Recent evidence suggests that in primates, as in rodents, the hippocampus shows a developmental continuum that affects memory abilities from infancy to adulthood. In primates relatively few hippocampal-dependent abilities (e.g. some aspects of recognition memory) are present in early infancy, whereas others (e.g. relational memory) begin to show adult-like characteristics around 2 years of age in monkeys and 5–7 years in humans. Profound and persistent memory loss resulting from insult to the hippocampus in infancy becomes evident in everyday behavior only later in childhood. This pattern of results suggests a maturational gradient within the medial temporal lobe memory system, with most abilities crucially dependent on the hippocampus emerging in later stages of development, supporting a model of hierarchical organization of memory within the medial temporal lobe.

### Introduction

Explicit memory is characterized by memories accessible to consciousness [1] and includes memories for facts and general knowledge (semantic memory), in addition to memory for personally experienced events (episodic memory). A neural network that comprises the hippocampus (dentate gyrus, Cornus Ammonis [CA] fields, and subicular complex) and its interconnections with adjacent medial temporal cortical areas is thought to mediate these two types of memory. Recent evidence in rodents, monkeys and humans suggests that the medial temporal cortical areas are crucial for familiarity-based item recognition [2–5], whereas the hippocampus is crucial for acquiring, storing and recollecting inter-item associations and their spatial, temporal and other contextual relationships [6–11]. In addition, as will be pointed out below, one form of item recognition appears to be dependent on the hippocampus, at least in part [12,13]. Crucial questions that remain to be answered, however, are when do these memory processes emerge during infancy and how do the brain systems that mediate them mature during ontogeny? Finally, given the higher degree of neural plasticity that is present in early infancy, what are the long-term behavioral and cognitive consequences of early insult to the hippocampus?

Research in rodents has indicated that memory abilities mediated by the hippocampus have a protracted development. Because in this species almost all neurogenesis in the dentate gyrus occurs entirely during postnatal life, it is possible to relate the onset of some memory processes to maturational changes in the hippocampus. Moreover, memory deficits following neonatal hippocampal damage in rodents emerge at an age when the hippocampus becomes functionally mature [14]. The close links among maturational events within the hippocampus, development of hippocampal-dependent memory abilities, and timing of memory deficits after early insult to the hippocampus have encouraged the extension of these comparisons to other species. This review provides an account of the most recent findings obtained in primates.

### Maturation of the hippocampus in primates

One striking difference between rodents and primates is that in primates neurogenesis in the hippocampus proper and dentate gyrus occurs almost entirely during prenatal life. However, many morphological and neurochemical changes in addition to refinement of synaptic connections within the hippocampus persist into the first postnatal years.

In the monkey [15], genesis of neurons in the dentate gyrus continues throughout gestation and is approximately 80% complete at birth, but tapers off between the fourth and the sixth postnatal months to a low level that might continue throughout adult life. The postnatal wave of synaptogenesis in the dentate gyrus peaks at 4–5 months of age and is accompanied by a 30% increase in spine density and in asymmetrical synapses in addition to a decrease in shaft synapses. In the CA fields, CA3 neurons increase in size, number, and the spines increase in complexity in the second half of the first postnatal year, and new mossy fiber synapses are formed throughout the first year. Finally, myelination of hippocampal afferents and efferents shows substantial postnatal maturation. This postnatal development of the hippocampus is also evidenced by an increase in hippocampal volume and changes in the ratio of gray to white matter from birth to 1 year of age, as revealed by a recent longitudinal structural magnetic resonance imaging (MRI) study [16].
Similarly, in the human hippocampus, immature cells continue to accrue within the dentate gyrus throughout the first year of life, and dendritic development and synapse formation persists until at least year five [17]. Myelination in the subicular and presubicular regions, a key relay zone between the hippocampus and many cortical areas, continues through adolescence and adulthood [18], with female subjects showing a greater extent of myelination between 6 and 29 years of age than that in males. A structural MR imaging study also demonstrated a dramatic increase in hippocampal volume in the second half of pregnancy, whereas a still larger increase takes place in the first to second postnatal year [19]. Small additional increases in hippocampal volume through adolescence and early adulthood have also been reported by others [20–22].

Thus, although the structural elements and synaptic connections necessary for memory formation are present in the newborn primates, the modifications of hippocampal circuits from birth to adulthood provide a basis for hippocampal-dependent memory processes to continue to mature during childhood. Growing experimental and clinical evidence demonstrates this progression [15,17,23–25,26,27].

**Emergence of hippocampal-dependent memory processes in primates**

One limiting factor for studying the development of explicit memory processes and their neural basis in animals and preverbal human infants is the recollective aspect of explicit memory. Research in this area has relied mostly on behavioral measures of recognition-based incidental memory, and on measures of relational memory based on conjunctive representations linking an item with other items, and with the spatial and temporal contexts of an episode or event. These memory abilities have been thought to constitute a precursor form of recollection that could be tested in both preverbal human infants [23,25] and animals [10]. For the purpose of comparing the data gathered in monkeys with those gathered in humans, we will focus here on memory paradigms that are sensitive to selective hippocampal damage in both species.

A form of recognition-based incidental memory is the earliest hippocampal-dependent mnemonic ability demonstrated in primates. Preferential viewing paradigms, which measure the subject’s tendency to fixate longer on novel stimuli than on familiar ones, provide a measure of this form of recognition memory in young animals and non-verbal human infants. Novelty preference is present as early as the first week or month of life in monkeys [28,29] and in the first few days and months in humans [30,31], and it is highly sensitive to selective hippocampal lesions in adult monkeys [12,13] and adult humans [32,33]. This indicates that some types of memory processes that ultimately become hippocampal-dependent are available early during development. Yet, the ability to learn relational associations between stimuli, as measured by the transverse patterning problem (A+ versus B−; B+ versus C−; C+ versus A−, where + indicates the reward) or by the bidirectional discrimination task (A+, AC−, CD+, BD−), does not reach adult-proficiency before 2 years in monkeys [15,34] and 5–6 years in humans [35]. Similarly, spatial memory abilities in monkeys, measured by a modified version of the preferential viewing task, are absent even at 9 months of age [36] and those in children, measured with spatial memory tasks adapted from the rodent literature (e.g. 8-arm maze, and Morris search task), do not reach adult proficiency before 6–8 years of age [37]. Given that performance on these nonspatial and spatial relational memory tasks is impaired in monkeys and humans with selective hippocampal damage [38–44] and that such performance activates the hippocampus in normal subjects during MR imaging studies [45–48], the complete set of data suggests that mnemonic abilities thought to be dependent on the hippocampus do not show a single pattern of development. Some processes (e.g. incidental, familiarity-based recognition memory) are present in the first months of life, whereas others involving more complex cognitive demands (e.g. relational memory, recollection-based recognition memory) mature over many years. The findings are consistent with the notion that context-free, incidental mnemonic abilities precede the development of context-rich, explicit memory [1], which only gradually emerges during childhood and becomes hippocampally dependent [8,9].

No direct links between morphological changes within the hippocampus and modifications of hippocampal-dependent memory processes during development have been established. Therefore, it has been proposed that the progressive maturation of relational or context-rich memory abilities in late infancy and childhood reflects the maturation of the functional architecture of the dentate gyrus, the hippocampus proper, and their progressive integrative participation with the medial temporal cortical areas in cognitive memory processes [15,17,24,25,27] (but see also Courage and Howe [26] for a review of the cognitive accounts thought to mediate the protracted development of explicit memory processes).

**Early insult to the hippocampus**

Despite many perinatal factors (e.g. hypoxia or anoxia, epilepsy) that can alter the normal development of the hippocampus [50–56], it is only recently that the significant impact of early hippocampal insult on explicit memory development in infants and young primates has started to be appreciated.

Lesions to the hippocampus in the second postnatal week in monkeys yield severe memory deficits when assessed in adulthood. Thus, unlike unoperated controls, those
with neonatal hippocampal lesions later show a delay-dependent recognition memory loss, as measured during the preferential viewing task but not during the delayed nonmatching-to-sample task [57,58]. As compared with the incidental nature of the preferential viewing task, the delayed nonmatching-to-sample task requires the individual to learn purposefully novelty-reward associations. Thus, the incidental nature of the recognition-based paradigm presumably taps cognitive processes mediated by the hippocampus, whereas the rule-based nonmatching-to-sample paradigm does not. The neonatally operated monkeys are also impaired later in learning to solve the transverse patterning problem, and in acquiring and retaining spatial information, as measured by a delayed nonmatching-to-location task [59]. Thus, the presence of a severe and enduring global memory impairment resulting from neonatal damage to the hippocampus demonstrates that, despite the special neural plasticity present early in life, no other structures or circuits can serve as a hippocampal substitute in enabling these forms of memory.

Further insights into the time course of the memory impairment have come from a recent longitudinal study [60] of recognition abilities at 1, 6 and 18 months of age measured by preferential viewing. This research shows that, although novelty preference is present as early as 1 month of age in monkeys (average looking time at novel stimuli: 67% at the shortest delay of 10s to 64% at the longest delay of 120s), this ability becomes stronger with age (75% at the shortest delay to 73% at the longest delay at 18 months). Other important results come from the performance of monkeys that have received selective neurotoxic hippocampal lesions between 10 and 12 days of age. Interestingly, novelty preference in these operated infant monkeys does not differ from that of control animals at the ages of 1 and 6 months. However, at 18 months, novelty preference, although not totally abolished, is significantly weaker in the monkeys with neonatal hippocampal damage than that in control animals at delays of 60s or longer. These data give credence to the view presented earlier that the progressive changes in incidental recognition abilities measured by preferential viewing reflect the gradual functional maturation of the hippocampus. They also suggest that this form of recognition memory seen at an early age in both control and operated monkeys could be mediated by the medial temporal cortical areas that are crucial for familiarity judgments and object memory in adults [2,4,5].

Case studies of explicit memory deficits and global amnesia in children were reported as long as two decades ago [61–64], but in the absence of detailed MRI-based anatomical information about the site and extent of medial temporal lobe pathology, it has been difficult to ascertain which aspects of the amnesic profile result from hippocampal damage per se. The recent application of quantified techniques to measure the volumes of medial temporal lobe regions on high-resolution structural MRI scans [65,66] has made it possible to relate the presence of hippocampal pathology to aspects of explicit memory in children and adolescents diagnosed with developmental amnesia (DA) associated with hypoxic or ischemic episodes suffered early in life [67,68,69]. In these recent studies, the neuropathological profile of patients with DA shows severe hippocampal pathology with volume reductions of ∼27–56% below normal on each side [70]. In addition, morphometric analyses of the whole brain show reduced gray matter density in the putamen and posterior thalamus bilaterally, and in the right retrosplenial cortex [68].

Typically, the neuropsychological profile of patients with DA shows a dissociation between semantic memory, which is relatively preserved [71,72], and episodic memory, which is severely and chronically impaired [67,68,69]. Whether the dissociation between episodic and semantic memory in DA reflects a qualitative distinction between these two components of explicit memory [9,73] or a quantitative one [74] is as yet unresolved. The episodic memory deficit in DA is global and encompasses verbal, nonverbal and spatial domains [67,68,75–77]. In fact, some aspects of episodic memory (e.g. route finding, remembering appointments, belongings, etc.) appear to be particularly vulnerable to hippocampal pathology, even when its extent is substantially below that seen in DA (i.e. mean bilateral volume reductions of only 8–9% [70,78]). Detailed studies of one of the patients with perinatal-onset bilateral hippocampal pathology (50% volume reduction below normal), Jon, have revealed other unusual features of this disorder. For example, on a standardized test directly equating recognition with recall, Jon shows verbal and nonverbal recognition within the normal range but marked impairment in recall in both domains, showing a standardized recall-recognition discrepancy score of 3, which represents the bottom of the scale for that test measure [79]. Furthermore, Jon appears to have preserved ability for familiarity judgments without recollection on recognition tests requiring remember versus know judgments [79], a dissociation that was also reflected in an event-related-potential (ERP) experiment involving word recognition [80]. Here, Jon showed normal modulation of the N400 (see glossary) waveform, an index of familiarity, but not of the late positive component (see glossary), a marker of recollection [81]. Finally, a fMRI study of Jon, who recalls public but few autobiographical events, revealed...
activation abnormalities for those personal events that he did recall [82]. Although Jon activated the same network of brain regions as the controls (albeit bilaterally), he showed a different communication pattern of hippocampal–cortical connectivity. Specifically, in contrast to controls who showed increased effective connectivity between parahippocampal cortex and hippocampus specifically during the retrieval of autobiographical events, Jon failed to show such an increase; instead, during the retrieval of such events, Jon showed increased interaction between the hippocampus and the retrosplenial cortex, and between the retrosplenial and the medial frontal cortex. Whether or not these unusual dissociations between recognition and recall, familiarity and recollection, and patterns of activation and effective connectivity are characteristic of groups of patients with DA remains to be determined.

Provided that the selective hippocampal pathology is sufficiently extensive and bilateral, the profile of DA ensues even when the responsible lesion is sustained very early in life [69]. Thus, direct comparison of a group with DA resulting from early-onset of hippocampal pathology (i.e. perinatal to 1 year of age) with a similar group with later-onset of pathology (i.e. age 6 to 14 years) shows an advantage for the early-onset group but only in the domain of immediate memory. In the domain of long-term memory, however, the two groups have similar profiles, both showing relative sparing of semantic memory combined with marked impairment in episodic memory [68*]. Finally, an interesting feature of DA in those cases with perinatal onset of pathology is that the episodic memory impairment is not evident at a young age, but gradually emerges into the middle childhood years [69]. It is possible, as discussed above, that the slow maturation of context-rich hippocampal memory function that only emerges gradually during childhood [8,9] is concealing the functional consequences of the selective hippocampal pathology. Because young children are not held accountable for reliable recall of events and episodes of their lives, the episodic memory deficit becomes noticeable only when children with DA are older and responsible for accurately recollecting their daily life events. It is suspected that the precursors of hippocampally dependent explicit memory (presumably mediated by the perirhinal cortices) are present at or shortly after birth in patients with DA, but fail to mature into context-rich hippocampally dependent functions in later life.

The profile of DA differs in several ways from the global amnesia commonly reported in adult-onset cases [83]. First, whereas the adult-onset cases typically show equally severe deficits in both semantic and episodic memory [84,85], the DA cases have serious deficits only in episodic memory. Second, unlike most adult-onset amnesic patients, who are impaired in both recall and recognition (but see Courage and Howe [26*]), the children with DA display marked deficits only in delayed recall, showing relatively preserved item recognition [67,79]. The reason(s) for the differences between early- and late-onset profiles of the amnesic disorder is not clear. One possibility is that the limited form in the developmental cases is the result of the selectivity of the hippocampal lesions (i.e. sparing the parahippocampal cortices [66]) in association with hypoxic or ischemic events [5]. Another possibility relates to increased plasticity and compensatory mechanisms that unfold as a result of early brain pathology [82]. A third possibility is the combined effects of the above factors with others that are as yet unidentified.

Taken together, the data on children are consistent with those reported on young nonhuman primates; despite the early onset of pathology, there is little evidence for sparing or recovery of those aspects of explicit memory that are crucially dependent on the hippocampus. Nevertheless, given the presence of additional pathology revealed by morphometric analyses in the group of patients with DA [68*], there is still an issue as to whether or not the hippocampal pathology per se is a sufficient condition for this limited form of amnesic disorder in children. Yet, the presence of a severe and persistent global memory loss observed in monkeys in which the neonatal neuropathology is known to be selectively restricted to the hippocampus, strongly implicates a dysfunction of the hippocampus in DA as well.

Conclusions

We have reviewed studies on the anatomical and functional maturation of the hippocampus and on the behavioral and cognitive consequences of early insult to this neural structure in humans and nonhuman primates. The available evidence to date suggests that the primate hippocampus appears to mature progressively during the first few years of life in both monkeys and humans. It is also notable that early damage to the hippocampus yields profound losses of context-rich memory abilities even when the damage occurs perinatally, indicating very little sparing of or recovery of function. Furthermore, the profound and chronic amnesic syndrome that results from early hippocampal pathology appears to be ‘dormant’ at an early age, presumably because context-rich hippocampal memory abilities develop gradually during childhood. Taken together, the experimental and clinical data indicate that infant monkeys and children with early hippocampal damage grow into their memory impairment, and do not support the general belief that early brain trauma leads to less functional deficits than the same trauma acquired in adulthood.

After early hippocampal pathology, both children and monkeys show a pronounced impairment in context-rich memory processes, including memory for unique events. In patients with DA, this impairment in the recall of events and episodes prevails despite the relative
preservation of semantic memory and recognition memory. Furthermore, in at least one patient, neonatal hippocampal pathology appears to impair recollection-based abilities, rather than familiarity-based recognition abilities, selectively. Whether or not the deficit in monkeys with neonatal hippocampal lesions in incidental item recognition using the visual paired comparison paradigm, particularly at long delays, is due to the same distinction between familiarity-based and recollection-based recognition remains to be determined. In the same way, it has yet to be demonstrated whether patients with DA show impairment in recognition of incidental unique items, especially at long delays.

The findings in primates reviewed here, together with those in rodents [86], support the model of hierarchical organization of cognitive memory [8,9]. This model proposes that the hippocampal circuit provides the necessary processing for the encoding and retrieval of context-rich episodes and events, whereas the perirhinal and entorhinal cortices subserve the formation of context-free cognitive memories.

This review also highlights the paucity of data that currently exist on the neural structures and circuits that support the development of memory processes in infancy and childhood, and suggests important directions for future research. Specifically, longitudinal studies using techniques and paradigms applicable to both species (e.g. evoked response potentials, visual paired comparison) covering the period from infancy to later childhood will provide much needed data on the functional maturation of hippocampally dependent memory processes. Metabolic activation studies in both monkeys and humans will be informative on the different types of memory and neural processes available at different time points during maturation, and further our understanding of how adult memory is achieved. Information obtained from such studies can be used to identify as early in life as possible those infants and children who are at risk of developing serious memory problems, with a view to implementing remedial intervention programs to improve learning and alleviate at least some of the profound socioemotional and learning difficulties that often characterize the development of children with DA.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

● of special interest
●● of outstanding interest


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This is a selective review of the impressive progress that has been made in the development of memory abilities in preverbal infants and children. The authors conclude that the basic processes needed to encode, store and retrieve information are present very early in life and that although significant developmental advances take place across early childhood, many of the processes that govern memory in preverbal children are common with those of verbal children and adults.


68. Vargha-Khadem F, Salmond CH, Watkins KE, Friston KJ, Gadian DG, Mishkin M: Developmental amnesia: effect of age at injury. Proc Natl Acad Sci USA 2003, 100:10055-10060. A comparison of the neuropsychological profiles of a group of patients with early-onset versus one with late-onset developmental amnesia showed a similar pattern in both groups with marked impairment in episodic memory and relatively preserved semantic memory. Morphometric analyses for both groups showed bilateral abnormalities in the hippocampus, putamen, and posterior thalamus, as well as in the right retrosplenial cortex. The study concludes that the effective age at injury for the syndrome of developmental amnesia associated with hypoxia or ischemia extends from birth to puberty.


70. Isaacs EB, Vargha-Khadem F, Lucas A, Mishkin M, Gadian DG: Developmental amnesia and its relationship to degree of hippocampal atrophy. Proc Natl Acad Sci USA 2003, 100:13060-13063. A group of adolescents that were extremely premature at birth and one with the diagnosis of developmental amnesia were compared with age-matched controls on measures of hippocampal volume and memory function. The authors conclude that early hippocampal pathology leads to developmental amnesia only when the volume of the hippocampus is reduced below normal by about 20–30% on each side.


