

Hippocampal-neocortical functional reorganization underlies children's cognitive development

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The importance of the hippocampal system for rapid learning and memory is well recognized, but its contributions to a cardinal feature of children's cognitive development—the transition from procedure-based to memory-based problem-solving strategies—are unknown. Here we show that the hippocampal system is pivotal to this strategic transition. Longitudinal functional magnetic resonance imaging (fMRI) in 7–9-year-old children revealed that the transition from use of counting to memory-based retrieval parallels increased hippocampal and decreased prefrontal-parietal engagement during arithmetic problem solving. Longitudinal improvements in retrieval-strategy use were predicted by increased hippocampal-neocortical functional connectivity. Beyond childhood, retrieval-strategy use continued to improve through adolescence into adulthood and was associated with decreased activation but more stable interproblem representations in the hippocampus. Our findings provide insights into the dynamic role of the hippocampus in the maturation of memory-based problem solving and establish a critical link between hippocampal-neocortical reorganization and children's cognitive development.

Children's cognitive development is analogous to 'overlapping waves'¹, whereby advances are not characterized by broad and abrupt shifts from one stage of thinking to another but rather by changes in the distributions of strategies children use for problem solving. At any given time, children have multiple approaches available to them: they may solve one addition problem by counting on their fingers and retrieve the answer to the next. The maturation of problem-solving skills is characterized by a gradual decrease in the use of inefficient procedures such as counting and an increase in the use of memory-based strategies^{1–4}. It has been thought that this transition occurs because the use of embodied procedures can facilitate the development of more advanced and efficient memory-based approaches, a key feature of expertise especially at early phase of knowledge acquisition^{1,3}. This pattern of strategy shifts has been found in children's arithmetic, spelling, reasoning and social problem solving, among others^{5,6}, but our understanding of the underlying neurodevelopmental processes is still in its infancy. At a behavioral level, the strategy shifts have been especially well characterized for numerical problem solving^{1,5,7}, making this domain an ideal model for studying the brain systems that underlie the general pattern of strategy shifts that characterizes children's cognitive development.

Early elementary school is a critical period for the acquisition and mastery of arithmetic fact knowledge. Two decades of behavioral studies in children have demonstrated that a shift to memory-based problem solving is a hallmark of children's cognitive development in arithmetic as well as other domains^{1,3,4}. Use of memory-based approaches to solve addition problems predicts children's later achievement in mathematics and children with dyscalculia do not fully transition to use of memory-based strategies^{8–10}. Even children

without dyscalculia show substantial variation in their transition to memory-based problem solving⁷, but nothing is known about the neural mechanisms that support more rapid gains in some children and slower gains in others. Arithmetic problem solving engages multiple neurocognitive systems, but the extent to which one region or another is engaged in these systems varies with children's degree of competence in the domain^{1,9,10}. Thus, longitudinal designs spanning the shift from procedure-based to memory-based strategies are critical for advancing our understanding of the brain systems pivotal to this transition^{9,10}.

The brain systems that contribute to numerical competence include numerical and quantity representation systems anchored in core parietal circuits^{2,11,12} and working memory systems in fronto-parietal cortices for active maintenance and manipulation of discrete quantities^{7,13,14}. Notably, recent studies in children have begun to emphasize neurodevelopmental models that go beyond parietal circuits foundational to numerical processing in adults. In particular, the hippocampal system appears to be critical for children's learning of mathematics in ways that are not evident in adults who have mastered basic skills^{15,16}. But there have been no investigations into the mechanisms by which the functional reorganization and refinement of neural activity patterns in the hippocampus, and its associated cortical circuits, contribute to the development of memory-based problem-solving skills.

Although the hippocampus is known to play a central role in memory for individual stimuli such as words and pictures¹⁷, its role in the early phase of knowledge acquisition in academic domains such as mathematics and language remains unknown. Influential models of memory formation posit that the hippocampal system fosters

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the gradual establishment of long-lasting knowledge represented in the neocortex, through its role in rapid learning and integration of new information into existing knowledge schema^{18–20}. In this view, the hippocampus has a critical, but time-limited, role in the early phase of knowledge acquisition, and this hippocampal dependence is reduced after reconfiguration of neocortical connections and stabilization of newly acquired knowledge, a process referred to as consolidation^{18,21}. Evidence for this model is primarily based on animal studies¹⁹, and how such mechanisms operate in humans, in particular during children's early learning, is unknown. Notably, no studies have investigated how the hippocampus supports the longitudinal shift from counting to memory-based problem solving in individual children and whether its involvement is limited to the early phase of skill acquisition. Based on the 'overlapping waves' model of cognitive development, we hypothesized that the emergence of memory-based problem solving would be associated with functional reorganization of the hippocampal-neocortical system.

An important open question in developmental cognitive neuroscience is how newly acquired labile skills and knowledge are transformed into more stable representations^{5,18}. Localization of brain activation has been the mainstay of approaches for examining functional reorganization with learning. This approach has provided useful information about the engagement of specific brain areas during problem solving, but it offers limited insights into the stability of the underlying neural representations. To mitigate this limitation, we used new trial-by-trial analyses of multivoxel pattern stability^{22,23} to investigate how neural representations of individual problems get refined with shifts to memory-based problem solving. We hypothesized that the hippocampal system would show more stable interproblem representations with the continued development of memory-based problem solving during adolescence and adulthood.

Here we tested these hypotheses by integrating longitudinal and cross-sectional fMRI and behavioral-strategy assessment of arithmetical problem solving in 28 typically developing children (ages 7–9) at two time points (time 1 and time 2) over a 1.2-year period, 20 adolescents (ages 14–17) and 20 adults (ages 19–22) (Fig. 1a,b and Supplementary Table 1). We focused on arithmetic problem solving because, as noted, strategy transitions in this domain are well understood and occur prominently within the age ranges we assessed in the longitudinal component. We assessed participants'

problem solving using a well-validated trial-by-trial measure that classified strategies based on self-report and experimenter observation^{22,27} (Online Methods). We conducted two fMRI experiments: one involving a block design to maximize efficiency and sensitivity²⁶ for examining overall task-related brain activation and connectivity associated with the transitions to memory-based strategies, and second, an event-related design to capture multivoxel activation patterns between arithmetic problems using innovative trial-by-trial stability analysis^{22,23,27}. The two fMRI tasks provided complementary information about the maturation of brain response, connectivity and stable interproblem representations. Consistent with our hypotheses, children's use of memory-based strategies increased and use of counting strategies decreased over the 1.2-year interval, a pattern that continued into adolescence and adulthood. In parallel, we observed significant functional reorganization of the medial temporal lobe (MTL)-neocortical system, characterized by changes in hippocampal activation, functional connectivity and interproblem representation stability. Our findings provide, to our knowledge, the first evidence for the emergence of fine-tuned hippocampal-neocortical circuits and stable brain representations leading to adult-like memory-based problem-solving skills, and establish a new link between hippocampal-neocortical systems and a cardinal feature of children's cognitive development.

RESULTS

Longitudinal changes in strategy use during childhood and further development through adolescence into adulthood

Longitudinal changes in children's problem solving between ages 7–9 involved increased use of memory-based strategies ($t_{27} = 2.43$, $P = 0.02$) and decreased use of counting strategies ($t_{27} = -2.16$, $P = 0.04$). Cross-sectional comparisons between children at time 2, adolescents and adults revealed that the transition to memory-based problem solving continued into adolescence and adulthood ($F_{2,65} > 3.78$, $P < 0.028$; Fig. 1c). *Post hoc* comparisons revealed greater memory-based strategy use in adolescents and adults than in children (Scheffé's $P < 0.03$). These results indicate that children's arithmetic skill development is characterized by gradual changes in the distributions of strategies from childhood through adolescence into adulthood, with use of counting strategies decreasing in frequency and use of memory-based strategies (i.e., 'retrieval fluency') increasing in frequency.

Figure 1 Experimental design and behavioral results. (a) Outline of the longitudinal fMRI study: 28 young children participated twice, first at time 1 (T1) and then 1.2 years later at time 2 (T2). Each child performed two arithmetic problem-solving tasks involving single-digit addition. The first task involved verbal production of the answer, during which problem-solving strategies were assessed, on a trial-by-trial basis (Online Methods), outside the scanner. Based on the child's self-report and experimenter observations, the use of strategies for solving each problem was classified into counting or retrieval or other. The second task involved verification of whether an answer presented with an arithmetic problem was correct or not and was performed during fMRI scanning. The control task involved ' $n + 1$ ' problems that are generally solved using a classic rule-based strategy with minimal changes in strategy with development. (b) Outline of the cross-sectional fMRI study: the same strategy assessment and fMRI tasks were performed by an additional group of 20 adolescents and 20 adults. (c) Developmental changes in the mix of strategies used for solving arithmetic problems, showing a gradual increase in memory-based retrieval and decrease in use of counting strategies. Solid lines represent data at T1 and T2 in children, and dotted lines represent data from adolescents and adults. (d) Developmental changes in task performance during fMRI from childhood ($n = 28$) through adolescence ($n = 20$) into adulthood ($n = 20$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Error bars, s.e.m.

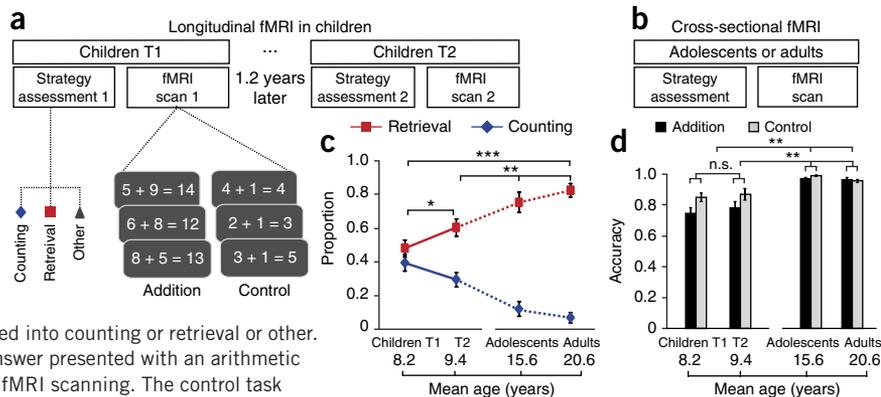
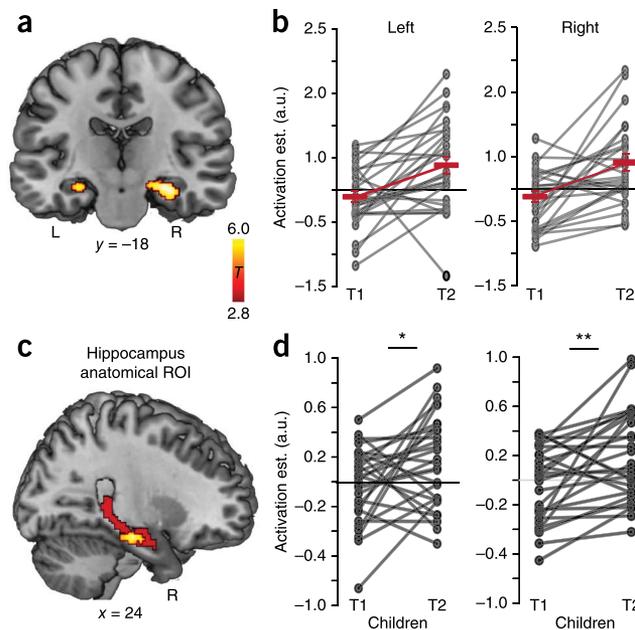


Figure 2 Longitudinal changes in hippocampal engagement during childhood. **(a)** Left and right hippocampus clusters which showed increased engagement during addition problem solving between time 1 (T1) and time 2 (T2). Color bar represents T values. **(b)** Each line represents individual developmental trajectories of hippocampal engagement over time. Bold red lines represent group means at T1 and T2. **(c)** Sagittal view of an anatomically defined ROI encompassing the entire right hippocampus (in red) and significant functional clusters from a (in hot orange). **(d)** Each line represents individual trajectories of hippocampal engagement over time within anatomically defined ROIs. * $P < 0.05$; ** $P < 0.01$. Error bars, s.e.m. L, left; R, right.



Longitudinal changes in fMRI task performance during childhood

We then examined longitudinal changes in accuracy and reaction times (RTs) from the block and event-related fMRI experiments in children. Separate repeated analyses of variance (ANOVAs) for accuracy and RTs in the block fMRI task (**Fig. 1d**), with task (addition versus control) and time (time 1 versus time 2) as within-subject factors, revealed a main effect of task for accuracy and RTs ($F_{1,27} > 13.04$, $P < 0.001$) and a main effect of time for RTs ($F_{1,27} = 14.82$, $P < 0.001$). Follow-up tests revealed that children had lower accuracy and slower response in solving addition than control problems ($t_{27} < -4.64$, $P < 0.001$) and that children became faster ($t_{27} > 2.65$, $P < 0.013$) over time (**Supplementary Fig. 1a,b**).

Longitudinal changes in the event-related fMRI task showed the same pattern; task effects for accuracy and RTs ($F_{1,19} = 46.24$, $P < 0.001$), and a main effect of time for RTs ($F_{1,19} = 28.43$, $P < 0.001$), with significant gains in RTs from time 1 to time 2 ($t_{19} = 6.87$, $P < 0.001$). Notably, we observed task-by-time interactions for both accuracy and RTs ($F_{1,19} > 4.97$, $P < 0.04$) (**Supplementary Fig. 1c,d**), with larger improvements in solving addition (accuracy: $t_{19} = 2.50$, $P = 0.022$; RTs: $t_{19} = 5.63$, $P < 0.001$) than control (accuracy: $t_{19} = 0.68$, $P = 0.50$; RTs: $t_{19} = 4.34$, $P < 0.001$) problems. Detailed results are provided in **Supplementary Results**. In sum, convergent results from the behavioral, block and event-related fMRI tasks provide robust evidence that children's problem-solving skills improved significantly over the 1.2-year interval.

Developmental changes in fMRI task performance from childhood through adolescence into adulthood

Analysis of cross-sectional behavioral data revealed main effects of group for both accuracy and RTs in the block and event-related fMRI tasks ($F_{2,65} > 12.28$, $P < 0.001$) (**Fig. 1d** and **Supplementary Fig. 1a–d**), with higher accuracy and faster RTs in adolescents and adults compared to children ($F_{2,65} > 46.79$, $P < 0.001$). We observed significant task-by-group interactions for both accuracy and RTs ($F_{2,65} > 6.26$, $P < 0.003$), with larger developmental improvements for addition ($P < 0.001$) than control ($P < 0.01$) problems (**Supplementary Fig. 1a,b**). We found the same pattern of results in the event-related fMRI task (**Supplementary Fig. 1b,d**). Detailed results are provided in **Supplementary Results**. These results provide robust evidence for improvements in problem-solving skills from childhood through adolescence into adulthood.

Longitudinal changes in hippocampal and prefrontal-parietal engagement during childhood

Next, we examined longitudinal changes in children's brain response during addition problem solving from time 1 to time 2. Collapsing data across the two time points, we found a widely distributed network of brain regions involved in solving addition problems, including the prefrontal cortex, parietal cortex, MTL as well as the striatum and cerebellum (**Supplementary Table 2** and **Supplementary Fig. 2**).

Compared to time 1, at time 2 children showed significantly higher activation in the bilateral hippocampus (peak at $(28, -20, -18)$ and $(-26, -22, -1)$, MNI coordinates **Fig. 2a**). In contrast, they showed reduced activation in the bilateral dorsolateral prefrontal cortex (DLPFC), left superior parietal lobule and right posterior parietal-occipital cortex (**Supplementary Fig. 3** and **Supplementary Table 3**), brain areas implicated in working memory, executive control and use of effortful counting strategies^{12,13}.

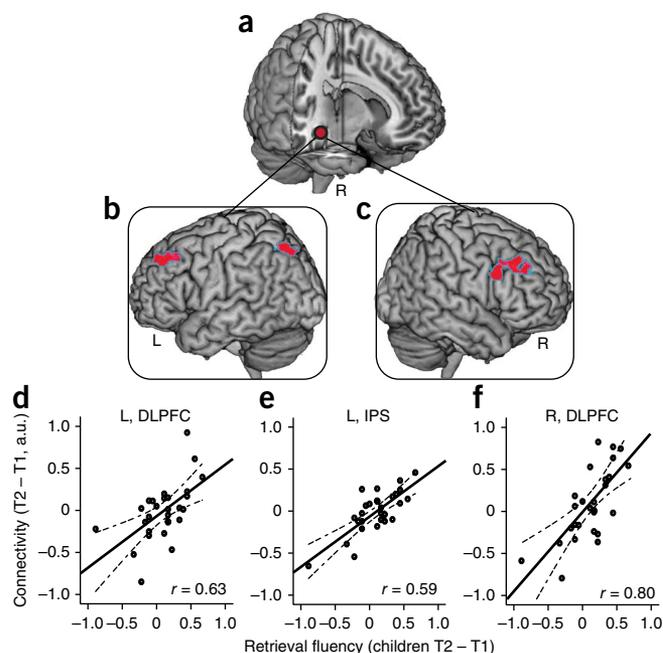
A follow-up region of interest (ROI) analysis of each child's longitudinal trajectory revealed that 23 of 28 children showed an increase in hippocampal activation over the 1.2-year period (**Fig. 2b**). Analysis of a priori anatomically defined ROIs (**Fig. 2c**) spanning the entire long axis of the hippocampus also revealed a significant increase in hippocampal engagement (left: $t_{27} = 2.39$, $P = 0.02$; right: $t_{27} = 3.26$, $P < 0.01$; **Fig. 2d**). These results point to a robust longitudinal increase in hippocampal engagement and decrease in prefrontal-parietal engagement during problem solving, which parallel the shift from effortful counting to efficient memory-based strategies.

Longitudinal changes in hippocampal-neocortical connectivity predict improved memory-based problem solving

We then investigated how changes in hippocampal engagement and its connectivity with the neocortex contribute to children's transition to memory-based problem solving. Despite significant longitudinal increases in hippocampal engagement, changes in hippocampal activation were not predictive of individual improvements in children's retrieval fluency, accuracy or RTs.

Rather, increases in children's retrieval-strategy use were predicted by the degree of hippocampal connectivity with other brain areas (**Fig. 3a–c**). We examined longitudinal changes in hippocampal connectivity with every voxel in the brain²⁸ (Online Methods). We observed significant increases in hippocampal functional connectivity with dorsolateral, ventrolateral and ventromedial prefrontal cortex, and anterior temporal cortex over time (**Supplementary Fig. 4a–c** and **Supplementary Table 4**). Individual improvements in fact-retrieval fluency were significantly correlated with the strength of hippocampal connectivity with multiple prefrontal and parietal cortical areas, including left and right DLPFC and left intraparietal sulcus regions (**Fig. 3d–f** and **Supplementary Table 4**) widely implicated in arithmetic problem

Figure 3 Longitudinal changes in hippocampal-neocortical functional coupling in relation to individual improvements in children's retrieval fluency. **(a)** Right hippocampus seed region used in task-related functional connectivity (i.e., psychophysiological interaction) analysis. **(b,c)** Left and right DLPFC, and the left intraparietal sulcus (IPS) regions that showed increased functional connectivity with the hippocampus, as a function of longitudinal improvements in retrieval fluency from time 1 (T1) to time 2 (T2). **(d-f)** Longitudinal changes in retrieval fluency versus in functional connectivity strength from T1 to T2. Dashed lines indicate 95% confidence intervals, and solid line indicates the best linear fit. The correlates are plotted for visualization purposes only. L, left; R, right.



solving^{4,11,12,29,30}. Using machine-learning algorithms with cross-validation^{16,31} (Online Methods), we confirmed that individual improvements in children's retrieval fluency from time 1 to time 2 could be reliably predicted by longitudinal changes in functional coupling of the hippocampus with the left DLPFC ($r_{(\text{predicted}, \text{observed})} = 0.53$) and right DLPFC ($r_{(\text{predicted}, \text{observed})} = 0.71$) and left intraparietal sulcus ($r_{(\text{predicted}, \text{observed})} = 0.51$) (Supplementary Table 5). These results demonstrate that changes in hippocampal-neocortical functional circuits, rather than hippocampal activation levels, underlie individual gains in use of memory-based problem solving.

Developmental changes in hippocampal engagement from childhood through adolescence into adulthood

To characterize how hippocampal engagement during arithmetic problem solving unfolds with longer-term development, we examined cross-sectional fMRI data from children (time 2), adolescents and adults at the whole brain level (Supplementary Fig. 5 and Supplementary Table 6). This analysis identified a cluster in the right hippocampus (peak at (32, -16, -18)) that showed a significant omnibus group effect (Fig. 4a,b and Supplementary Table 7). A follow-up ROI analysis confirmed a main effect of group ($F_{2,65} = 8.61$, $P < 0.001$), with larger hippocampal engagement for children at time 2 compared to adolescents and adults (Scheffe's $P < 0.009$). There were no differences between adolescents and adults ($P = 0.87$) nor between them and children at time 1 ($t_{46} < 1$).

Additional analyses using anatomically defined hippocampal ROIs again revealed a main effect of group in the left ($F_{2,65} = 3.35$, $P = 0.04$) and right ($F_{2,65} = 3.91$, $P = 0.025$) hippocampus (Fig. 4c). We observed the strongest engagement in children at time 2 (Scheffe's $P_S < 0.05$), with no differences between adolescents and adults ($P = 0.68$). These developmental changes were independent of general performance improvements (Supplementary Fig. 6). Together with longitudinal fMRI data, these results demonstrate that hippocampal engagement during problem solving increases initially during middle childhood and subsequently decreases, reaching adult-like levels by adolescence.

Maturation of neural representational stability from childhood through adolescence into adulthood

To further investigate the maturation and stabilization of neural representations underlying arithmetic problem solving, we analyzed event-related fMRI data acquired from a subgroup of 20 children as well as the entire group of adolescents and adults (Fig. 5a). We implemented an innovative multivariate pattern analysis that provides a measure of the stability of neural representations, by examining trial-by-trial similarity of multivoxel activation patterns (Fig. 5c) associated with each correctly solved problem. This approach has superior sensitivity and reliability for capturing fine-grained spatially distributed activation patterns associated with learning and memory^{22,23,27}. We first performed a whole-brain analysis using a searchlight algorithm^{27,32} to determine which brain areas exhibited developmental changes in interproblem stability. This analysis revealed that the left and right hippocampus (peak at (-24, -12, -14), (-22, -32, -4) and (22, -14, -14) MNI coordinates; Fig. 5d,e) showed significant increases in interproblem multivoxel pattern stability from childhood through adolescence

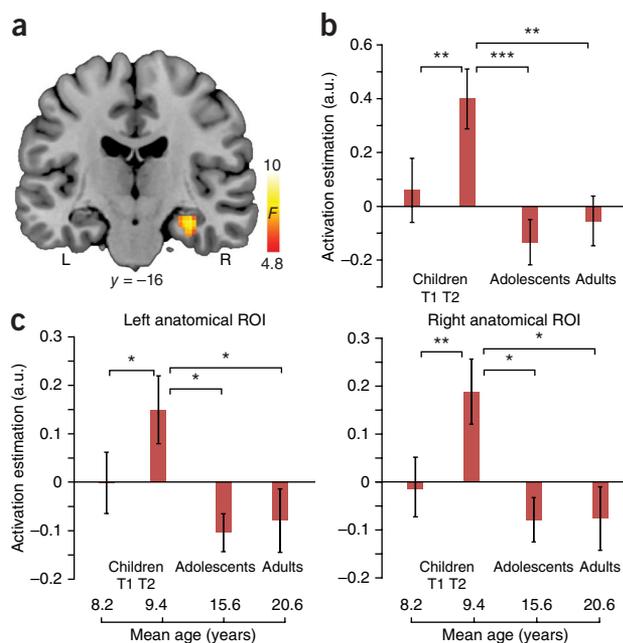


Figure 4 Longitudinal changes in hippocampal engagement during childhood and further development through adolescence into adulthood. **(a)** Right hippocampus showing main effect of group across children ($n = 28$), adolescents ($n = 20$) and adults ($n = 20$) (omnibus F contrast). **(b)** Developmental changes in the functionally defined hippocampus cluster. T1, time 1; T2, time 2. **(c)** Developmental changes in the engagement of anatomically defined hippocampal ROIs (ROI mask is shown in Fig. 2c). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Error bars, s.e.m. L, left; R, right.

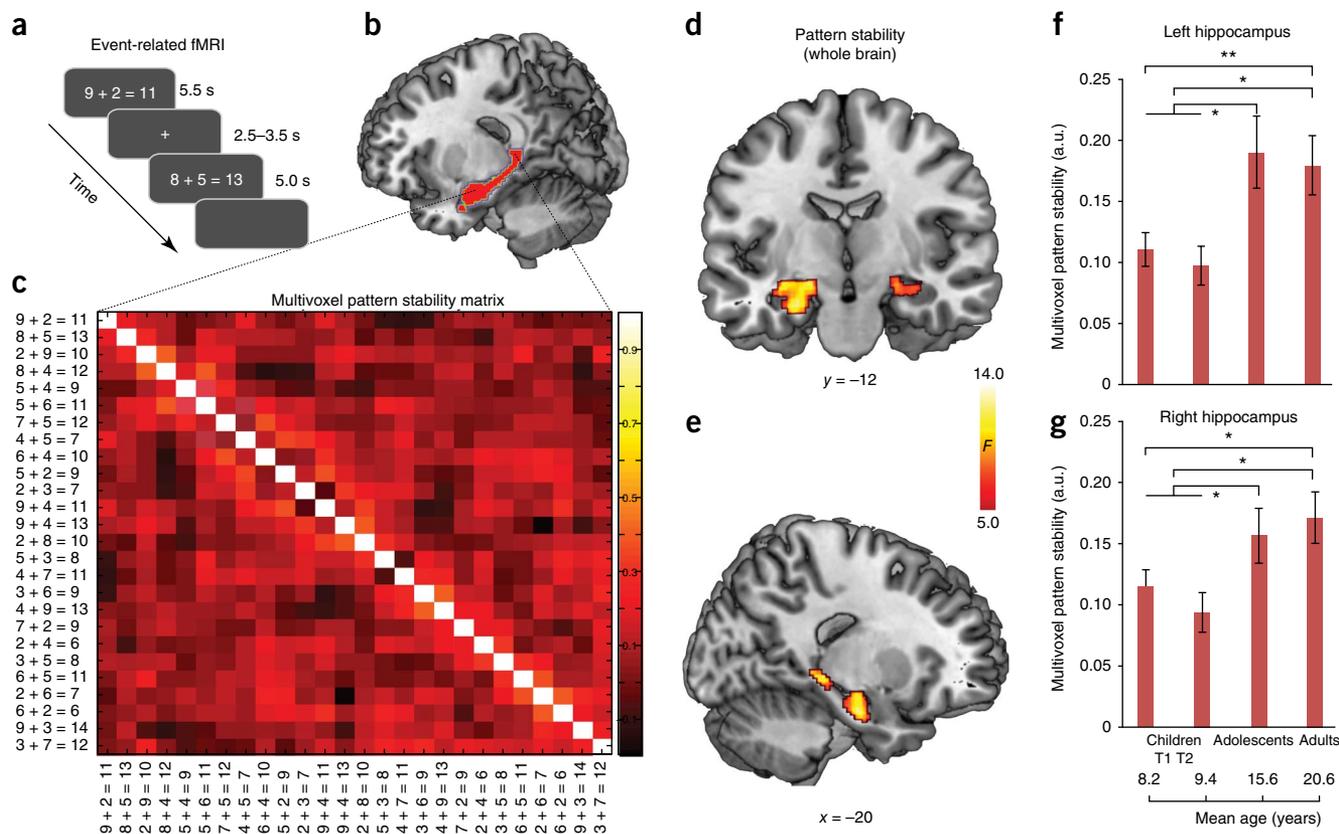


Figure 5 Interproblem multivoxel pattern stability in the hippocampus in children at time 1 (T1) and time 2 (T2), adolescents and adults. **(a)** Event-related fMRI design of arithmetic problem-solving task. **(b)** Sagittal slice of predefined region of interest (ROI) in the hippocampus used for the inter-problem pattern stability analysis. **(c)** 26 × 26 correlation matrix representing trial-by-trial brain activation pattern stability in the hippocampus during addition problem solving. Color bar represents omnibus F values. **(d, e)** Results of whole-brain analysis showing hippocampal regions that showed significant increases in interproblem multivoxel pattern stability from childhood through adolescence into adulthood. **(f, g)** Interproblem pattern stability in the left and right hippocampus for problems correctly solved by children at T1 and T2, adolescents and adults. Note that only correctly performed trials (problems) from each participant's event-related fMRI data were used in the analysis. a.u., arbitrary units; L, left; R, right. * $P < 0.05$; ** $P < 0.01$. Error bars, s.e.m.

into adulthood. We also observed increased interproblem stability in multiple prefrontal and temporal regions (**Supplementary Fig. 7** and **Supplementary Table 8**).

Additional analyses using anatomically defined hippocampal ROIs (**Fig. 5b**) again revealed significant developmental changes in interproblem representation stability in the left and right hippocampus in children (time 1 or time 2), adolescents and adults ($F_{2,57} > 3.35$, $P_S < 0.04$) (**Fig. 5f, g**). Follow-up analyses revealed no differences between children at time 1 and time 2 but higher interproblem stability in the left and right hippocampus in adolescents and adults compared to children (Scheffé's $P_S < 0.05$). We observed similar results even after equating the number of correct problems across groups (**Supplementary Fig. 8a, b** and **Supplementary Table 9**). In sum, converging results from the whole-brain and ROI analyses indicate that interproblem multivoxel patterns in the hippocampus become significantly more stable with development, reaching adult-like levels during adolescence.

DISCUSSION

By integrating unique longitudinal and cross-sectional brain imaging data with behavioral strategy assessments, we examined the functional maturation of brain systems underlying the transition from counting to memory-based problem solving. Consistent with the 'overlapping waves' model, children's use of memory-based strategies increased and use of counting strategies decreased over time.

The MTL-neocortical system emerged as a key locus supporting this transition, characterized by increased hippocampal engagement, decreased prefrontal-parietal engagement and increased functional connectivity between the hippocampus and multiple cortical regions. Increased hippocampal connectivity with prefrontal-parietal circuits predicted longitudinal gains in retrieval fluency. Beyond childhood, overall hippocampal engagement decreased through adolescence into adulthood. Interproblem multivoxel activation patterns in the hippocampus became more stable, reaching adult-like levels by adolescence. Our findings point to a pivotal role of the hippocampus and its functional circuits, in both the early emergence of children's memory-based problem solving and in the fine-tuning and stabilization of local-circuit representations in the development of adult-like problem solving by adolescence.

Longitudinal changes in hippocampal-neocortical engagement in the transition to memory-based problem solving

We observed a shift from the use of counting to memory-based strategies in children over a 1.2-year interval, and this was associated with increased hippocampal engagement in problem solving. During this period, children showed decreased prefrontal-parietal engagement as observed in previous cross-sectional studies^{4,33}. The greater prefrontal and posterior parietal recruitment especially at time 1 likely reflects high levels of working memory and executive processing needed for

implementing counting strategies^{7,25}, especially at a stage when children are still learning to solve arithmetic problems^{5,8,34}. The increased hippocampal engagement is consistent with its known role in learning and memory for encoding and retrieval of facts and events^{17,18,21}, and matches our observation of greater reliance on memory-based retrieval of addition facts from time 1 to time 2. Thus, our longitudinal findings suggest that the recruitment of hippocampal-dependent memory processes is important in the development of children's memory-based problem-solving strategies.

Our findings suggest a significant shift in the engagement of the hippocampal-dependent memory system and a concomitant decrease in the engagement of the prefrontal-parietal working memory system, consistent with our behavioral findings of a strategy shift to declarative memory-based retrieval during the early stages of arithmetic learning and skill acquisition^{1,3}. Although no such longitudinal studies have yet been performed, a similar process may also apply to other academic domains and to language acquisition in young children^{35,36}. Our findings are a substantial advancement over previous cross-sectional studies^{17,18} and provide to our knowledge the first longitudinal evidence for the importance of the hippocampal-dependent memory system in children's cognitive development.

The developmental origins of the emergence of hippocampal activity and strategy shifts lie in children's educational experiences involving considerable practice with problems of the type used in our study³⁷. One possibility, consistent with the known functions of the hippocampus^{17,18,38}, is that children learn to associate individual problems with the correct answers. Repeated problem solving during the early stages of arithmetic skill development also contributes to memory re-encoding and consolidation, thus resulting in enhanced hippocampal activity and ability to recall basic arithmetic facts^{4,16,18}. It is also noteworthy that our findings are consistent with theoretical and computational models of early cognitive development, which posit that children learn and acquire knowledge through experience-dependent plasticity in the MTL memory system^{36,39}.

Longitudinal changes in hippocampal-neocortical connectivity predict children's gains in memory-based strategy use

Coordinated interactions between the hippocampus and neocortex are known to be important in memory formation and knowledge acquisition^{18,19}. In conjunction with the longitudinal increase in hippocampal engagement, we observed that increased hippocampal functional coupling with prefrontal and parietal cortices was positively correlated with individual gains in use of memory-based strategies. Moving beyond standard regression approaches, prediction analyses based on machine-learning algorithms confirmed that changes in hippocampal functional coupling with prefrontal-parietal systems indeed predicted longitudinal gains in fact-retrieval fluency. These results suggest that hippocampal-neocortical functional reorganization, rather than changes in regional activation by themselves, are important in children's shift from effortful counting to more efficient memory-based problem solving. Consistent with this view, a recent study found that increased intrinsic connectivity of the hippocampus with the neocortex predicted performance gains after 8 weeks of mathematics tutoring in children ages 7–9 (ref. 16). More broadly, hippocampal-neocortical interactions have been implicated in human episodic memory^{17,21} and the early stage of conceptual learning in adults^{18,40}, but there has been limited evidence for its role in the development of children's memory-based problem-solving skills. Findings from our longitudinal study in children thus establish a link between hippocampal-neocortical functional

reorganization and the emergence of memory-based problem solving during childhood.

Developmental changes in hippocampal engagement and interproblem representational stability

Beyond childhood, use of memory-based strategies continued to improve, reaching an adult-like level during adolescence. After the initial increase in hippocampal engagement during middle childhood, this hippocampal dependency decreased during adolescence and adulthood despite additional improvements in memory-based problem solving. This pattern of initial increase and subsequent decrease in activation provides support for models of long-term memory consolidation, which posit that the hippocampus has a time-limited role in the early phase of knowledge acquisition^{18,19}. Consistent with this pattern of developmental change, previous studies of adults have reported no reliable hippocampal engagement in basic arithmetic tasks. Together with the above longitudinal results, our findings suggest the hippocampal system is critical to children's early learning of arithmetic facts^{15,18}, the retrieval of which is largely dependent on the neocortex in adults^{4,12,18}. Through further schooling and experience with mathematics, fact retrieval becomes increasingly independent of the hippocampal memory system during adolescence and adulthood.

Our observed changes in task-related mean activation and connectivity provide insights into hippocampal-neocortical functional reorganization underlying the shift to memory-based problem solving but leave unclear the nature of neural processing and stability of representations associated with solving of individual problems. Although mean hippocampal activation decreased during adolescence, we observed that interproblem pattern stability in the hippocampus, prefrontal and temporal cortices increased with the refinement of memory-based problem solving from childhood to adolescence and adulthood. Our findings complement univariate analysis of mean activation and connectivity and provide new evidence that hippocampal multivoxel patterns become more stable with skill development.

Our results show for the first time that with development, neural representations of basic arithmetic facts become more stable during adolescence and adulthood. At that point, although retrieval of arithmetic facts no longer requires the same level of engagement of the hippocampus-dependent memory system, the manner in which it is engaged becomes more stable across individual problems. This pattern of results is consistent with recent adult studies in memory-encoding and -retrieval tasks that found that greater pattern similarity across stimuli in the MTL predicts better behavioral performance, through strengthening of discrete information distributed over neocortical regions^{22,23,27}. These developmental changes likely reflect fine-tuned integration and reconfiguration of local functional circuits through experience-dependent plasticity^{42–44}. Our findings provide new insights into the mechanisms by which the hippocampus contributes to the maturation of memory-based problem-solving skills from childhood through adolescence into adulthood and to knowledge acquisition in academically relevant domains such as mathematics.

Finally, it should be noted that while the multivariate approach we used has been demonstrated to have superior sensitivity to capture fine-grained activation patterns across spatially distributed voxels^{22,27}, the precise neuronal mechanisms underlying formation of such stable multivoxel patterns remain unknown. Further studies with high-resolution imaging and dense neuronal recordings are needed to clarify the neural basis of the 'representations' detected here.

Conclusion

By characterizing parallel changes in task-related brain activation, functional connectivity as well as stability of distributed neural representations with development, our study provides new insights into the mechanisms through which hippocampal-neocortical functional reorganization promotes the shift from use of effortful procedure-based to more efficient memory-based problem solving from childhood through adolescence into adulthood. More broadly, our study elucidates key neurobiological mechanisms underlying a cardinal feature of children's cognitive development.

METHODS

Methods and any associated references are available in the [online version of the paper](#).

Note: Any Supplementary Information and Source Data files are available in the [online version of the paper](#).

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AUTHOR CONTRIBUTIONS

S.Q. and V.M. designed research; S.Q., S.C., T.C. and M.R.-L. performed research; S.Q. and T.C. analyzed data; S.Q., D.C.G. and V.M. wrote the paper.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

Participants. A total of 68 children, adolescents and adults participated in this study. Twenty-eight typically developing children participated in a longitudinal fMRI study, and twenty healthy adolescents and twenty healthy young adults participated in a cross-sectional fMRI study. All participants were right-handed, and had no history of neurological or psychiatric diseases and no current use of any medication. Twenty-eight children (15 boys and 13 girls) were scanned twice (once at time 1 and once at time 2) separated by ~1.2 years. To minimize age-related variability within each group, children were selected from narrow age range of 7–9 (at the first time point; mean age, 8.26 ± 0.53 ; at the second time point, mean age, 9.45 ± 0.88), adolescents and adults were selected from narrow age ranges of 14–17 (mean age, 15.61 ± 1.40) and 19–22 (mean age, 20.50 ± 1.07), respectively. All participants had intelligence quotient (IQ) above 95 and below 135, as measured by the Wechsler abbreviated scales of intelligence (WASI). Verbal, performance and full-scale IQ scores were normalized according to each participant's age. Participants with dyscalculia or poor mathematics achievement, as assessed by the Wechsler individual achievement test (WIAT-II), and attention deficit hyperactivity disorder (ADHD), as assessed by the child behavior checklist (CBCL), were excluded. Participant demographics and statistics, including age, IQ and gender, are summarized in **Supplementary Table 1**. The study protocol was approved by the Stanford University Institutional Review Board. Written informed consent was obtained from each participant as well as the child's legal guardian before their participation. Participants with root mean squared head motion exceeding a voxel's width during MR scanning, were excluded from further analyses.

Children were recruited from elementary schools in the San Francisco Bay Area as part of a prospective longitudinal imaging study of cognitive development. After behavioral and cognitive assessments and MRI scanning at time 1, all potential participants were invited back for time-2 assessments and MRI scanning ~1 year later. We included any child who had good quality behavioral and brain imaging data (see below) at both time points. Adolescents and adults were recruited from high schools and community colleges around the Stanford University campus.

General experimental procedures. Each participant performed two single-digit addition problem solving tasks. The first involved verbal production of the answer to the problem (for example, “3 + 8”), during which trial-by-trial strategy assessments were assessed outside the MRI scanner. The second was an arithmetic verification task which was performed during fMRI scanning (**Fig. 1a,b**). Details of the two arithmetic tasks are described below.

Strategy assessment. In the strategy assessment task, each participant's mix of strategies for solving standard single-digit addition problems was assessed using a standardized, well-validated trial-by-trial measurement that classified strategies based on experimenter observation and participant's self-report^{24,25}. In this task, a set of 18 addition problems was carefully designed by selecting two addends from 2 to 9 (for example, “2 + 9 = ?”), and sums ranging from 6 to 17. Problems with two identical addends (for example, “5 + 5”) or with addends of 0 and 1 (for example, “8 + 1” or “8 + 0”) were excluded because they are known to evince less strategy variability^{7,24,35}. Half of the problems were randomly presented in larger addend plus smaller addend format (“9 + 2 = ?”), and the other half were presented in the opposite format (“3 + 8 = ?”).

During strategy assessment, 18 problems were centrally presented one by one on the computer screen, and there was no repetition in the set. Participants were asked to solve each problem without the use of paper and pencil as quickly as possible and to state the answer out loud. Note that participants were explicitly instructed to use whatever strategy was easiest for them to get the answer. Participants were also asked to report how they solved each problem immediately after stating the answer. For each problem, the experimenter took detailed notes of overt signs of counting, such as finger usage, lip movement or audible counting, and these were compared against each participant's self-report of how the problem was solved. Based on each participant's self-reported strategy and experimenter's observations, mixed strategies for solving addition problems were classified into two major categories of interest: ‘counting’ (such as counting fingers, verbal counting, count by numbers or counting in mind) and ‘direct retrieval’ (such as just know, remember or guess responses). Trials in which the experimenter noted overt signs of counting even when the child reported a retrieval strategy were

classified as a ‘counting’ trial. For each participant, we computed the proportion of trials in which memory-based direct retrieval or counting strategies were used, and remaining trials were endorsed into a category of no interest. This approach allows us to quantify the frequency of memory-based strategy use, i.e., ‘retrieval fluency’, which provides a reliable assessment of putative memory-based strategy use in arithmetic problem solving^{7,24}.

Block design fMRI task. Participants solved an arithmetic verification task^{7,35} during fMRI scanning. We used a block design fMRI paradigm to optimize signal detection and task-dependent functional connectivity analysis²⁶. The task consisted of 16 blocks with four alternating conditions: solving standard single-digit addition problems (for example, “5 + 9 = 14”), solving ‘plus 1’ (for example, “5 + 1 = 6”) as a control addition condition, identifying the number “5” in a string of symbols and numbers and passively viewing fixation. In the standard addition condition, equations with two different single-digit addends (for example, “5 + 9 = 14”) were presented on the center of screen for 5 s, and participants were asked to judge whether the current equation was correct or not by a button press. Half of the equations were correct and the other half were incorrect. In each equation, one addend varied from 2 to 9 and the other varied from 2 to 5. Equations with two identical addends (i.e., tie problems) such as “5 + 5 = 10” were excluded. To avoid large variations in difficulty for addition equations, incorrect answers were restricted to a deviation by ± 2 or ± 1 from the correct answer, and the range of values of the smaller addend was restricted to ≤ 5 to allow children to execute the minimum counting strategy within the allotted 5-s window provided for each problem in the scanner^{15,35}. The control addition task was the same as the addition task except that one addend ranged from 2 to 9 whereas the other was always “1” (for example, $5 + 1 = 7$). We used the “ $n + 1$ ” problem as a control task based on our previous studies^{15,35}, as its format is very similar to the standard addition task and requires the same level of response selection. It is already known that children show less variability in strategy use for solving “ $n + 1$ ” problems, making it an ideal control task for our study^{4,35}.

In each condition, equations were displayed on the center of the screen for 5 s with an intertrial interval of 500 ms. There were 18 trials of each task condition, broken up into four blocks of four or five trials; thus, each block lasted either 22 or 27.5 s. The order of the blocks was pseudorandomized across participants with the standard addition and control addition blocks always separated by either a number identification or a passive fixation block. Orders of addition and non-addition conditions were equally likely. The total length of the experimental run was 6 min and 36 s.

Event-related fMRI task. After the block design fMRI experiment, participants underwent an event-related fMRI while they were performing a similar arithmetic verification task. The event-related fMRI experiment was designed to examine changes in trial-by-trial multivoxel pattern stability^{22,27} with development in terms of the ‘overlapping waves’ model. The task consisted of 52 trials in total: half of them were standard single-digit addition problems and the other half were ‘plus 1’ problems as a control condition. Each trial consisted of a two-digit equation presented at the center of screen for 5.0 s and followed by a fixation period jittered from 2.5 s to 3.5 s. Participants were asked to press a button indicating whether the answer was correct or not. Half of the equations were correct and the other half were incorrect. The order of 52 addition and control trials was pseudorandomized across participants with the standard addition and control addition problems always interleaved by a low-level fixation period. The total length of the experimental run was 6 min and 30 s. The other settings were identical with the block design fMRI task. For this event-related fMRI experiment, data for 8 children were excluded from further analyses because of either their incompleteness for the two time points or bad quality of fMRI data.

Behavioral data analysis. Participant demographic data and behavioral performance in strategy assessment, and in block and event-related fMRI tasks were analyzed using Statistical Product and Service Solutions (SPSS, version 20.0, IBM). We conducted 2-by-2 repeated-measures ANOVA with strategy (retrieval versus counting) and time (children at time 1 versus at time 2) as within-subject factors to examine longitudinal changes in the mix of strategies. We then conducted separate ANOVAs with strategy as a within-subject factor and group (children time 2 versus adolescents versus adults) as a between-subject factor to examine cross-sectional changes in the mix of strategies for addition problem solving from

childhood, through adolescence into adulthood. Similarly, separate ANOVAs were conducted for accuracy and reaction times in the arithmetic verification task in both block design and event-related fMRI. Scheffé's procedure was used to correct for multiple comparisons in *post hoc* tests.

fMRI data acquisition. Whole-brain functional images were acquired from a 3T GE Signa scanner (General Electric) using a custom-built head coil with a T2*-sensitive gradient echo spiral in-out pulse sequence based on blood oxygenation level-dependent (BOLD) contrast⁴⁵. Twenty-nine axial slices (4.0 mm thickness, 0.5 mm skip) parallel to the anterior and posterior commissure (AC-PC) line and covering the whole brain were imaged with the following parameters: volume repetition time (TR) = 2.0 s, echo time (TE) = 25 ms, 80° flip angle, matrix size 64 × 64, field of view 200 × 200 mm and an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional images. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan.

fMRI data analysis. Preprocessing. Images were preprocessed using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). The first eight volumes were discarded for stabilization of the MR signal. Remaining functional images were realigned to correct for rigid-body motion. Subsequently, images were slice timing-corrected, normalized into a standard stereotaxic space and resampled into 2-mm isotropic voxels. Finally, images were spatially smoothed by convolving an isotropic 3D-Gaussian kernel (6-mm full width at half maximum).

Univariate general linear model analysis. To assess task-related brain responses in the block-design data, the addition and control conditions, along with the number identification condition were modeled as separate boxcar regressors and convolved with the canonical hemodynamic response function (HRF) implemented in SPM8. Additionally, motion parameters from the realignment procedure were included to regress out effects of head movement on brain response. We used high-pass filtering using a cutoff of 1/128 Hz, global intensity normalization and corrections for serial correlations in fMRI using a first-order autoregressive model (AR(1)) in the general linear model (GLM) framework.

Contrast images for addition versus control conditions, generated at the individual level fixed-effects analyses, were submitted to a second-level group analysis treating participants as a random factor. A paired *t*-test was first conducted to examine longitudinal changes in brain activity associated with arithmetic problem solving over time (time 1 versus time 2). One-way ANOVA were then conducted to examine cross-sectional changes in brain activity across children at time 2, adolescents and adults. Significant clusters were determined using a height threshold of $P < 0.01$ and an extent threshold of $P < 0.05$ with family-wise error corrections for multiple comparisons based on nonstationary suprathreshold cluster-size distributions computed using Monte Carlo simulations⁴⁶.

To characterize developmental changes in hippocampal engagement in addition problem solving, we performed a complementary ROI analysis using the entire hippocampus. Separate ROI masks for the hippocampus in left and right hemispheres were anatomically defined using the anatomical automatic labeling (AAL) template of the hippocampus. Parameter estimates (or β weights) associated with the two conditions of interest were extracted from these ROIs at the individual level using MarsBar (<http://marsbar.sourceforge.net/>) and averaged across voxels within each region. Subsequently, extracted data were visualized using bar graphs and submitted for statistical testing in SPSS 20.0. In order to create more precise masks of the hippocampus for children, we manually drew the left and right hippocampus (Supplementary Fig. 9) based on high-resolution T1-weighted brain templates from twelve 8.5-year-old children⁴⁷, and then transformed in the same stereotaxic standardized MNI space. We followed a widely used protocol described in ref. 48, integrated with landmarks included in ref. 49 to demarcate the child hippocampus. We used the ITK-SNAP (<http://www.itksnap.org/>) image viewer and segmentation tool to view and segment the MRI images. As shown in Supplementary Figure 9, we found very similar pattern of results when using adult AAL masks and hand-drawn hippocampal masks based on pediatric brain images.

Task-dependent functional connectivity analysis. Task-dependent functional connectivity was examined using psychophysiological interaction (PPI) analysis²⁸. This analysis examined condition-specific modulation of functional connectivity of a specific ROI (the hippocampal seed here) with the rest of the brain, after removing potentially confounding influences of overall task activation and common driving inputs. The hippocampal seed was defined as a 6-mm sphere centered at the local peak of the cluster that showed significant longitudinal changes in brain activation between time 1 and time 2 in children. The mean time series from the seed ROI were then deconvolved so as to uncover neuronal activity (i.e., physiological variable) and multiplied with the task design vector contrasting the addition and control conditions (i.e., a binary psychological variable) to form a psychophysiological interaction vector. This interaction vector was convolved with a canonical HRF to form the PPI regressor of interest. The psychological variable representing the task conditions (addition versus control) as well as the mean-corrected time series of the seed ROI were also included in the GLM to remove overall task-related activation and the effects of common driving inputs on brain connectivity. Brain regions showing significant PPI effects were determined by testing for a positive slope of the PPI regressor.

Contrast images corresponding to PPI effects at the individual-subject level were then entered into a group level statistical analysis. Developmental changes in retrieval fluency (i.e., the frequency of retrieval-strategy use) from time 1 to time 2 were included as covariates of interest to determine brain areas in which longitudinal changes in retrieval fluency were associated with longitudinal changes in task-dependent functional connectivity of the hippocampus. Note that we did not use changes in accuracy and RTs for the arithmetic tasks as a measure of strategic transitions, because these two measures are not specifically related to use of counting and memory-related strategies during problem solving. Similar to the GLM analysis above, significant clusters were determined using a height threshold of $P < 0.01$ and an extent threshold of $P < 0.05$ with family-wise error corrections for multiple comparisons based on nonstationary suprathreshold cluster-size distributions computed using Monte Carlo simulations⁴⁶. To illustrate the brain-behavior relations, we extracted data from significant clusters and plotted correlations for visualization purposes only.

Prediction analysis. To confirm the robustness of the relation between longitudinal changes in hippocampal connectivity with frontoparietal cortex and individual changes in retrieval fluency between time 1 and time 2, we used a machine-learning approach with balanced fourfold cross-validation^{16,31}. The prediction analysis was conducted for confirmatory purposes because conventional regression models assess correlation coefficients, which are sensitive to outliers and are correlational with no predictive value^{16,31}. Longitudinal change in retrieval fluency was entered as a dependent variable, and hippocampal connectivity was entered as an independent variable into a linear regression algorithm. $r_{(\text{predicted}, \text{observed})}$, a measure of how well the independent variable predicts the dependent variable, was estimated using a balanced fourfold cross-validation procedure. Data for these two variables from all children in the longitudinal experiment were divided into four folds so that the distributions of dependent and independent variables were balanced across folds. A linear regression model was built using three folds, leaving out one fold, and this model was then used to predict the data in the left-out fold^{16,31}. This procedure was repeated four times to compute a final $r_{(\text{predicted}, \text{observed})}$ representing the correlation between the data predicted by the regression model and the observed data. Finally, the statistical significance of the model was assessed using a nonparametric testing approach. The empirical null distribution of $r_{(\text{predicted}, \text{observed})}$ was estimated by generating 1,000 surrogate data sets under the null hypothesis that there was no association between changes in retrieval fluency and hippocampal activity (or hippocampal functional connectivity). Each surrogate data set D_i of size equal to the observed data set was generated by permuting the labels on the observed data points. The $r_{(\text{predicted}, \text{observed})i}$ was computed using the actual labels of D_i and predicted labels using the fourfold-balanced cross-validation procedure described above. This procedure produced a null distribution of $r_{(\text{predicted}, \text{observed})}$ for the regression model. The statistical significance (P value) of the model was then determined by counting the number of $r_{(\text{predicted}, \text{observed})i}$ greater than $r_{(\text{predicted}, \text{observed})}$ and then dividing that count by the number of D_i data sets (1,000 in our case).

Multivoxel pattern stability analysis of event-related fMRI data. *Trial-wise estimation of brain responses.* To assess task-related brain responses during solving each addition problem, each problem was modeled as a separate regressor with a duration of 5.0 s and convolved with a canonical hemodynamic response function (HRF) implemented in SPM8. This resulted in with 26 regressors for standard addition problems and 26 regressors for control problems. Contrast images for correct addition problems versus rest fixation condition, generated at the individual level fixed-effects analyses, were submitted to subsequent multivariate pattern stability analyses for the hippocampal ROIs as well as for the whole brain.

ROI-based pattern stability analysis. Beta weights representing voxel-wise brain activation for each addition (but not control) problems was extracted from voxels within the entire left and right anatomically defined hippocampal ROI masks separately, and then reshaped into a single dimensional vector. Pairwise correlations among correct problems of interest were then computed among distributed voxels of each ROI. This ends up with $N \times (N - 1)/2$ pairwise correlation coefficients, where N represents the number of correctly solved problems. Pairwise correlation coefficients were then averaged as a measure of multivoxel pattern stability between individual problems correctly solved. Averaged interproblem pattern stability scores in the left and right hippocampus were separately computed for each participant. Note that any differences in overall mean signal of individual voxels in a given ROI would not impact the computation of multivoxel pattern stability. Separate one-way ANOVAs were conducted to compare differences in interproblem pattern stability in the hippocampus from childhood (either time 1 or time 2) through adolescence into adulthood.

Whole-brain pattern stability analysis. A newly developed searchlight mapping method^{27,32} was implemented to obtain a measure of interproblem pattern

stability in the neighborhood surrounding each voxel in each participant's brain. Briefly, a 6-mm spherical region of interest (so-called the 'searchlight') centered on each voxel was first selected, and then interproblem stability scores only for correctly solved problems in the sphere were computed using a pairwise correlation method. Pairwise correlation maps of two consecutive neighbor trials were excluded in order to mitigate potential collinearity because of close proximity in time. The averaged similarity scores were assigned to the central voxel and run through every voxel across the whole brain to create participant-specific searchlight maps. These searchlight maps were subsequently entered into a second-level random effects analysis to determine changes in pattern stability among children (at either time 1 or time 2) adolescent and adult groups. Significant clusters were determined using a height threshold of $P < 0.01$ and an extent threshold of $P < 0.05$ family-wise error correction for multiple comparisons based on Monte Carlo simulations⁴⁷.

A **Supplementary Methods Checklist** is available.

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