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Development of the declarative memory system in the human brain

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Brain regions that are involved in memory formation, particularly medial temporal lobe (MTL) structures and lateral prefrontal cortex (PFC), have been identified in adults, but not in children. We investigated the development of brain regions involved in memory formation in 49 children and adults (ages 8–24), who studied scenes during functional magnetic resonance imaging. Recognition memory for vividly recollected scenes improved with age. There was greater activation for subsequently remembered scenes than there was for forgotten scenes in MTL and PFC regions. These activations increased with age in specific PFC, but not in MTL, regions. PFC, but not MTL, activations correlated with developmental gains in memory for details of experiences. Voxel-based morphometry indicated that gray matter volume in PFC, but not in MTL, regions reduced with age. These results suggest that PFC regions that are important for the formation of detailed memories for experiences have a prolonged maturational trajectory.

The neural systems mediating declarative or explicit memory (memory for events and facts) in adults have been identified through convergent lesion and functional neuroimaging evidence, but little is known about the normal development of declarative memory systems from childhood through adulthood. In adults, MTL structures, including the hippocampus and surrounding perirhinal and parahippocampal cortices, are essential for the formation of new declarative memories; bilateral MTL injury results in global amnesia that is defined by an inability to form new declarative memories[1,2]. PFC is not essential for memory formation, but PFC lesions impair declarative memory for contextual details of an experience (source memory)[3,4]. Functional neuroimaging studies in healthy adults have found that greater magnitudes of MTL and PFC activation during encoding correlate, on a stimulus-by-stimulus or event-related basis, with successful memory formation, as evidenced by accurate subsequent memory for scenes, words and faces[5–9].

Behavioral evidence indicates that declarative memory ability develops from childhood, through adolescence, and into young adulthood (for example[10–13]). These studies generally report a slower improvement with age for memory tasks that demand greater detail in recollection, such as the context in which information was presented, relative to the information itself[11,14]. The slower development of memory for context has been associated with the maturation of PFC functioning in evoked response potentials studies of the development of recognition memory for item and source[15,16].

Postmortem and structural imaging evidence indicates that PFC maturation appears to continue into late adolescence[17–20], but there is less clear evidence about the trajectory of MTL maturation in the human brain[21–24]. These anatomical findings, however, raise the possibility that PFC memory functions could develop more slowly than MTL memory functions in the human brain.

In this study, we examined the normal development of activations related to successful memory formation, as measured by functional magnetic resonance imaging (fMRI), in 49 healthy children and adults, ranging from 8 to 24 years old. Participants viewed indoor and outdoor scenes during a scanned study phase. Afterwards, they received a recognition memory test with the previously studied scenes and new (foil) scenes. For scenes judged as having been seen at study, participants rated their memories as 'remember' (R responses which indicated a vivid memory accompanied by details of the experience) or 'familiar' (K responses which indicated that participants know they have studied the scene, but that the memory was not accompanied by details of the experience). We examined whether activations in brain regions associated with successful memory formation changed from childhood to adulthood. Further, we related activations in memory-related regions with developmental gains in the formation of contextually detailed memories assessed with a source memory task. Finally, we examined brain morphology in the same memory-related regions with voxel-based morphometry (VBM) analysis, which provides a structural measure of gray matter concentration.

RESULTS

Behavior

Participants correctly recognized 0.51 ± 0.14 (mean probability ± s.d.) of the pictures as 'Old' (hits for R and K responses combined) and correctly responded 'New' (correct rejections) for 0.79 ± 0.14 of the new pictures. Recognition accuracy (hits + correct rejections) was

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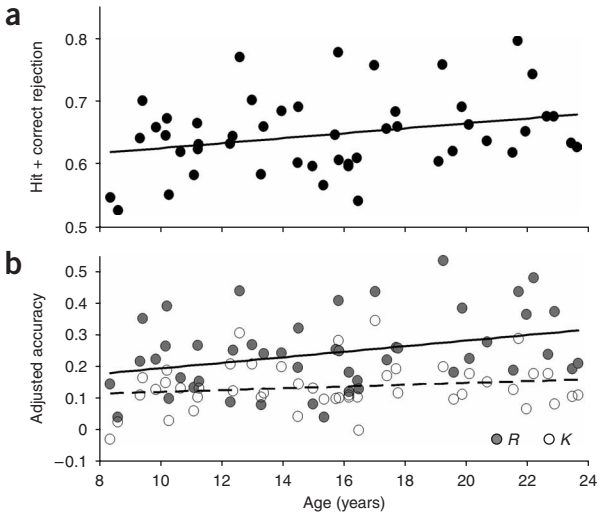

Figure 1 Recognition memory for scenes improved significantly with age, specifically for recollection (*R*) and not familiarity (*K*) indices. (**a**) Recognition accuracy, measured as the overall probability for correct Old and New responses (hits + correct rejections). (**b**) Recognition index *R* ($R_{HIT} - R_{FA}$) (filled circles) and familiarity index *K* ($K_{HIT} - K_{FA}$, adjusted for being mathematically constrained by remember responses) (open circles) plotted against the participants' age.

0.65 ± 0.06, and increased with age significantly ($r = 0.29$, $P < 0.05$; **Fig. 1a**). For correctly recognized studied scenes, 0.28 ± 0.13 were categorized as remembered (R_{HIT}) and 0.22 ± 0.08 were categorized as familiar (K_{HIT}). There was a positive correlation between age and recognition accuracy for remember responses ($R = R_{HIT}$ – false positive R (R_{FA}), $r = 0.33$, $P = 0.02$). In contrast, neither the adjusted familiarity index (*K*, $r = 0.17$) nor the corrected K responses (K_{HIT} – false positive K (K_{FA}), $r = –0.01$) were correlated with age (**Fig. 1b**).

There was a significant interaction of memory type (*R, K*) by age-group (children, ages 8–12, $n = 17$; adolescents, ages 13–17, $n = 18$; adults, ages 19–24, $n = 14$; $F_{2,44} = 4.67$, $P = 0.01$) such that *R* indices grew disproportionately higher with age. Finally, there were significantly more K_{FA} responses (0.18 ± 0.11) than R_{FA} responses (0.05 ± 0.05, $F_{1,44} = 88.8$, $P < 0.001$), which reflects that a false memory is usually less vivid and specific than an accurate memory. Notably, there was no interaction of the type of false positive response (K_{FA} and R_{FA}) with age-group ($F_{2,44} < 1$), indicating that children and adults were using similar criteria for making R and K judgments. Thus, there was an age-related gain in recognition memory only for memories that were accompanied by recollection of details from the original experience.

Imaging

Age correlations in subsequent memory

By identifying activations that were greater for scenes that were subsequently remembered than for scenes that were forgotten (F) (contrast R > F), we could examine whether brain regions associated with successful memory formation changed from childhood to adulthood. Across all 49 participants, activations associated with successful memory formation were found in a large bilateral posterior cluster spanning the middle occipital cortex, extending ventrally into the middle temporal, fusiform and parahippocampal gyri (PHG), and dorsally into the precuneus and superior parietal lobule, and in several PFC regions (**Table 1** and **Fig. 2**).

Activations associated with memory formation were selected as regions of interest (ROIs) to examine for developmental changes (**Table 1** and **Supplementary Table 1** online). For the PFC, we

Table 1 Subsequent memory activations

			MNI coordinates				
		BA	*X*	*Y*	*Z*	Peak *T* value	No. voxels
Remembered > Forgotten (R > F)							
Right	Precuneus	7	26	–76	40	12.29	18,100
	Parahippocampal gyrus	37	32	–40	–12	11.84	
	Superior occipital gyrus	19	34	–82	26	10.04	
Right	Inferior frontal gyrus	9	44	10	26	6.2	599^{AGE}
	Middle frontal gyrus	9	56	22	34	3.9	
Left	Middle/inferior frontal gyrus	47/11	–36	34	–14	6.12	171
Left	Precentral gyrus	6	–50	–2	56	5.74	65
	Middle frontal gyrus	6	–52	8	48	3.83	
Left	Inferior/middle frontal gyrus	46	–46	32	14	5.38	158^{AGE}
Right	Middle frontal gyrus	11/47	30	36	–14	5.12	76
Right	Superior frontal gyrus	6	26	–12	76	5.1	67
	Precentral gyrus	6	36	–12	70	4.4	
Left	Inferior/middle frontal gyrus	9	–40	6	30	4.99	319
Right	Inferior/middle frontal gyrus	46	38	32	16	4.25	168
Right	Medial frontal gyrus	6	22	4	52	3.94	36
Left	Medial frontal gyrus	11	–2	44	–14	3.66	10
Medial temporal lobe ROIs							
Left	Hippocampus		–32	–28	–14	6.58	118
Right	Hippocampus		32	–34	–8	6.99	94
Left	Parahippocampal gyrus	37/36/19	–32	–42	–14	9.14	1,184
Right	Parahippocampal gyrus	37/36/19	32	–40	–12	11.84	1,268

^{AGE} denotes significant increase of activation with age across participants ($P < 0.05$).

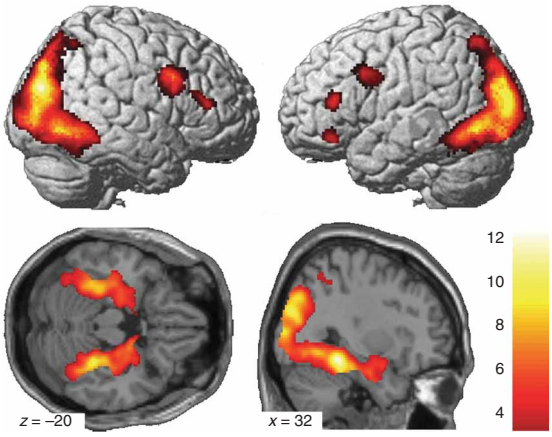

Figure 2 Subsequent memory activations (R > F) across all 49 participants, ages 8–24 years. Activation maps are rendered on standard brain right and left lateral views (top), and on horizontal and coronal sections (bottom). MNI coordinates presented at the bottom of each section. $P < 0.001$, uncorrected; cluster threshold ≥ 80 contiguous voxels. *T* value scale presented on the bottom right.

examined functionally defined clusters of activation ROIs in left and right dorsolateral prefrontal cortex (DLPFC) Brodmann Area (BA) 46, left and right DLPFC BA 9, left and right ventrolateral prefrontal cortex (VLPFC) BA 11 and 47, left and right precentral gyrus BA 6, and medial frontal gyrus (left BA 11, right BA 6). Subsequent memory-related activations increased with age in two PFC ROIs, left BA 46 ($r = 0.30$, $P = 0.04$) and right BA 9 ($r = 0.30$, $P = 0.04$) (**Fig. 3a**), and a trend was noted in left BA 9 ($r = 0.23$, $P = 0.11$). No correlations with age were found in the other PFC ROIs ($-0.02 < r < 0.13$, *P*'s > 0.39). We examined MTL activation with four functional ROIs that were restricted to the anatomical landmarks of the left and right hippocampus and left and right PHG BA 37, 36 and 19. There were no correlations between age and activation in any MTL ROIs ($-0.03 < r < 0.18$, *P*'s > 0.22; **Fig. 3b**). Thus in specific PFC regions associated with successful memory formation, activation increased with age, but in MTL regions that are also associated with successful memory formation there were no age-related activation changes (**Fig. 4**).

We also examined activations that were associated with the formation of memories that supported subsequent familiarity (contrast K > F; **Supplementary Table 1** and **Fig. 5**). No correlations with age were found for K > F contrast activations in PFC and MTL ROIs defined either by the K > F contrast ($-0.05 < r < 0.08$, *P*'s > 0.57) or by the R > F contrast (PFC ROIs, $-0.20 < r < 0.22$, *P*'s > 0.13; MTL ROIs, $0.02 < r < 0.06$, *P*'s > 0.67). Thus, there were no age-related changes in either memory or brain activation for recognition memory that occurred without recollection of the details from the original experience.

To investigate the increase in R, but not K, responses with age, we examined activation that was associated with the subsequently remembered scenes versus the subsequently familiar scenes (contrast R > K; **Supplementary Table 1**). Activation significantly increased with age in the left BA 9 ROI (defined by R > K, $r = 0.33$, $P = 0.02$). No correlations with age were found for R > K contrast activations in other PFC and MTL ROIs ($-0.13 < r < 0.18$, *P*'s > 0.21). Thus, the increase in R, but not K, responses with age was related specifically to growth of activation in left BA 9.

A further analysis examined the relation between age and correctly recognized scenes, a more objective measure of memory formation (**Supplementary Table 1**). ROIs were defined by activations that were greater for all of the correctly recognized scenes than for the forgotten scenes (contrast R + K > F). These ROIs were similar to those defined by the R > F contrast (**Table 1**). Activations for subsequently remembered scenes increased with age in two PFC regions, left BA 46 ($r = 0.30$, $P = 0.04$) and right BA 9 and 46 ($r = 0.29$, $P < 0.05$). Activations for subsequently remembered scenes did not correlate with age in other PFC ($-0.26 < r < 0.21$, *P*'s > 0.07) or MTL ROIs ($-0.01 < r < 0.15$, *P*'s > 0.30). Thus, in specific PFC regions, but not in MTL regions, activation related to subsequent recognition increased with age.

We carried out analyses to examine how individual differences in recognition performance related to activation magnitudes (contrast R > F) in the ROIs. Across all participants, activations correlated positively with recognition accuracy in several PFC regions (left VLPFC BA 11 and 47, $r = 0.37$, $P = 0.01$; right medial frontal gyrus BA 6, $r = 0.34$, $P = 0.02$; left precentral gyrus BA 6, $r = 0.32$, $P = 0.03$; trends in left PFC BA 46 and right superior frontal gyrus BA 6, *P*'s < 0.1) and multiple MTL ROIs (left PHG, $r = 0.32$, $P = 0.03$; right PHG, $r = 0.33$, $P = 0.02$; trends in left hippocampus, $r = 0.27$, $P = 0.06$; right hippocampus, $r = 0.25$, $P = 0.08$). Thus the relations between recognition accuracy and activation reflect both age-related and age-independent individual differences.

Relation of prefrontal function to source memory

These findings, consistent with previous behavioral reports[11], suggest that the ability to create a memory that is vivid and rich in contextual details improves with age. In a separate session (not scanned), the same participants viewed line drawings in a study phase. Each line drawing was presented in red or green on the left or right side of the computer

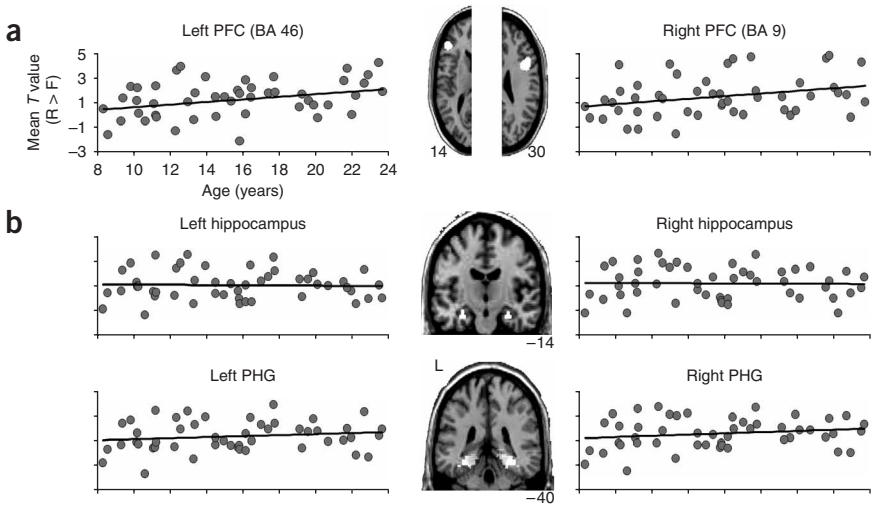

Figure 3 Activation associated with successful memory formation increased with age in PFC, but not MTL, ROIs across age. (**a**,**b**) Plots of correlations of the individual mean *T* values in the contrast R > F per ROI across the whole age range are shown on both sides of the brain images depicting PFC in horizontal slices (**a**) and MTL ROI locations in coronal slices (**b**). MNI *z* and *y* coordinates are presented in the bottom of the PFC and MTL ROIs' images, respectively.

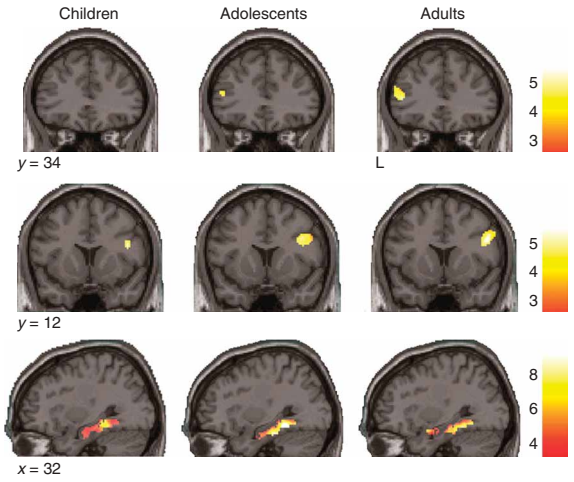

Figure 4 Activations associated with successful memory formation (R > F) for children, adolescents and young adults. Activation maps are overlaid on standard T1 image. Activations centered in the PFC BA 46 (top) and PFC BA 9 (middle) are overlaid on coronal sections and activations in MTL (including parahippocampal gyri and hippocampus) are overlaid on sagittal sections (bottom) ($P < 0.005$, uncorrected, T value scale presented on the right, note different range used for PFC and MTL activations). MNI coordinates presented at bottom of each section. Children, $n = 17$, 9 male, mean age = 10.7, range 8–12 years of age; adolescents, $n = 18$, 9 male, mean age = 15.7, range 13–17 years of age; adults, $n = 14$, 7 male, mean age = 21.7, range 19–24 years of age. This three-group stratification is illustrative, but statistical analyses were conducted with age as a continuum.

monitor along with a judgment of either animacy or size. At test, participants saw centrally presented, black-and-white drawings, half of which had been seen during the study phase. They made three kinds of memory judgments: (i) whether the drawing had (old items) or had not (new items) been seen at study, (ii) for drawings judged old, whether the memory was an R or K experience, and (iii) for drawings judged old, recollections (source memory) about the original color, location and judgment associated with that drawing.

Source memory scores increased with age ($r = 0.50$, $P < 0.001$) and correlated with R ($r = 0.38$, $P = 0.001$), but not K ($r = –0.10$), indices from the scanner task. Further, source memory scores for old items judged as remember increased with age ($r = 0.26$, $P = 0.04$, one-tailed), indicating that there were more details in recollected memory with age (source memory scores for old, familiar items did not correlate with age, $r = 0.11$, one-tailed). Source memory scores positively correlated with the activations (contrast R > F) in BA 9 ROIs (right, $r = 0.34$, $P = 0.02$; left, $r = 0.35$, $P = 0.01$), but not in left BA 46 ($r = 0.23$, $P = 0.12$). Source memory scores did not correlate with activation in any other ROI. With age being controlled, there were no reliable correlations between source memory scores and any activation. Finally, unlike the R > F activations, source memory scores did not correlate with the K > F activations in any ROI (P's > 0.16). Thus, PFC activations that increased with age were related to both subjective (R/K recognition judgments) and objective (source experiment) measures of detailed recollection.

VBM analysis

We examined brain morphology in the same memory-related ROIs with VBM analysis, which provides a structural measure of gray matter concentration (**Fig. 5**). There were strong negative correlations between gray matter concentration and age in both PFC regions that showed subsequent memory age-effects (left BA 46, $r = –0.65$, $P < 0.001$; right BA 9, $r = –0.65$, $P < 0.001$). Gray matter concentration in the other frontal ROIs also showed negative correlations with age (for example, right BA 46, $r = –0.44$, $P = 0.002$; left BA 9, $r = –0.63$, $P < 0.001$; left BA 11 and 47, $r = –0.45$, $P = 0.001$). The negative correlations between age and VBM measures are generally interpreted as reflecting pruning of immature neurons, but it is not possible to make direct relations between gross imaging measures and fine cellular processes.

In the MTL ROIs, where there were no age-related subsequent memory effects, there were no significant correlations between gray matter concentration and age (hippocampus left, $r = 0.07$, $P = 0.61$; hippocampus right, $r = –0.01$, $P = 0.93$; PHG left, $r = –0.23$, $P = 0.11$; PHG right, $r = –0.22$, $P = 0.14$). Thus, measures of morphology aligned with the functional findings, indicating that there are age-related changes in PFC, but not MTL, regions associated with successful memory formation. Linear correlations were examined to match the linear correlations used in the analyses throughout our study but, the relationship between VBM measurements and age, as well as between VBM measures and functional activation, may be more complicated and better described in a nonlinear fashion.

DISCUSSION

This is the first study to examine the development of declarative memory using an event-related fMRI design. Recognition accuracy increased moderately, but significantly, from age 8 to age 24. Consistent with previous reports[10,16] the growth of recognition accuracy occurred

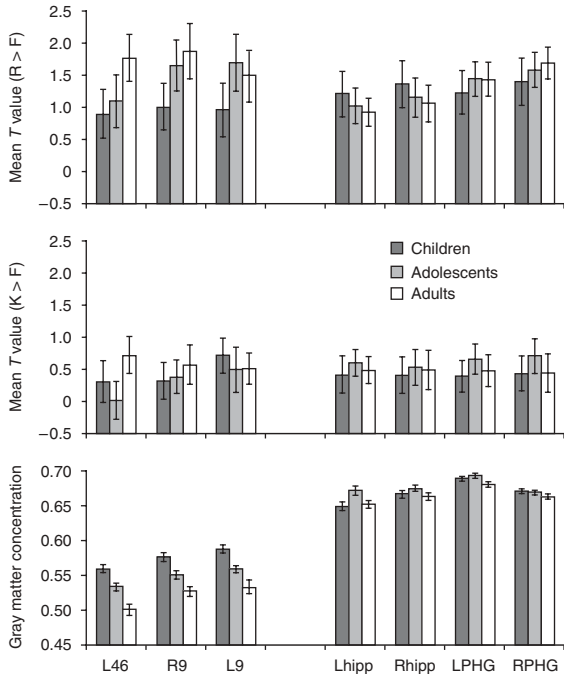

Figure 5 Subsequent memory effects and gray matter concentrations in children, adolescents and young adults. Group mean T values of activation for R > F (top) and K > F (middle), and group mean gray-matter concentrations (bottom) are plotted for children, adolescents and adults in PFC and MTL ROIs (error bars represent s.e.m). L46, left BA 46; R9, right BA 9; L9, left BA 9; Lhipp, left hippocampus; Rhipp, right hippocampus; LPHG, left PHG; RPHG, right PHG. ROIs as in **Figure 3**; children, adolescents and adults groups as in **Figure 4**.

specifically for recognition that was accompanied by recollection of having seen specific scenes (*R*). In contrast, recognition in the absence of recollection (or familiarity-based recognition, *K*) did not change with age. This development of declarative memory formation was associated with age-related growths of activations in specific dorsolateral PFC regions, whereas memory-related activations in the MTL remained constant across this age span. Thus, the normal development of declarative memory for scenes reflected a dissociation between MTL activations that appeared fully developed by age 8 and dorsolateral PFC activations that grew steadily from age 8 to age 24. These findings implicate a faster developmental trajectory for MTL functions and a slower developmental trajectory for PFC functions that contribute to memory formation.

There has been a paucity of neuroimaging studies on the development of declarative memory. A study comparing the encoding of novel versus repeated scenes in participants of ages 11–19 found age-related reductions in left MTL (including hippocampus and entorhinal cortex) activation, and increased functional connectivity between left entorhinal and left DLPFC regions[25]. Another study examining story comprehension found that children of ages 7–8 failed to show the anterior MTL (including hippocampus) and PFC activation that is shown by older children of ages 10–18 (ref. 26). Neither prior study was event-related in design, which precluded a direct examination of the relation between the magnitude of activation and memory formation.

MTL structures are known to be essential for declarative memory formation, and MTL activations were associated with memory formation in the present study, but this association did not change with age. MTL activations in hippocampal and parahippocampal regions were greater for remembered than for forgotten scenes. Furthermore, across participants, greater activations of left and right parahippocampal cortices were significantly correlated with superior recognition memory, and trends toward significance correlations were evident in both hippocampi. Thus, the present study was sensitive to relations between MTL activation and memory formation both within and across participants, but age did not alter these relations. The MTL ROIs in which activations were related to memory formation, but not age, did not show reliable correlations between VBM measures and age. There is little evidence favoring a protracted maturation of MTL structure, but this may reflect subregional variation in developmental trajectories that are more difficult to measure[22]. The absence of age-related differences in MTL structure and function may reflect a limit of measurement sensitivity. In this study, however, there was no reliable influence of age on MTL function or structure.

Interpretation of the absence of a developmental influence on MTL-memory relations is constrained by the specific design of this study. The present study used a scene recognition memory procedure that is known to produce robust MTL and PFC activations that are associated with memory formation in adults (for example[5,6]). This procedure was used so that any developmental changes could be readily measured and interpreted relative to adult patterns of activation. In the range of memory encoding tasks, however, scene recognition may minimize many memory processes that are engaged by other sorts of tasks that involve more voluntary strategies. Imaging studies have reported more complex patterns of activation that can differ across MTL structures when more complex encoding tasks are administered[7,27]. When participants judge whether 250 somewhat similar-looking pictures depict indoor or outdoor scenes, they may engage in a relatively passive form of memory encoding that does not reveal MTL encoding processes that are engaged by other tasks that encourage more active and controlled encoding processes[28]. Similarly, although developmental changes were seen in PFC activations associated with recollection for scenes, recognition memory for scenes may not have revealed PFC functions that are associated with memory tasks demanding greater contextual detail. Indeed, the correlation between age and recognition memory for scenes was lower than that between age and source memory for drawings. Future studies that employ memory-encoding tasks that manipulate controlled processing or request relational memory construction can reveal whether MTL activations vary with age, or PFC activations vary more powerfully with age, under such circumstances.

There were multiple influences of age on PFC function and structure in memory-related ROIs. There were significant age-related increases of activation related to memory formation that could support recollection in left BA 46 and right BA 9, and a trend toward significance in left BA 9, whereas activation in frontal regions defined by the formation of memories that could support only familiarity-based recognition showed no influence of age. There was an age-related increase of activation associated specifically with recollective memory processes in left BA 9. The three strongest VBM correlations with age occurred in the same three PFC regions that showed the greatest activation correlations with age (left BA 46, right BA 9 and left BA 9). The protracted influence of age on dorsolateral PFC structure and function is consonant with convergent evidence that the PFC matures slower than many other brain regions[29]. Both postmortem and imaging evidence suggest that the frontal lobes show a protracted developmental trajectory[17,18,20], with the DLPFC maturing slowest among PFC regions[20].

A challenge in interpreting developmental findings is that many psychological and neural mechanisms are undergoing parallel maturation, and it is difficult to distinguish between correlated and causal maturational findings. For example, height correlates with age in development, and yet it is unlikely that a growth in height mediates a growth in recognition memory or a growth in PFC function. Statistically, one can covary age or other age-related factors[30,31], but this introduces the risk that the statistical control eliminates the actual developmental causal factor (for example, statistically controlling for height may eliminate any influence of age on height). When the relation between activation and memory performance was examined directly, independent of age, correlations were found in brain regions that did not show age-related correlations, including VLPFC, bilateral parahippocampal cortex and bilateral hippocampi. Thus, variation of activations in these regions must have reflected variation in psychological factors not mediated by age that influenced memory encoding. Therefore, although age and recognition performance were correlated, there was specificity in terms of which brain areas associated with successful memory formation were (dorsolateral PFC areas) or were not (ventral PFC and MTL) influenced by age.

Methodological challenges that can arise when comparing brain activations between children and adults include movement in the scanner, anatomic normalization and potential differences in the blood oxygenation level-dependent hemodynamic response function (HRF). Movement parameters were modeled as confounds in the general linear model of the individual first-level parametric designs, and there was no developmental correlation with stimulus-correlated motion. Normalization to a common neurological space was used to compare activations across participants. Although there are concerns that the use of a common adult template could be inappropriate for children[32], there is empirical evidence that a common stereotactic space is appropriate for children that are 7 years of age or older because anatomic normalization differences between children and adults are small relative to the resolution of fMRI data[33]. For children younger than 7 years of age, pediatric templates may be preferable[32], but this would preclude direct comparisons across ages (necessitating an ROI

approach). Finally, there is substantial variability of the HRF across adults and even across individual brain regions[34–38], and this raises the possibility that neural responses and HRF responses may be coupled differently in children than adults. In sensory and motor areas, however, there appear to be minimal differences in the time courses and locations of functional activation foci between children and adults[39]. Our findings that age-related increases in activation were localized in specific PFC ROIs, but that activation in other PFC and MTL ROIs associated with memory formation did not correlate with age, makes it unlikely that our findings are the result of an artifact caused by the difficulties in conducting pediatric imaging studies outlined above.

A limitation of our study is that we examined development in a cross-sectional design, whereas a longitudinal design is optimal for the study of development. Indeed, one longitudinal study of structural brain development found a relation between the rate of structural development and intelligence test scores that could not have been observed in a cross-sectional design[40]. All published fMRI studies of development, with a single exception[41], have been cross-sectional, as have the vast majority of behavioral developmental studies of infants and children. One fMRI study examined the development of cognitive control in both a cross-sectional and longitudinal design[41]. Indeed, the longitudinal design was more sensitive than the cross-sectional design in detecting developmental differences. However, developmental differences that were found in the cross-sectional comparison were similar to those found in the longitudinal comparison. Therefore, a future longitudinal study may reveal additional, and more definitive, development of the declarative memory system.

An important question is what aspect of memory encoding is mediated by PFC regions that are related to memory formation and that increase in activation with age. The present findings indicate that the PFC regions that showed age-related growth in activation have a specific role in the formation of episodic memories that are contextually rich, detailed and temporally and spatially specific. The interpretation that immature PFC structure and function limit the episodic specificity of memory formation through development is consistent with two related lines of evidence. First, adult PFC lesions disproportionately impair the contextual specificity of memories so that patients have relatively or fully intact recognition memory, but are impaired in recollecting the source of an experience[3,4]. Large MTL lesions, on the other hand, result in a broader and much more severe amnesia that compromises all aspects of declarative memory, but does not selectively compromise source memory[42]. Second, in the present study, age had a strong influence on the source memory task carried out by the same individuals that carried out the scanner task. Magnitudes of activation in left and right BA 9 correlated with superior source memory, but activations in MTL regions did not.

Developmental influences on recognition memory occurred selectively for detailed recollection (*R*), with no apparent influence of age on familiarity (*K*). The separation of correct recognition responses into recollection and familiarity reflects reports from participants about their subjective memory retrieval experience, and this raises the question as to whether those reports reflect similar criteria in children and adults. The behavioral evidence from our study indicates that there was little, if any, developmental influence on the criteria for K responses, because source accuracy for K responses did not correlate with age in the source memory experiment. There was, however, a developmental difference in the criteria used to categorize R responses, with greater source accuracy occurring for adults than for children for R responses in the source memory experiment. This raises the possibility that comparing activations in children and adults for subjective recollective (R) experiences of scenes viewed during scanning resulted in a comparison of less detailed memories in children versus more detailed memories in adults. However, when recognition memory was defined by the objective measure of recognition accuracy, independent of subjective retrieval reports, the same influence of development on activation was found: namely an age-related growth of PFC activation, but not MTL activation, for scenes later remembered than for scenes later forgotten. Thus, whether activation analyses were based on subjective reports of memory vividness or objective measures of memory accuracy, the development of PFC activation was associated with the development of recognition memory. The developmental role for PFC function in memory formation is consistent with evidence that gray matter reduction in frontal cortices in 7–16-year-old children correlated with memory improvement, independent of chronological age[43].

Thus, we found evidence in favor of different developmental trajectories for MTL and PFC contributions to declarative memory formation from ages 8–24. In MTL regions, there was no reliable influence of age on either fMRI activations associated with memory formation or VBM measures of structure. These findings indicate that MTL contributions to declarative memory formation may mature relatively early. In PFC regions, there were reliable influences of age on both fMRI activations associated with memory formation and VBM measures of structure. The age-influenced fMRI activations in PFC were associated directly with the development of the recollective component of recognition memory and indirectly with source memory and the specificity of episodic memories. Thus, the immaturity of PFC areas appears to limit the episodic specificity of memories such that memories are less likely to be subjectively vivid or objectively detailed. In broad terms, a distinction can be made between two patterns of immature brain function in children; children could either use a neural network that differs from adults, or use a weaker version of the same network used by adults[44]. In our study, children appeared to have used the same MTL-PFC declarative-memory system as adults, but showed immaturity in the PFC components of that system.

Finally, there has been great interest in the potential relation between cognitive neuroscience and education, although this relation has been fraught with misunderstanding[45]. A very large part of education involves learning through the formation of declarative memories, and yet surprisingly little is known about the development of the declarative memory system that is essential for learning information and that may often fail in learning disorders. Our study contributes toward a neurobiological understanding of how children learn as compared with how adults learn. Future studies of a wider range of memory processes, including those that are more overtly related to education, are needed to strengthen the relation between education and functional brain development.

METHODS

Participants. Fifty-two volunteers were recruited from the Stanford University community and provided informed consent as indicated by a Stanford University IRB-approved protocol. Neuroimaging data are presented for 49 participants (25 male, 8–24 years of age) who met data quality criteria (described below). All participants were right-handed, had normal visual acuity and were screened for histories of any psychiatric or medical illnesses. Participants were paid $20 per h for their participation in the scanning session and $10 for an initial, 1-h-long behavioral testing session.

Materials. Five hundred pictures of indoor and outdoor scenes were used, and randomly divided into ten lists of 50 pictures (each comprised of 25 indoor and 25 outdoor scenes). Five lists were presented during the study, and the remaining five lists were presented as foils during the recognition-memory

test. Lists were counterbalanced across participants, such that all lists were presented equally often as study and test items across participants.

Memory task. Participants were scanned as they studied 250 pictures of indoor and outdoor scenes. Each picture was presented for 3 s with a 1-s intertrial interval. The participants were explicitly instructed to memorize the scenes for a later memory test. Participants judged whether each scene depicted an indoor or outdoor scene, and indicated their judgment by pressing one response box button with their right index finger to indicate an indoor picture or another button with their right middle finger to indicate an outdoor picture. The instructions (indoor/outdoor) appeared on the bottom of the screen, prompting participants to use the appropriate button press. Following the scanning procedure, participants were given a recognition test consisting of 250 old and 250 new pictures presented on a computer screen. For each picture, participants first judged whether they have seen it before in the study phase (Old) or not (New). If they responded Old, a follow-up question appeared on the screen to which participants had to indicate whether they 'actually remember' seeing the picture (R) or whether the picture 'just looks familiar' (K)[10]. Participants were instructed to make R responses if they had a vivid, clear memory of studying the picture and could recall specific episodic information like what button they pressed, what the picture looked like on the screen, what they were thinking at the time or anything that made the memory distinct. K responses were made if participants knew they had studied the scene, but could not recall details of the experience. Studied items that elicited a New response were categorized as forgotten items (F). In this self-paced recognition test, each trial lasted a maximum of 8 s. Recognition accuracy (probability of correct Old and New responses) and the probability of R and K responses (for previously seen pictures: R_{HIT}, K_{HIT}; or false positive for previously unseen pictures: R_{FA}, K_{FA}) were calculated. In addition, recognition accuracy for R responses was indexed by the discrimination measure $R = R_{HIT} - R_{FA}$. To provide an index for familiarity (K), the discrimination measure $K_{HIT} - K_{FA}$ was adjusted for being mathematically constrained by R responses[46]. False positive data were missing from two participants as a result of technical difficulty. Participants were highly accurate (97.3%) in making indoor/outdoor judgments during scanning (on average, 243.4 ± 7.8; children, 241.1 ± 8.9; adolescents, 244.7 ± 5.3; adults 244.3 ± 5.6; recorded correct responses from 250 trials). There was, however, a trend toward a significant and positive correlation between age and accuracy in the task ($r = 0.27$, $P = 0.06$). Therefore, only studied items that elicited correct indoor/outdoor responses were used in the imaging analysis. This prevented the small influence of age on accuracy in the encoding phase from influencing the subsequent memory analyses.

MRI data acquisition. Data were acquired on a 1.5T General Electric Signa scanner using a small head coil. Prior to the functional scans, we acquired T1-weighted whole-brain anatomy images (256 × 256 voxels, 0.86-mm inplane resolution, 1.2-mm slice thickness), as well as 24 contiguous, 6-mm anatomical images, oriented parallel to the line connecting the anterior and posterior commissures, covering the entire brain (spin-echo T2-weighted anatomical images; 3.75-mm inplane resolusion). Functional images were then obtained in the same 24 slice locations as the anatomical images using a T2*-sensitive two-dimensional gradient-echo[47] (repetition time = 2 s, echo time = 30 ms, flip angle = 60°, 64 × 64 voxels, 3.75-mm inplane resolution) to minimize signal dropout in ventral regions of interest. The memory task was imaged in five functional runs, each with 50 picture stimuli. In the beginning of each run, participants were shown a 10-s countdown on the screen, during which 5 TR were collected to allow for signal stabilization. Functional runs lasted 3 min and 28 s, in which 102 images were collected. The first two volumes of each run were discarded. Medical tape was placed such that the front and bottom of the chin were connected to the coil in order to restrict head movement.

Data quality assessment and preprocessing. Data were visually inspected and reviewed for artifacts and motion using custom software (http://web.mit.edu/swg/software.htm). Functional data was subjected to artifact detection if motion exceeded 3 mm in any direction (absolute maximum). Five participants were detected by this criterion and outlier images (deviant greater than 1% of the mean global intensity) were excluded from further analysis of their data (ages 8, 10, 10, 11 and 14, 3 male). Data from one of these participants, and one additional participant, were excluded as a result of sustained image artifacts (male, age 12; female, age 10). In addition, data from one scanned participant (male, age 8) were excluded for behavioral noncompliance; no familiar (F) responses were made in three of the five scanned sessions. SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/spm2.html) was used in all analyses. Images went through slice timing correction (to slice twelve), and motion correction using sinc interpolation. The anatomical (inplane) image was coregistered to the mean functional image that was created during motion correction. Functional images were then spatially normalized based on parameters determined by normalizing the anatomical (inplane) image to the T2 Montreal Neurological Institute template). Finally, images were spatially smoothed with an isotropic Gaussian kernel of 6-mm full-width at half maximum.

Statistical analysis. Analysis of the movement parameters obtained during realignment showed that younger participants moved more, as evident in a negative correlation between age and two of the six movement dimensions (z-axis transformation, $r = -0.31$, $P = 0.03$; pitch rotation, $r = -0.29$, $P < 0.05$; no correlation with age was evident in the other four dimensions, $-0.27 < r < -0.07$, P's > 0.06). There was no reliable correlation between age and the amount of stimulus-correlated motion in any of the trial types in all six movement parameters ($-0.22 < r < 0.23$, P's > 0.11). Therefore, to minimize artifacts due to differences in movement across ages, movement parameters (the six movement parameters assessed during realignment) were introduced as nuisance covariates in participants' statistical models (first-level analysis). Inclusion of motion parameters ensured that the variance related to residual head motion is explicitly modeled, and hence would not result in false positives.

Individual general linear model–based analyses were conducted in MNI space. Models included regressors of interest generated by convolving task events with a canonical model of the HRF as implemented in SPM2. Trials in the scanned study phase were categorized as three possible types determined by the recognition test (R, K and F) and regressor functions were constructed for each of the three trial types. Linear combination of the regressors was used in defining contrast of interest. These included: (i) contrast R > F; (ii) contrast K > F; (iii) contrast R > K. Individual subjects' effects were estimated using a fixed-effects model across the five sessions. Contrasts constructed at the single participant level were then input into a second-level group analysis using a random-effects model. Group contrasts were constructed using a one-sample t-test. All reported clusters survived a P threshold of 0.001 (uncorrected), and consisted of ten or more contiguous voxels. Functional ROIs were created from the activation map including all 49 participants in the contrast R > F (**Fig. 2**). Prefrontal ROIs were defined as the distinct clusters of activation identified in the group activation map. MTL regions were constructed form the group activation map in the contrast R > F by constraining the activation with specific anatomical landmarks of the hippocampus and PHG (using the Wake Forest University PickAtlas tool). Age-related comparisons were made in these functionally defined regions taken from the activation map of all 49 participants to minimize explicit biases toward a specific age range. Data were extracted from individual participant's T statistic images corresponding to the contrast R > F and were then subjected to a correlation test (Pearson's r, two-tailed) with age as a continuous measure. Correlations with recognition accuracy were also tested. Similar analyses were applied to activations defined in the contrasts K > F, R > K and R + K > F.

Voxel-based morphometry. An optimized method of voxel-based morphometry (VBM)[48,49] analysis was carried out using the SPM2 package. Data from two participants (included in the functional dataset) were excluded from the VBM analysis as a result of technical error (one) and artifact in the anatomical T1-image (one). Data from another participant previously excluded from the functional imaging analysis was included in the VBM analysis. Thus a custom-made template included images from 48 participants. Age differences in gray matter concentrations were tested by extracting individuals' data (normalized gray matter segmented images) in the previously identified functional ROIs.

Source memory task. All participants were given a source memory task in a separate session before the scan session. Participants studied two unique sets of 16 line drawings[50] presented on one side of a computer screen in either red or

green colors, and were asked one of two questions ('is this a living thing?' or 'is this bigger than a shoe box?'). A recognition test followed each study set in which the studied line drawings and an additional 16 foils were displayed. The participants made an old/new recognition decision for each item. For items categorized as old, participants made a remember/familiar judgment and then answer three specific source questions assessing memory for the side (left or right), the color (red or green) and the question (animacy or size) that followed each display in the study phase. Source memory score was the percentage of correct source judgments made for all drawings identified correctly as old. In addition, the percentages of correct source judgments for old drawings judged as being remembered or familiar were calculated.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

N.O., Y.-C.K. and J.D.E.G. designed the experiments. N.O., Y.-C.K., P.S.-H. H.K. and S.W.-G. collected and analyzed the data. N.O., S.W.-G. and J.D.E.G. wrote the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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