5e-4	1.1	0.27	0.2	4.4e-4	3.2e-4	1.4	0.18	0.18	2.5e-4	2.0e-4	1.3	0.21
Start-Age x ΔAge x ΔTail	-0.19	-1.0e-3	7.4e-4	-1.4	0.18	0.41	2.4e-3	9.6e-4	2.5	0.012	0.024	8.3e-5	5.6e-4	0.15	0.88

Note: Female is reference sex. For unstandardized betas, volume is in cubic millimeters and age is in years.

