Developmental fMRI study of episodic verbal memory encoding in children

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ABSTRACT

Background: Understanding the maturation and organization of cognitive function in the brain is a central objective of both child neurology and developmental cognitive neuroscience. This study focuses on episodic memory encoding of verbal information by children, a cognitive domain not previously studied using fMRI.

Methods: Children from 7 to 19 years of age were scanned at 1.5-T field strength using event-related fMRI while performing a novel verbal memory encoding paradigm in which words were incidentally encoded. A subsequent memory analysis was performed. SPM2 was utilized for whole brain and region-of-interest analyses of data. Both whole-sample intragroup analyses and intergroup analyses of the sample divided into 2 subgroups by age were conducted.

Results: Importantly, behavioral memory performance was equal across the age range of children studied. Encoding-related activation in the left hippocampus and bilateral basal ganglia declined as age increased. In addition, while robust blood oxygen level-dependent signal was found in left prefrontal cortex with task performance, no encoding-related age-modulated prefrontal activation was observed in either hemisphere.

Conclusion: These data are consistent with a developmental pattern of verbal memory encoding function in which left hippocampal and bilateral basal ganglionic activations are more robust earlier in childhood but then decline with age. No encoding-related activation was found in prefrontal cortex which may relate to this region's recognized delay in biologic maturation in humans. These data represent the first fMRI demonstration of verbal encoding function in children and are relevant developmentally and clinically. *Neurology*® 2010;75:2110-2116

GLOSSARY

BOLD = blood oxygenation level-dependent; **DM** = differences in subsequent memory; **F** = misses; **H** = high-confidence hits; **L** = low-confidence hits; **MTL** = medial temporal lobe; **NS** = not significant; **PFC** = prefrontal cortex; **ROI** = region of interest.

The developmental organization of explicit long-term memory in children remains relatively unexplored. We report developmental fMRI data in children on episodic encoding of verbal information, an explicit long-term memory process. Medial temporal lobes (hippocampus, related areas; MTL) and prefrontal cortex (PFC) mediate episodic encoding in adults. These regions' involvement in episodic encoding has been demonstrated by fMRI studies using the subsequent-memory (DM) paradigm. Encoding-related brain activity for items subsequently remembered is contrasted with encoding activity for items forgotten to reveal regions associated with successful episodic memory encoding. These studies have consistently reported PFC and MTL activation.¹

Sparse fMRI data exist for episodic encoding by children. Recently, a subsequent-memory approach was used to study episodic encoding in children who intentionally studied scene

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pictures followed by a postscan memory test. No difference existed between adults and children in MTL, but age-related activation differences appeared in PFC.²

The present study of 7- to 19-year-old children extends these findings in 3 important ways. First, we used verbal stimuli to interrogate left MTL function in verbal encoding, a finding documented in adults^{3,4} but not children. Second, we employed an incidental rather than intentional encoding task to minimize participant age-related encoding strategy use.⁵ Third, we addressed age-related neural organization for verbal memory encoding while maintaining memory performance equivalence across subjects. While age-related difference in mnemonic performance is relevant, it provides a potential confound when trying to identify differences in brain organization related to age rather than to ability or strategy.^{6,7}

METHODS Participants. A total of 24 healthy children (age range 7–19 years, mean 13.8 ± 3.6 years: 7–11 years, 5 subjects; 11–15 years, 7 subjects; 15–17 years, 6 subjects; 17–19 years, 6 subjects; 9 male, all right-handed, mean full-scale IQ 112.8 ± 11.6 , native English speakers) were studied. Informed consent by parents and assent by subjects were obtained as approved by Children's Hospital Boston Committee on Clinical Investigation.

Standard protocol, approvals, registrations, and patient consents. Informed, written consent by parents and assent by subjects were obtained as approved by Children's Hospital Boston Committee on Clinical Investigation.

Behavioral procedure. Stimuli were short familiar words. The encoding task was phonologically based and incidental (rather than intentional to minimize encoding strategy use). The encoding task was elaborative and required word generation, to promote subsequent memory.⁸ During each trial, participants used a phoneme-substitution rule to self-generate a third word from 2 consecutively presented words. Participants replaced the initial phoneme of the second word with the initial phoneme of the first word to form a third standard-English word (figure 1). The first word of the pair was presented aurally via headphones while an image depicting the word appeared on the left side of a screen. After 1,000 msec, the second word was presented aurally and its corresponding image appeared on the screen's right. Images remained onscreen for an additional 4,000 msec, followed by 1,000 msec of blank screen. Total trial length was 6,000 msec. A variable interstimulus interval (2,000–8,000 msec) was used during which participants passively viewed a fixation cross-hair to optimize the event-related fMRI response. A single functional scan comprised 93 trials. The 93 word pairs used were selected after piloting demonstrated subjects could generate the desired target word at 100% accuracy for each trial.

Fifteen minutes after scanning, participants completed an unexpected recognition test for target words generated during

scanning in which 186 words were presented one by one on-screen in pseudorandom order, such that scan target words were equally represented in both halves of the test. Half the items were target words generated during the scan (old items); half were novel words neither generated nor presented during scanning (new items). For each, participants were asked "Is this word one you made in the scanner?" and responded 1) "definitely yes," indicating high confidence; 2) "yes," for low confidence; or 3) "no," if they did not recognize the word as one generated. Each word remained onscreen until the participant responded with the appropriate keystroke. Next, participants' encoding trials corresponding to target words generated during scanning were conditionalized as one of 3 types of trials: high-confidence hits (H), low-confidence hits (L), or misses (F).

Stimulus materials. A total of 279 concrete nouns were selected from the MRC Psycholinguistic database (In: MRC Psycholinguistic Database[online]. Available at: www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). Words were 1–2 syllables and 3–7 letters long (mean 4.2; SD 0.9). A total of 93 word pairs were constructed for the phoneme substitution task, so that only one target word was possible for each pair. Auditory recordings of these 186 words were downloaded from the Merriam-Webster Web site (<http://www.m-w.com>). Pictures corresponding to these 186 words were 3×3 -inch color drawings from www.clipart.com. The remaining 93 nouns served as foils in the postscan recognition test. A separate behavioral pilot study verified that children in the study's target age range could complete the task of forming the third word from the word pair provided within 5–6 seconds at a 100% success rate.

Imaging procedure. Participants were scanned on a 1.5-T General Electric scanner, for high-resolution T1-weighted anatomic images (spoiled gradient recalled) and T2*-weighted EPI functional images (repetition time = 2,000 msec, 240-mm field of view, 64×64 matrix, 363 volume acquisition single run, echo time = 50 msec, 17 axial slices, 7 mm thickness). Two initial volumes were discarded to allow for T1 equilibration. Head motion was minimized with foam cushions arranged around the head.

Data were preprocessed and analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London). Differences in slice acquisition timing were corrected by resampling all slices in time to match the first slice. Data were spatially normalized to an EPI template in MNI305 stereotactic space.⁹ Images were resampled into 2 mm^3 voxels and smoothed with an 8-mm full width at half maximum isotropic Gaussian kernel.

Statistical analyses employed the general linear model, a trial duration = 3 repetition times, and a canonical hemodynamic response function. Response type (i.e., H, L, F) effects were estimated using a subject-specific fixed-effects model with low-frequency signal components treated as confounds. Linear contrasts were used to obtain subject-specific estimates for effects of interest. A second-level analysis followed, treating subjects as a random effect, using a one-sample *t* test against a contrast value of zero at each voxel. Statistical parametric maps were created for the encoding task: all trials > baseline, and for the contrast of interest: H > F, and were characterized on the basis of blood oxygenation level-dependent (BOLD) signal using, at the voxel level, a height threshold of $p < 0.001$, and a cluster size threshold of 18 contiguous voxels to reduce probability of type 1 error.¹⁰

Regions of interest (ROIs) were identified based on the activation map from whole brain analysis using clusters that survived thresholding criteria in the task contrast. Parameter estimates extracted from these ROIs for each subject were used to observe activation levels associated with each effect of interest in these regions.

Figure 1 Experimental design

(A) The structure of one trial. Participants heard 2 nouns sequentially, accompanied by an image corresponding to each noun. Participants were instructed to use a phoneme-substitution rule in order to create a third word. In this example, the first sound in “pen” is substituted for the first sound in “tool” which when performed and integrated by the participant with the remainder of the second word produces the third word “pool.” (B) The format of a functional run exemplified by a few trials. In all, 93 word pairs were presented. Published with permission of JUPITERIMAGES (www.clipart.com).

Age-related differences in subsequent memory (DM)-associated brain activation were explored, using regression analysis, in which age was entered as a predictor of the effects of interest. Following this regression analysis, a second-level analysis was re-run, in which children were classified into younger (ages 7–14 years, 12 participants) and older (ages 15–19 years, 12 participants) subgroups (cutoff line chosen for practical reasons to pro-

vide sufficient subgroup size for analysis). A 2-tailed *t* test was used for intergroup comparison.

RESULTS Behavioral data. In postscan recognition testing, participants remembered an average of 66% target words generated during scan: 38% with high confidence and 28% with low confidence (table 1). Memory performance did not correlate with age. Age did not significantly predict hits ($r = 0.22$, NS) or a composite measure of hits + correct rejections² ($r = 0.26$, NS, figure 2A). Division of participants into younger and older groups (see Methods) revealed no difference between the 2 age groups for hits [$t(22) = 1.3$, $p > 0.1$] or for corrected recognition [hits – false alarms; $t(22) = 1.4$, $p > 0.1$], indicating that age had no effect upon behavioral performance within the group of children studied.

Additionally, comparison of the participants’ behavioral performance to that of an adult group which

Table 1 Behavioral performance^a

Response	Target words			New words		
	Total	Young	Older	Total	Young	Older
Old HC	0.38 (0.14)	0.34 (0.14)	0.41 (0.12)	0.02 (0.003)	0.02 (0.03)	0.02 (0.02)
Old LC	0.28 (0.11)	0.26 (0.11)	0.29 (0.12)	0.18 (0.13)	0.19 (0.14)	0.16 (0.12)
New	0.34 (0.12)	0.38 (0.12)	0.29 (0.10)	0.80 (0.15)	0.77 (0.17)	0.81 (0.12)

Abbreviations: HC = high confidence; LC = low confidence.

^a Distribution of responses provided by participants for target words and foil words presented in the postscan recognition test. Data are presented as a percentage (SD) of either target words or new words.

Figure 2 Recognition performance did not vary as a function of age

(A) A plot showing no significant correlation between the behavioral measure hits + correct rejections (the probability of hits + the probability of correct rejection) and age. (B) Three different behavioral measures of memory performance—probability of hits, probability of corrected recognition (probability of hits – probability of false alarms), and probability of correct rejections—show no difference between the developmental group reported here and a group of adults performing the same task in a separate behavioral experiment. Error bars represent SEM.

performed the identical task without scanning ($n = 18$; age range 19–31) revealed no difference between the groups [hits: $t(40) < 1$; corrected recognition: $t(40) < 1$; figure 2, A and B] with respect to numbers of high-confidence hits, low-confidence hits, and misses, demonstrating that the experimental paradigm eliminated age-related performance effects on the episodic memory measures.

Imaging data. The word-generation task, compared to fixation baseline, activated bilateral posterior areas in occipital, parietal, and posterior temporal cortices. Basal ganglionic, prefrontal, and hippocampal areas activated by the task were left-lateralized (figure e-1 on the *Neurology*® Web site at www.neurology.org). Next, we sought brain regions wherein encoding activation for high-confidence subsequently remembered words exceeded that of subsequently forgotten words (subsequent memory effect, $H > F$) across the entire group of participants. This contrast yielded left anterior hip-

pocampal (figure 3A) and parahippocampal, bilateral basal ganglionic (putamen/pallidum), medial parietal and frontal, and cerebellar regions (table e-1 for full list of regional activations). Despite robust lateral, left $>$ right PFC activation during task performance (figure e-1A), no lateral PFC activation was identified for the $H > F$ contrast.

Hippocampus and age. We sought correlations between subject age and DM effect in MTL. As subject age increased, the DM effect in left hippocampus ($r = -0.43$, $p = 0.034$, figure 3B) but not right hippocampus ($r = -0.14$, NS) declined. Age-related left hippocampal activation was further examined by dividing participants into younger and older groups followed by DM analysis of both groups. A 2 (memory conditions: H and F; within subjects) $\times$ 2 (age groups: younger and older) mixed analysis of variance revealed significant interaction of age group and DM ($F_{1,22} = 11.2$, $p < 0.003$). The younger group exhibited significant DM effect ($p < 0.0009$; figure 3C); no such difference was observed in the older group ($p > 0.1$).

PFC and age. No PFC was identified in the $H > F$ contrast. Activation differences between younger and older participants may escape detection in the whole group contrast due to opposite but otherwise equal activation patterns in the 2 groups. Consequently, we selected a left PFC region from the all $>$ baseline contrast for ROI analysis closely approximating the region reported in a study of pictorial memory in children² to demonstrate developmentally dependent activation ($x = -46$, $y = 32$, $z = 14$; present study: $x = -52$, $y = 32$, $z = 10$; figure 4A). Regression analysis of age with respect to parameter estimate difference for H and F trials extracted from this region failed to yield significant correlation ($r = -0.17$, NS; figure 4B), as did a separate comparison of parameter estimates for younger and older participants (figure 4C). While threshold reduction to 0.009 revealed a left frontal region with higher signal for H compared to F trials, no age-dependent memory effect was found ($r = 0.24$, NS).

Age-related analyses were performed on all other regions identified in the DM contrast. Only bilateral basal ganglia showed significant correlation with age (right putamen/pallidum [$x = 25$, $y = 7$, $z = -6$] $r = -0.43$, $p < 0.02$; left putamen/pallidum [$x = -21$, $y = 10$, $z = -9$] $r = -0.41$, $p < 0.05$). Like left hippocampus, the bi-basal ganglionic DM signal declined as age increased.

DISCUSSION This study had 2 goals: 1) to identify regional brain activations in children that support successful verbal episodic encoding, and 2) to exam-

Figure 3 Subsequent memory effect in the left hippocampus ($x = -28, y = -14, z = -18$; voxel extent: 121 voxels)

(A) Across the whole age group studied, the left hippocampus shows robust activation (at center of crosshair). (B) Correlation of the subsequent memory effect as provided by left hippocampal activation with age of subjects in the sample studied; $r = -0.43, p = 0.034$. (C) Subsequent memory effect in the left hippocampus for the sample studied, subdivided into the younger and the older subgroups. Error bars represent SEM. Hits = words remembered with high confidence; forgotten = words forgotten. Note how the subsequent memory effect (i.e., magnitude of signal parameter hits - magnitude of signal parameter for forgotten words) declines with age within the left hippocampus.

ine changes in these regional activations during childhood development. We found a DM effect in left temporal lobe and basal ganglia in the children we studied, which consisted of declining BOLD signal with increasing age. No DM effect was found in PFC in the cohort, even though this region was robustly engaged by the encoding task in all children studied.

Prefrontal cortex and MTL follow different developmental trajectories during childhood. Neuroanatomic data indicate that PFC matures later than other brain regions. Final synaptic density in human middle frontal gyrus is not attained until mid to late adolescence. MRI-based structural measures such as

gray matter thickness, myelination density, and synaptic pruning suggest prolonged development of prefrontal regions, some achieving full maturation in early adulthood.¹¹⁻¹⁶

MTL presents a complex developmental picture. While cross-sectional imaging studies indicate that MTL reaches structural maturation in early childhood,¹⁷ a recent longitudinal study suggests that hippocampal maturation continues throughout childhood.¹⁸ This study found gradual reduction of anterior and concomitant increase in posterior hippocampal cortical thickness with age among children 4 to 25 years old.

These regional neuroanatomic maturational changes suggest neural organizational differences of memory processes between children and adults. This idea finds strong support in current neuropsychological data. The characteristics of amnesia following MTL injury in adulthood differ from those found in children. One child demonstrated preserved delayed recognition performance but severely impaired delayed recall; adult amnesiacs typically are impaired on both.¹⁹ Further, while adult amnesiacs often demonstrate episodic and semantic memory impairments, episodic memory is impaired in developmental amnesia while semantic memory can remain intact.²⁰ These reports indicate that similar damage to the same neural structure at different ages can result in different mnemonic impairment. The incidental encoding word-generation paradigm employed in the current study equated memory performance across the participants' age range and minimized the confound of cross-age behavioral performance difference. This equivalence may have resulted from the paradigm's intended design to reduce use of encoding and retention strategies known to enhance adult performance.^{5,21-23} Consequently, we believe that the age-related regional activation differences found in left hippocampus and bilateral basal ganglia in the sample studied result from developmentally dependent change in the functional organization of verbal episodic memory during childhood.

The observed left hippocampal and bilateral basal ganglionic decline in DM-related BOLD signal with advancing age found in the children studied is consistent with other reports indicating developmentally dependent change in these regions. Anatomically in children, the volume of the anterior hippocampus declines with age while posterior hippocampal volume increases, to which postnatal myelination, synaptogenesis, synaptic pruning, or apoptosis may contribute.¹⁸ Additionally, studies of learned response shifts to behavioral stimuli demonstrate that striatal/pallidal and hippocampal/parahippocampal activations are larger and more ventrally extended in children than in adults, indicating increasingly spe-

Figure 4 No subsequent memory effect was observed in the left PFC

(A) A region of interest functionally defined from the task > baseline contrast, whose coordinates ($x = -52$, $y = 32$, $z = 10$) are close to the left PFC region reported in reference 2 to demonstrate an age-modulated subsequent memory effect ($x = -46$, $y = 32$, $z = 14$). No such effect was observed in the present study: both words remembered with high confidence and those forgotten activated this region to a similar extent. (B) This was also the case when younger and older groups were examined separately. (C) No correlation was found between the difference in parameter estimates' values associated with words remembered with high confidence and those forgotten, and age.

cific age-dependent neural activation.²⁴ Finally, left frontal lobe activation attenuation with increasing age has been observed for performance of a verbal fluency task in adults as compared to children.²⁵

Notably, no DM effect emerged in PFC despite its robust engagement by all trials regardless of recognition status. These findings differ from those in adults who typically demonstrate DM effects in PFC and MTL. The absence of a DM effect in PFC in the present study should be interpreted cautiously, as failure to detect a DM effect in the PFC may reflect statistical power insufficiency of the pediatric group studied. Additionally, this discrepancy may be related to experimental design. To address this question, we ran an additional similarly designed experiment on an adult group (appendix e-1). Behaviorally, adults and children demonstrated no difference in memory performance using the third-word paradigm (table e-2). Importantly, the adult group revealed both left hippocampal and left PFC DM-related fMRI activations (see figure e-2). Confirmation in adults of these 2 expected regional activations renders it unlikely that our results in children obtained with the same methods are due to experimental design.

Alternatively, the absence of a DM-related activation in the PFC may reflect true developmental organizational change in brain areas supporting episodic

encoding. PFC may not contribute significantly to verbal memory encoding early in childhood, assuming a more important role later in adolescence and beyond. Developmentally dependent neural network revision has been observed with fMRI study of working memory in young children and adults with equivalent levels of task performance.²⁵ Thus, successful encoding of verbal episodes may depend more on hippocampus during early childhood, with PFC less central to the mnemonic process than will occur later in life. Moreover, with maturation, successful episodic encoding may derive from enhanced connectivity between MTL and PFC regions (for more on these theoretical ideas, see reference ²⁶). Indeed, while hippocampal activation may decline with age, its connectivity with PFC regions increases with age.²⁷

Only one other published study utilized event-related fMRI to examine developmental episodic encoding in children.² This study, however, employed pictorial stimuli, and required intentional encoding of presented color photographs. No age-related hippocampal modulation of subsequent memory effect was observed, but direct correlation between age and encoding-related activation emerged in PFC. Importantly, the behavioral results revealed significant age-related variation in memory performance. The present study extends this finding in important ways. First, it examines verbal memory encoding of self-generated words by children. The left-lateralization of age-dependent medial temporal lobe activation likely derives from the verbal encoding task; bilateral medial temporal activation has been associated with pictorial encoding.^{3,28,29} Second, the constancy of memory performance across the cohort's age range is unique and enables a more direct interpretation of observed brain activation changes. Finally, while our participants' ages ranged from 7 to 19 years, almost one-third of subjects studied² exceeded 19 years. Thus, these young adults may have imparted some of the observed PFC effect. In that study, children 8–12 years old showed no PFC subsequent memory effect, only scant effect emerged in 13- to 17-year-olds, while a larger region appeared in adults (19–24 years)² (figure 4).

These results have clinical relevance to buttress their developmental significance. Approximately 25% of children with epilepsy prove refractory to medical therapy.³⁰ Children with refractory temporal lobe epilepsy may be treated with temporal lobectomy. Consequently, presurgical, noninvasive temporal lobe localization of verbal mnemonic function by fMRI would be highly desirable, especially when electrographic/neuroimaging data indicate left temporal epileptogenesis.^{29,31} While this has been investigated in adults, investigation is lacking in children.³²

The current data from typically developing children represent the first step toward presurgical functional localization of verbal memory encoding in children with epilepsy.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Maril and Dr. Rivkin.

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REFERENCES

- Paller KA, Wagner AD. Observing the transformation of experience into memory. *Trends Cogn Sci* 2002;6:93–102.
- Ofen N, Kao YC, Sokol-Hessner P, Kim H, Whitfield-Gabrieli S, Gabrieli JDE. Development of the declarative memory system in the human brain. *Nat Neurosci* 2007;10:1198–1205.
- Kelley WM, Miezin FM, McDermott KB, et al. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 1998;20:927–936.
- Papanicolaou AC, Simos PG, Castillo EM, Breier JI, Katz JS, Wright AA. The hippocampus and memory of verbal and pictorial material. *Learning Memory* 2002;9:99–104.
- Schneider W, Bjorklund DF. Memory. In: Damon W, ed. *Handbook of Child Psychology: Volume 2: Cognition, Perception and Language*. New York: John Wiley & Sons, Inc.; 1998:467–521.
- Durston S, Pol HEH, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H. Anatomical MRI of the developing human brain: what have we learned? *J Am Acad Child Adolesc Psychiatry* 2001;40:1012–1020.
- Schlaggar BL, Brown TT, Lugar HM, Visscher KM, Miezin FM, Petersen SE. Functional neuroanatomical differences between adults and school-age children in the processing of single words [see comment]. *Science* 2002;296:1476–1479.
- Bertsch S, Pesta BJ, Wiscott R, McDaniel MA. The generation effect: a meta-analytic review. *Mem Cogn* 2007;35:201–210.
- Cocosco CA, Kollokian V, Kwan RK-S, Evans AC. BrainWeb: online interface to a 3D MRI simulated brain database. *Neuroimage* 1997;5:S425.
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 1995;33:636–647.
- Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 1999;2:861–863.
- Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA* 2004;101:8174–8179.
- Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol* 1997;387:167–178.
- Klingberg T, Vaidya CJ, Gabrieli JD, Moseley ME, Hedehus M. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport* 1999;10:2817–2821.
- Shaw P, Kabani NJ, Lerch JP, et al. Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci* 2008;28:3586–3594.
- Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci* 2004;24:8223–8231.
- Serres L. Morphological changes of the human hippocampal formation from midgestation to early childhood. In: Nelson CA, Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience*. Cambridge, MA: MIT Press; 2001.
- Gogtay N, Nugent TF, Herman DH, et al. Dynamic mapping of normal human hippocampal development. *Hippocampus* 2006;16:664–672.
- Baddeley A, Vargha-Khadem F, Mishkin M. Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *J Cogn Neurosci* 2001;13:357–369.
- Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 1997;277:376–380.
- McGregor KK, Friedman RM, Reilly RM, Newman RM. Semantic representation and naming in young children. *J Speech Lang Hear Res* 2002;45:332–346.
- Murphy K, McKone E, Slee J. Dissociations between implicit and explicit memory in children: the role of strategic processing and the knowledge base. *J Exp Child Psychol* 2003;84:124–165.
- Schneider W, Pressley M. *Memory Development Between 2 and 20*, 2nd ed. Mahwah, NJ: Erlbaum; 1997.
- Casey BJ, Thomas KM, Davidson MC, Kunz K, Franzen PL. Dissociating striatal and hippocampal function developmentally with a stimulus-response compatibility task. *J Neurosci* 2002;22:8647–8652.
- Ciesielski KT, Lesnik PG, Savoy RL, Grant EP, Ahlfors SP. Developmental neural networks in children performing a Categorical n-back task. *Neuroimage* 2006;33:980–990.
- Nelson III CA, Thomas KM, de Haan M. Neural bases of cognitive development. In: Kuhn D, Siegler RS, Damon W, Lerner RM, eds. *Handbook of Child Psychology: Vol. 2, Cognition, Perception, and Language*. Hoboken, NJ: John Wiley & Sons Inc.; 2006:3–57.
- Menon V, Boyett-Anderson JM, Reiss AL. Maturation of medial temporal lobe response and connectivity during memory encoding. *Cogn Brain Res* 2005;25:379–385.
- Jansen A, Sehlmeier C, Pfeiderer B, et al. Assessment of verbal memory by fMRI: lateralization and functional neuroanatomy. *Clin Neurol Neurosurg* 2009;111:57–62.
- Rosazza C, Minati L, Ghielmetti F, et al. Engagement of the medial temporal lobe in verbal and nonverbal memory: assessment with functional MR imaging in healthy subjects. *Am J Neuroradiol* 2009;30:1134–1141.
- Blume WT. Temporal lobe epilepsy surgery in childhood: rationale for greater use. *Can J Neurol Sci* 1997;24:95–98.
- Cheung MC, Chan AS, Lam JMK, Chan YL. Pre- and postoperative fMRI and clinical memory performance in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2009;80:1099–1106.
- Golby AJ, Poldrack RA, Illes J, Chen D, Desmond JE, Gabrieli JDE. Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. *Epilepsia* 2002;43:855–863.