Nonhuman primate models of hippocampal development and dysfunction

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Nonhuman primates provide highly valuable animal models that have significantly advanced our understanding of numerous behavioral and biological phenomena in humans. Here, we reviewed a series of developmental neuropsychological studies that informed us on the timing of development of the hippocampus and of hippocampal-dependent cognitive functions in primates. Data indicate that, in primates, the emergence of adult-like proficiency on behavioral tasks sensitive to hippocampal dysfunction is a stepwise process and reflects the gradual maturation of different hippocampal circuits and their connections with other neural structures. Profound and persistent memory loss resulting from insult to the hippocampus in infancy was absent in early infancy but became evident later in childhood and persisted in adulthood, indicating very little sparing or recovery of function. Finally, the early hippocampal insult resulted in both adaptive and maladaptive neuroplasticity: i.e., sparing contextual memory, but affecting working memory processes as well as emotional reactivity and hypothalamic–pituitary–adrenal (HPA) axis functioning. The results provide significant information on the emergence of hippocampal-dependent functions in humans, on the time course of memory impairment in human cases with early hippocampal insult, and on the clinical implication of the hippocampus in developmental neuropsychiatric disorders.

recognition memory | spatial memory | working memory | developmental amnesia | schizophrenia

Decades of research in many species, including humans, have demonstrated that the hippocampus plays a pivotal role in memory function and specifically in memory of personal events, very often labeled relational memory, episodic memory, or autobiographical memory (1). Furthermore, the clinical aspects of diseases that affect the hippocampus indicate that the hippocampus is implicated in many other cognitive domains, including emotion and stress regulation (2). The hippocampus exhibits a prominent vulnerability, and hippocampal cell loss follows hypoxic, ischemic, or metabolic noxious events, epileptogenic processes, and early stress. This vulnerability has been tightly associated with a clinical spectrum of hippocampal dysfunction, which encompasses normal aging and a wide range of neurological disorders (epilepsy, stroke, encephalitis, trauma, and Alzheimer's disease), but also developmental psychiatric disorders, such as autism spectrum disorders and schizophrenia (for review, see ref. 3). Given that many of these psychiatric disorders in humans have a developmental origin, a better understanding of the normal morphological, neurochemical, and functional development of the hippocampus and of the maturational timing of behavioral and cognitive changes that follow its early dysfunction is clearly needed. Rodent studies have already provided evidence that the anatomical, chemical, and functional maturation of the hippocampal formation continues until around 21 d after birth (for review, see refs. 4–7) and that neonatal damage to the ventral hippocampus results in developmental neurobiological and behavioral abnormalities emerging later in adolescence and mimicking the most devastating symptoms and neurobiological features of schizophrenia (for review, see ref. 8). Yet, because of similar brain development through adolescence and of progressive increase in the participation of the hippocampus and its interactions with the prefrontal cortex in the mediation of memory performance, nonhuman primates are particularly well-suited for modeling higher cognitive functions qualitatively similar to humans and might enable researchers to better understand how the structural development of distinct hippocampal circuits might contribute to the functional maturation of distinct hippocampus-dependent memory processes (e.g., processes dependent on a functional hippocampus). Over the last decade, information about the structural, functional, and behavioral changes occurring throughout ontogeny has begun to accumulate in monkeys. Although there is still much to be discovered, we thought it timely to put into perspective the latest findings in hope of shedding light on memory development in general and, particularly, on the role of medial temporal lobe structures, and of the hippocampus in particular, on memory development in infant macaques. In the first part of this review, we summarize recent data on the morphological and neurobiological development of the hippocampus in primates, as well as on the time course of development of hippocampal-dependent memory functions. The long-term behavioral consequences and brain reorganization following early insult to this brain region is then described in an attempt to provide new insights in the pathophysiology and etiology of devastating human mental disorders. Finally, future directions in this field of research are discussed.

Hippocampal Morphological Development

Buried within the temporal lobe, the hippocampus is an elongated structure with a remarkable regular organization from its rostral pole abutting the posterior amygdala to its caudal part just below the splenium of the corpus callosum. Morphologically, the hippocampus can be subdivided into hippocampus proper—dentate gyrus (DG), the cornu ammonis (CA) fields 1 to 3, and the subiculum—and the parahippocampal complex, which includes the medial and lateral entorhinal cortex (ERh), the perirhinal cortex (PRh), and areas TH/TF (Fig. 1). Highly processed perceptual information from cortical areas flows through the

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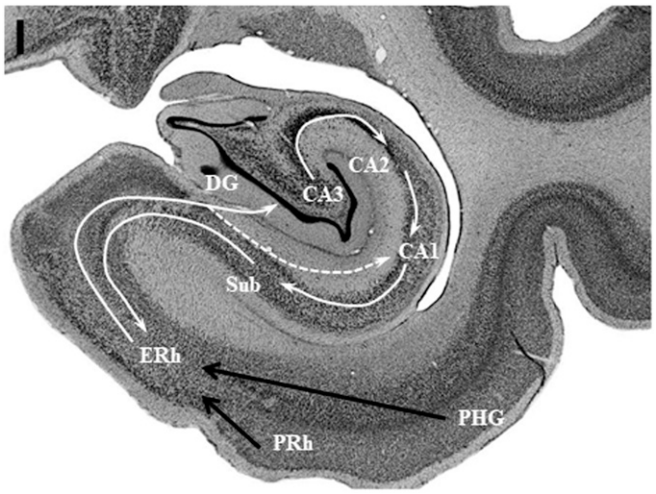

Fig. 1. Thionin-stained section through the midbody of the hippocampus of rhesus monkeys. Arrows represent the flow of information through the trisynaptic circuits: i.e., Erh to DG to CA3 to CA2 to CA1 to Sub and back to ERh (continuous white arrow) and a more direct pathway (dashed white arrow). For both pathways, information from medial temporal cortical areas is relayed within the entorhinal cortex (black arrows). CA3, CA2, CA1, fields of the hippocampus proper; DG, dentate gyrus; ERh, entorhinal cortex; PHG, parahippocampal cortical areas; PRh, perirhinal cortex; Sub, subiculum.

adult hippocampal formation from the periphery through the superficial layers of the ERh, to the DG, CA3, CA2, CA1, and subiculum, before finally reaching the deep layers of the ERh, from where information is broadcast to the rest of the cortical mantle. This forms the well-established trisynaptic pathway of the hippocampal formation known to support spatial memory and navigation (9). A more direct pathway also exists and links ERh directly to the CA1 (10) (see detailed anatomical organization of the hippocampus in ref. 11). Recent longitudinal structural neuroimaging studies in monkeys revealed an increase in overall hippocampal volume, as well as changes in the ratio of hippocampal gray to white matter from birth to 2 y of age (12, 13). These volumetric changes have been associated with significant microstructural and neurochemical changes, as well as fine tuning of intrinsic synaptic connections that span several years after birth (14–16). Thus, neurogenesis in the DG is ~80% complete at birth, and nearly 20% of neurons are added postnatally. In addition, in the second half of the first postnatal year, CA3 neurons increase in number and in size, and their spines increase in complexity. Throughout the first postnatal year, synapses from axons of dentate neurons contacting the dendrites of the CA3 cells (mossy fiber pathway) are formed, and there is an increase in the myelination of hippocampal afferent and efferent fibers. Also, the CA3 pyramidal cells (the second station of the trisynaptic pathway) show synaptic changes beyond the first postnatal year. Although the neurotransmitter systems within the hippocampus, both cholinergic and GABAergic, are present at birth, they undergo considerable remodeling postnatally (17), and changes in gene expression patterns (18) have been reported earlier in the CA1 (from birth to 6 mo) than in the CA3 (from 1 y to young adulthood). By contrast, afferent projections from the ERh to the CA1, the so-called "direct pathway," are present at birth and mature over the first few months of life. Similar developmental morphological changes have also been identified in the human hippocampal formation. The cytoarchitectonic layers in newborn infants are well-developed and contain an adult-like number of neurons. Yet, significant postnatal morphological changes have been identified between the neonatal period and late childhood. Thus, dendritic and axonal growth, dendritic arborization, and spine and synapse formations, as well as neurochemical maturation of principal and nonprincipal cells, suggest significant morphological and functional modifications of the hippocampal neuronal network in human as well (19).

The 2 main cortical-hippocampal pathways seem to support specific memory processes, as revealed by metabolic activity studies in adult monkeys, with the trisynaptic pathway (DG, CA1, and CA3) more particularly supporting spatial memory (20) and the direct entorhinal-CA1 pathway more particularly supporting recognition memory and working memory (10). Given that these 2 pathways appear to develop at different tempos, it is tempting to suggest that memory processes supported by the ERh-CA1 pathway emerge earlier (recognition memory) than those supported by the trisynaptic pathway (spatial working memory) (for review, see ref. 21). In addition, other functions mediated by allocortical areas, such as the perirhinal cortex, might mature even earlier than those mediated by neocortical-hippocampal circuits (22). This proposal has received support from recent developmental neuropsychological studies in monkeys reviewed below.

Differential Time Courses of Hippocampal Memory Development

The hippocampus is critical for the acquisition, storage, and recollection of interitem relations and their context and supports recollection of specific episodes or events (1). Measuring the development of these memory processes in very young infants (both monkeys and humans) necessitates the design of memory tasks that could be 1) sensitive to selective hippocampal damage, 2) administered to nonverbal subjects with immature motoric functions, and 3) used longitudinally from infancy through adulthood without significant task modifications so as not to modify the cognitive demands necessary to solve the task. One of these tasks, the visual paired comparison (VPC) task, measures incidental recognition memory and is based on the unique tendency of primates to direct their attention to novel stimuli appearing in their environment. It generally assesses the distribution of time spent looking at familiar and novel stimuli, with longer time looking at the novel stimulus indicative of incidental recognition memory. By varying the length of the delays between familiarization and test or the type of stimuli, one can examine the strength of memory trace of a familiar stimulus over time (Object-VPC) and spatial memory processes (Location-VPC and Object-in-Place VPC). With the use of these tasks, we investigated the role of the medial temporal lobe structures, including the hippocampus, in object and spatial recognition memory in adult monkeys to ensure that the tasks were sensitive to selective hippocampal damage, assessed the development of these memory processes from infancy through early adulthood, and inferred on the neural structures associated with maturational shifts in task performance (23).

First, the role of the hippocampus in object and spatial memory was assessed in adult control animals and animals with bilateral adult-onset excitotoxic hippocampal lesions (24). Delay-dependent object memory was measured with the Object-VPC using delays varying from 10 s to 120 s and colored pictures of objects (Fig. 2, *Top*). As compared to control animals that showed novelty preference scores above 64% looking at the novel objects across all delays, animals with hippocampal lesions showed novelty preference scores similar to those of controls at the short delays of 10, 20, and 30 s (60%, 59%, and 64%, respectively), but no preference at the longer delays of 60 and 120 s (51.5% and 52%, respectively), indicating an inability to maintain the trace of the familiar stimulus at delays longer than 60 s and beyond. The data indicated a delay-dependent forgetting that has usually been reported in adults with hippocampal damage.

The basic Object-VPC task was then slightly modified to measure memory for spatial location (Location-VPC) and memory for the

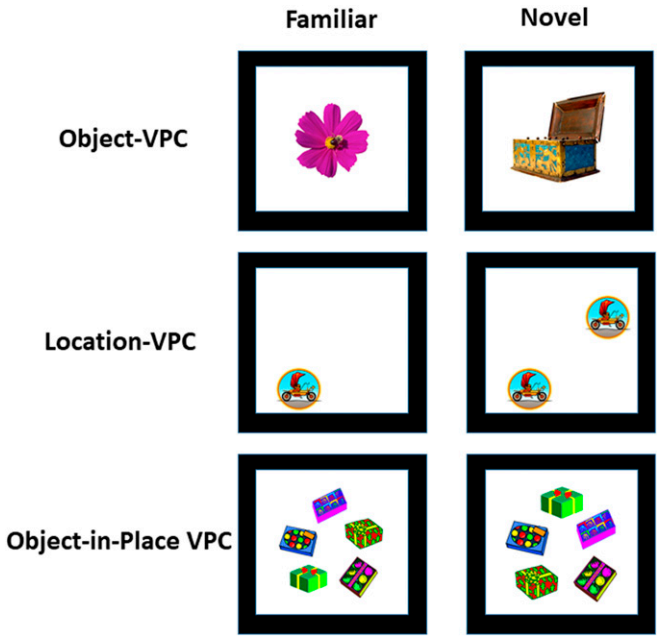

Fig. 2. Exemplars of stimuli used in each of the 3 VPC tasks. New stimuli were used for each trial of a task and across all 3 tasks. For the Object-VPC, the comparison was between a single familiar object and novel objects, and delays between familiarization and recognition test varied between 10 s and 120 s. For the Location-VPC, the comparison was between a single object in a location of the screen and the same object in a new location. For the Object-in-Place VPC, the comparison was between an array of 5 objects and the same objects with permuted locations of 3 of the objects. For the last 2 spatial VPC tasks, the delays between familiarization and recognition test were set at 5 s.

spatial relationships between several stimuli (Object-in-Place VPC) (25). For the Location-VPC, animals were familiarized with an object presented on a specific location on the screen, and, after a short delay (5 s), the same object was present in the same location together with an identical object in a different location of the screen (Fig. 2, *Middle*). Thus, in this version of the task, novelty preference is not provided by the perceptual characteristics of the object but rather by the new location it occupies on the screen. Location memory was unaffected by lesions of the hippocampus, in that both animals with adult-onset hippocampal lesions and controls looked longer at objects occurring in a new location (61.2% and 65.9%, respectively). Thus, in the absence of a functional hippocampus, memory for spatial location could likely be maintained, at least for short delays, by other medial temporal cortical areas. Indeed, although novelty preference for spatial location was not affected by perirhinal lesions (64.8%), it was abolished by lesions of areas TH/TF on the parahippocampal gyrus (47.5%), a cortical area that receives spatial information from the parietal cortex and transmits this information to the hippocampus via the entorhinal cortex (25). For the Object-in-Place VPC task, the familiar stimulus was composed of 5 different objects displayed in a circular array on the screen. The novel stimulus included the same array of 5 objects, but the location of 3 objects within the array was interchanged (Fig. 2, *Bottom*). Therefore, in this case, novelty preference was inferred by the new locations occupied by 3 of the familiar objects within the array. As compared to their normal spatial location memory, animals with adult-onset hippocampal lesions displayed a loss of novelty preference in the Object-in-Place VPC (51.3% as compared to 58.9% for the controls), indicating a difficulty in encoding and retrieving object–place associations. Taken together, the findings indicate that the hippocampus may be more critical for associative response: i.e., novelty attributed to the rearrangement of learned configurations of items even if item information within the configurations is highly familiar, than for simple location or objects, which might be mediated by cortical areas on the parahippocampal gyrus.

The same 3 VPC tasks were then used to trace the development of hippocampal-dependent memory processes and the involvement of the hippocampus on performance. Thus, memory performance was investigated in normally developing infant monkeys and in infant monkeys that were given selective hippocampal lesions in the first postnatal weeks. Although scores of the normal infants traced the developmental time course of performance on the tasks, those of the experimental infants provided a unique opportunity to answer several critical questions: Can memory develop despite injury to a critical component of the medial temporal lobe circuit early in life? If yes, can it develop normally due to plasticity of the developing neural system or could certain memory processes be impaired? Furthermore, if memory deficits follow early hippocampal damage, is the magnitude of these deficits similar to that found in adult-onset hippocampal damage or is it unique to development? Finally, knowledge on the timing of emergence of any memory impairment was also significant because it could offer clues on when during development the hippocampus might normally begin to have a role in memory.

Sham-operated newborn infant monkeys and newborn monkeys with selective bilateral excitotoxic hippocampal lesions received at 10 to 12 d of age were given the Object-VPC task at 1.5, 6, 18, and 48 mo using delays of 10, 30, 60, and 120 s (26). For the sham-operated controls, object recognition memory was present as early as 1.5 mo (novelty preference averaged 65% and did not differ across all delays), became more robust at 6 mo (i.e., averaging 73% and similar at all delays), but became delay-dependent by 18 mo of age (i.e., decreasing from 74% at 10 s delay to 65% at 120 s delay). Interestingly, the infants with neonatal hippocampal lesions performed as well as the sham-operated controls at the 2 youngest ages, but, at 18 mo, they showed a forgetting that became evident only at the longest delays of 120 s, but not at the shorter delays. The studies provided several significant results. First, the emergence of the delay-dependent recognition memory later in maturation (18 mo) in the sham-operated animals suggests that the brain structures mediating these early developing recognition abilities may undergo significant modifications after 6 mo of age in monkeys. Second, the normal novelty scores at all delays for animals with neonatal hippocampal lesions at least until 6 mo of age together with their impairment that only emerged at an age when memory performance in the sham-operated controls became delay-dependent, suggested that 1) in the absence of a functional hippocampus, performance in early infancy could be mediated by structures others than the hippocampus and 2) the protracted emergence of a recognition impairment following neonatal hippocampal lesions at 18 mo suggests that the hippocampus may contribute to object recognition after the first year. In fact, a follow-up developmental study in monkeys supported the former proposal and revealed that neonatal perirhinal cortex (PRh) damage results in impairment at all delays of the Object-VPC task as early as 1.5 mo (22). For the later proposal, protracted involvement of the hippocampus in object recognition memory correlates with the profound functional remodeling within the hippocampus and parallels the maturation of the trisynaptic hippocampal circuit after the first year of age (17). Thus, early memory systems are more widely distributed in the immature brain and become more localized with age (27). Finally, the delay-dependent memory deficit observed at 18 mo was still present in adulthood (28), demonstrating enduring object recognition deficits after neonatal hippocampal damage. Novelty preference of animals with early onset hippocampal lesions (Neo-H) was compared to that of animals with adult onset hippocampal lesions (Ad-H). For this comparison, the Object-VPC task used black/white stimuli very similar to each other

Table 1. Novelty preference after early-onset vs. adult-onset hippocampal lesions

	Delays				
	Object-VPC with similar objects			Location-VPC	Object-in-Place VPC
Groups	10 s	60 s	120 s	5 s	5 s
Ad-C	67.0 ± 2.5	61.4 ± 0.6	61.5 ± 3.0	65.9 ± 2.5	58.9 ± 3.9
Ad-H	59.0 ± 3.3*	52.8 ± 2.6*	54.1 ± 0.9*	61.2 ± 2.9	50.3 ± 2.7*
Neo-C	65.6 ± 2.8	65.3 ± 1.5	65.2 ± 1.1	65.7 ± 3.0	60.0 ± 2.5
Neo-H	64.7 ± 3.0	66.2 ± 2.8	53.2 ± 1.0*	67.2 ± 1.9	48.9 ± 5.0*

*Indicates significant difference between animals with adult-onset hippocampal lesions (Ad-H) and their controls (Ad-C), as well as between adult animals with early-onset hippocampal lesions (Neo-H) and their controls (Neo-C). Stimuli used for comparisons between early-onset versus adult-onset hippocampal lesions were ambiguous similar black/white objects. Note the impairment in both the Ad-H and Neo-H groups at the longest delay of the Object-VPC (27) and in the Object-in-Place VPC, but not in the Location-VPC (23).

(e.g., 2 phones, 2 trees, etc.) and 10-, 60-, and 120-s delays. As shown in Table 1, respective to their control groups (Neo-C and Ad-C), the Neo-H group was impaired only at the longest delays whereas the Ad-H group was impaired at all delays. Thus, novelty preference at delays of 10 and 60 s was stronger in the Neo-H group than in the Ad-H group, but both groups performed at chance levels at the longest delay of 120 s. These results suggested that object recognition memory was somewhat less severe following early-onset than adult-onset hippocampal lesions.

The same 2 groups of infant monkeys were also given the Location-VPC and Object-in-Place VPC to measure spatial relational memory at 8, 18, and 60 mo of age (29). Different developmental trajectories emerged for these 2 types of spatial memory processes. First, for the control group, strong novelty preference emerged only at 18 mo on the Location-VPC whereas it did emerge only in adulthood (60 mo) for the Object-in-Place VPC. Thus, memory for location, as memory for single objects reported above, becomes evident during the second year whereas memory for spatial relationships among objects emerges much later, presumably during the third year. Furthermore, the neonatal hippocampal lesions did impact memory for spatial location at an age (18 mo) when this type of memory became apparent in the sham-operated controls. However, this effect was only transient since, as adults, monkeys with Neo-H lesions showed novelty scores in the normal range, a finding totally consistent with the intact memory for locations found in adult animals with adult-onset hippocampal lesions (ref. 25 and Table 1). Given that memory for spatial location is mediated by cortical areas TH/TF (25), the recovery of location memory functions in animals with neonatal hippocampal lesions with further maturation could have resulted from functional recovery within TH/TF areas that were spared after the neonatal hippocampal lesions. In contrast to the transient lack of novelty preference in the Location-VPC after the Neo-H lesions, novelty preference for object-place associations dropped to chance in adulthood: i.e., at the age when normal controls began to display strong novelty preference in the task. In addition, the magnitude of the spatial relational memory impairment was as severe as that noted after adult-onset lesions (Table 1). Notably, the spatial relational memory (object–place association) deficit is in line with a similar memory impairment the same animals demonstrated in another relational memory task when they were required to form memory for place–food associations in a free-foraging spatial memory task (30). Thus, the 2 forms of spatial memory processes have a different developmental time course, with encoding and remembering object locations emerging earlier (~second year) than encoding and remembering spatial relationships among objects (~4 to 5 y).

To summarize, hippocampal-dependent memory abilities do not show a single pattern of development, with object and location memory maturing earlier than object–place relational memory. Taking into consideration the maturation of the hippocampal circuits discussed above, it appears that some memory processes (e.g., object recognition memory) are present in the first months of life and are supported by allocortical areas (perirhinal cortex) but become dependent on the direct ERh-CA1 pathway over the first year when, at this age, delay-dependent memory and allocentric representation of the environment (object–location) first emerge. By contrast, performance on others memory tasks requiring greater cognitive demands, such as learning spatial relations between stimuli, emerges later at a time when the trisynaptic hippocampal pathway (entorhinal cortex to dentate gyrus to CA3 to CA1 to subiculum and back to entorhinal cortex) becomes functionally mature. It is also important to note that, for other relational memory tasks sensitive to hippocampal lesions, such as oddity, transverse patterning, biconditional discrimination, and spatial navigation tasks, there is a time in childhood when monkeys perform at chance, followed by a period during peri-puberty (2 to 4 y) when they can master the task but are still poorer than adults to finally reach adult proficiency in late adolescence and early adulthood. Thus, emergence of the ability to solve hippocampal-dependent tasks appears to follow a stepwise process, but, at the same time, proficiency to perform on these memory tasks gradually increases until adult mastery is achieved (21). Thus, the development of adult-like proficiency on memory tasks sensitive to hippocampal dysfunction is likely to reflect the gradual maturation of the different hippocampal circuits and their connections with other neural structures (21, 31, 32).

Early Hippocampal Insult and Long-Term Outcomes

In addition to providing interesting information on the development of memory processes in primates, the early damage to the hippocampus gave us the unique opportunity to measure the impact of this early injury on plastic changes during development. Early brain damage may result in both adaptive and maladaptive neuroplasticity. In this section, we report that neonatal hippocampal lesions in monkeys resulted in sparing of contextual memory (e.g., the improved memory for specific information when the context present at encoding and retrieval is the same) and impaired working memory, as well as alterations in emotional reactivity and stress regulation. The control monkeys and those with neonatal hippocampal lesions that were used to document the impairment in hippocampal-dependent memory (see above) were given additional cognitive tasks when they reached early adulthood to better assess the extent of functional deficit or sparing following the early lesions.

First, as compared to adult-onset hippocampal lesions that impaired contextual memory (33–35), neonatal hippocampal lesions spared this ability. Hippocampal lesions in adult marmoset monkeys impaired acquisition of biconditional discrimination

problems when information about the background context onto which objects are presented was required to indicate which object was rewarded (34). Similarly, rhesus monkeys with adult-onset hippocampal lesions had greater difficulty recognizing an object when its background was different from that used during encoding (35). By contrast, adult monkeys with early-onset hippocampal lesions showed normal performance when they had to recognize an object when presented in a background different from the background used at encoding or when they had to learn biconditional discrimination problems (36). Thus, the sparing of contextual learning and memory likely resulted from the early onset of the hippocampal lesions that allowed for significant functional compensation by other brain structures playing an active role in processing contextual information, such as areas within the parahippocampal cortex (TH/TF) (34), the perirhinal cortex (35–41), and the prefrontal cortex (42, 43).

Second, the same neonatal hippocampal damage impacted working memory processes known to be supported by hippocampal–prefrontal interactions. Thus, animals with neonatal hippocampal lesions were profoundly impaired in the monitoring of information in working memory, as measured with a serial order memory task (44). Given the role of the dorsolateral prefrontal cortex (DLPFC) in working memory (45) and the protracted maturation of DLPFC function that extends until late adolescence and adulthood (46), it is possible that the working memory deficit was the result of disrupted interactions between a dysfunctional hippocampus and an indirectly altered maturation of the DLPFC. In support for this proposal, we found that, despite the indirect nature of the connections between the hippocampus and DLPFC (47–50), monkeys with neonatal hippocampal lesions had significant alterations in the direct hippocampal projections to the ventromedial prefrontal cortex, which, in turn, project to the DLPFC (50), as well as a decrease in functional connectivity within DLPFC cortical networks (52). Both anatomical and functional changes in the PFC correlated with the magnitude of the working memory deficits observed in the same animals (51, 52). Thus, given that these changes do not occur after adult-onset hippocampal lesions (53), it is possible that the early hippocampal lesions had also altered the protracted maturation of the DLPFC.

Finally, as mentioned in the Introduction, the hippocampus is not only critical for memory processes but also plays an important role in emotional regulation (2). Animals with neonatal hippocampal lesions and their controls were also given the human intruder task to assess emotional reactivity to a social stressor presenting different levels of threat at 2 mo, 4 mo, and as adults, and hypothalamic–pituitary–adrenal (HPA) axis reactivity to emotionally charged stimuli (54). During infancy, unlike controls, neonatal hippocampal lesioned monkeys exhibited enhanced expression of emotional behaviors, such as freezing, anxiety-like, and self-directed behaviors. Upon reaching adulthood, they exhibited reduced hostility, but increased anxiety-like and self-directed behaviors that were associated with a blunted cortisol response to the human intruder. In addition, although they showed the typical diurnal cortisol decline throughout the day, they had lower cortisol concentrations in the morning as compared to controls. Taken together, these data suggest that an intact hippocampus during development plays a larger role beyond that of inhibitory/negative feedback regulation of the HPA axis stress activation and may be critical for HPA axis basal functioning as well. Such emotional changes after neonatal hippocampal lesions were also reported by others (55, 56).

Relationship to Human Hippocampal Development and Neuropsychiatric Disorders

Given the similarities between nonhuman primates and humans in both brain and cognitive development, as well as neuroendocrine functioning, the results reviewed above provide significant information on the emergence of hippocampal-dependent functions in humans, the time course of memory impairment in cases with early hippocampal insult, and the clinical implication of the hippocampus in developmental neuropsychiatric disorders.

Research on the development of hippocampal-dependent memory in humans has indicated a protracted postnatal time course similar to that described for the monkeys. Although object recognition processes are present very early in life (57), the ability to remember the location of an object in an egocentric frame of reference (spatial location memory) is present in infants younger than 3 y (58, 59) whereas the ability to encode and remember object–place relationships emerges after 3 y of age, with substantial improvement still present until 7 y (60, 61). Concurrently, progressive increases in hippocampal volumes identified via longitudinal neuroimaging studies (62–65) may support the progressive maturation of hippocampal-dependent memory processes in humans (65). Thus, as described for monkeys, it is likely that microstructural hippocampal remodeling, not detectable through neuroimaging techniques but revealed through postmortem histological studies (19), supports the progressive maturation of memory processes in humans. It is also interesting to note that, as alluded by others (16, 66, 67), increases in hippocampal neurogenesis, more intense in the dentate gyrus, as well as microstructural changes in hippocampal circuits (19) in infancy, may also be at the source of infantile amnesia, the inability to recollect events of our first few years of life. However, all evidence indicating an association between hippocampal morphological changes and memory changes over development is correlational and does not provide causal relations at the present time.

The second contribution of the nonhuman primate research relates to the time course and extent of memory impairment following early hippocampal insult in humans. Developmental amnesia resulting from hypoxic–ischemic insult in the perinatal period is associated with memory deficits that include impairment in incidental recognition memory measured by the object VPC task, as well as spatial relational and episodic memory (for review, see refs. 68–70). Interestingly, as for monkeys, the memory deficits were protracted, becoming apparent only when infants reach school age. Thus, the findings in infant monkeys (see above) suggest that, for humans as well, the early developing hippocampal-dependent memory abilities may be supported by structures other than the hippocampus. In addition, the working memory deficits reported in monkeys with neonatal hippocampal lesions were recently demonstrated in cases with developmental amnesia (71), suggesting that these working memory deficits may be associated with dysfunction of hippocampal–prefrontal circuits in humans as well. Thus, a better understanding of the neural bases of performance in tasks of infant memory will also increase their usefulness for tracking the earliest signs of cognitive memory deficits in children at risk owing to conditions that affect the hippocampus, such as hypoxic–ischemic injury, pediatric temporal lobe epilepsy, and others.

Finally, studies of hippocampal morphological and functional development and of its interactions with the prefrontal cortex are of major clinical interest given the learning and memory deficits generally associated with developmental neuropsychiatric disorders (e.g., schizophrenia, autism spectrum disorders, anxiety disorders). These disorders share common factors (developmental components, genetic predisposition, and frontal/hippocampal pathology), with similarly impaired cognitive functions but of different time courses and severity. For example, schizophrenic patients suffer both episodic and working memory deficits that have been linked to neurobiological changes in the hippocampus and the prefrontal cortex (72–74) and that are generally refractory to treatment. Moreover, changes in emotional reactivity and blunted cortisol awakening response were reported in first-episode psychosis and did not appear related to increased exposure to psychosocial stressors (75, 76). Thus, lasting changes in episodic and working memory deficits and changes in emotional reactivity and in

HPA axis functioning following early hippocampal insult in monkeys share some similarities to those reported in schizophrenic patients. Although schizophrenia does not present with a direct hippocampal lesion, the early developmental insult to hippocampus in monkeys, however nonspecific it may be, yields dysfunctional peri-adolescent hippocampal–prefrontal circuits that expressed as a complex syndrome encompassing positive, negative, and cognitive-like symptom components observed in schizophrenia.

Future Directions

The remarkable parallel between the neurobiological and functional development of the hippocampus and its interactions with other brain structures in primates clearly demonstrates the significant benefits of using a comparative neuropsychological approach to further our understanding of the neural circuits underlying the maturation of cognitive processes in humans and their derailment in developmental neuropsychiatric disorders. Although significant progress has been made in recent years in our understanding of the developmental morphology and functions of the hippocampus, future studies should prioritize search for more causal relationships between microstructural and functional hippocampal changes using newly developed tools, such as genetic and chemogenetic manipulations.

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