# Memory and Socioemotional Behavior in Monkeys after Hippocampal Damage Incurred in Infancy or in Adulthood

Jocelyne Bachevalier, Maria C. Alvarado, and Ludise Malkova

*The present study reviews the long-term effects of neonatal hippocampal damage in monkeys on the development of memory functions and socioemotional behavior. The results showed that neonatal damage to the hippocampal formation impairs specific memory processes, such as those subserving automatic (as opposed to effortful) recognition memory and relational learning, while sparing the abilities to acquire skills, such as object discriminations. Furthermore, the neonatal hippocampectomy led to a progressive loss of social affiliation and a protracted emergence of locomotor stereotypies. While the memory losses following neonatal hippocampal lesions resemble those found after similar lesions acquired in adulthood, only the neonatal lesions resulted in a protracted emergence of abnormal behaviors. These later findings suggested that, presumably, the neonatal lesions impacted on neural systems remote from the site of damage. This was confirmed by our more recent neurobiological studies, demonstrating that neonatal, but not late, lesions of the medial temporal lobe region, disrupt the normal behavioral and cognitive processes subserved by the prefrontal cortex and the caudate nucleus. All together the data support the neurodevelopmental hypothesis viewing early insult to the medial temporal region as the origin of developmental psychosis in humans, such as schizophrenia.* Biol Psychiatry 1999;46:329–339 © *1999 Society of Biological Psychiatry*

**Key Words:** Social behavior, stereotypy, hippocampal formation, nonhuman primates

## Introduction

Numerous neuropathological reports in humans and lesion studies in monkeys have shown that damage to the medial temporal lobe (MTL) region, including the hippocampal formation and adjacent cortical areas, yields a severe and global anterograde amnesia (Scoville and Milner 1957; Damasio et al 1985; Zola-Morgan et al 1986; Rempel-Clower et al 1996; Mishkin et al 1984a, 1984b; Zola-Morgan and Squire 1985). When the insult also involved the amygdaloid complex, additional disorders of emotional regulation and social interactions occur (Kling and Brothers 1992; Aggleton 1992; Adolphs et al 1994, 1995; Young et al 1996). As yet, there is little evidence to suggest that the same behavioral syndrome will result from medial temporal damage incurred in early infancy.

Our long-term neurobehavioral studies in monkeys have shown that medial temporal lobe (amygdala, hippocampus, and adjacent cortical areas) damage, when incurred in the first postnatal month, yields a severe global, and long-lasting anterograde amnesia (Bachevalier and Mishkin 1994; Malkova et al 1995). This profound memory loss occurred in early infancy (10 months of age) and remained unchanged when the animals reached adulthood (4–5 years of age). It was characterized by a profound impairment in the recognition of visual, tactile, and spatial information, leaving intact the ability to learn visual and tactile discriminations by trial and error. These effects of neonatal MTL lesions on memory processes corroborate those found in adult monkeys (4–5 years of age) that had received similar lesions in adulthood (Mishkin et al 1984a; Zola-Morgan and Squire 1985). The results thus demonstrate that the MTL structures are crucial for some types of memory processes (e.g., recognition memory) but not others (e.g., discrimination learning), a finding that has been substantiated in several species, including humans (Squire 1992). They also indicate that compensatory mechanisms do not always operate to assure recovery of function after early brain damage.

The anterograde amnesia following neonatal MTL lesions was also associated with profound behavioral abnormalities that emerged during the first year postnatally and remained present until the animals reached adulthood (Bachevalier et al 1999b; Malkova et al 1997). These behavioral changes included a lack of social interactions, reduction in eye contacts, blank facial expressions, and stereotypies (Bachevalier et al 1999b). Interestingly, the

From the University of Texas Health Science Center, Houston, Texas (JB, MCA); and Laboratory of Neuropsychology, NIMH, Bethesda, Maryland (LM).
Address reprint requests to Jocelyne Bachevalier, Department of Neurobiology and Anatomy, University of Texas Health Science Center, 6431 Fannin, Houston, TX, 77030.
Received October 9, 1998; revised February 23, 1999; accepted May 12, 1999.


0006-3223/99/$20.00
PII S0006-3223(99)00123-7

neonatal MTL lesions yielded a loss of social bonds that was greater in magnitude than that found after late lesions (Malkova et al 1997). In addition to the reduction in social interactions, the neonatal lesions resulted in the development of abnormal behaviors that had never been reported in adult monkeys with the same lesions (Malkova et al 1997). Thus, in the case of the socioemotional behavior, the pattern of results suggest that, the neonatal MTL damage may have caused a reorganization in neural systems associated with the MTL region and this reorganization may have been functionally more debilitating than beneficiary.

More recently, we investigated whether the full-fledged behavioral syndrome seen after the neonatal MTL lesions could be considered as a single complex syndrome or whether it might be fractionated by damaging specific components of the medial temporal lobe. As discussed by others (Zola-Morgan et al 1991), it is possible that the pathology responsible for the socioemotional disturbances may not be combined amygdalohippocampal damage but damage to the amygdala alone (e.g., Thompson 1981). Conversely, it is also possible that the amnesic syndrome following neonatal MTL damage may have resulted from damage to the hippocampal formation only (e.g., Mahut and Moss 1986). The following sections will review the effects of neonatal damage to the hippocampal formation on memory functions and socioemotional behavior in monkeys. In addition, to assess whether the behavioral outcome of hippocampal damage depends on the time of injury, the behavioral effects of neonatal hippocampal lesions will be compared to those of hippocampal lesions acquired in adulthood. Finally, the effects of hippocampal damage on reorganization in neural systems associated with the hippocampal formation, such as the prefrontal cortex and the caudate nucleus, will be discussed. The results provide support to the view that schizophrenia, whose major symptoms appear after puberty, results from an early dysfunction within the medial temporal lobe that disrupts developmental events in later-maturing structures, such as the prefrontal cortex (Feinberg 1982; Kovelman and Scheibel 1994; Weinberger 1987; Jones and Murray 1991).

## Methodology for Developmental Studies

The following is a brief summary of the methods used for the developmental studies reviewed below. Specific details may be found in Beauregard et al (1995) and Bachevalier et al (1999a). Details for the monkeys receiving the lesion in adulthood can be found in the published studies cited for each behavioral measure below.

### *Surgery*

Six newborn monkeys *(Macaca mulatta)* received bilateral aspiration lesions of the hippocampal formation (Group H) and 6 others served as age-matched unoperated controls (Group C). All surgeries were performed aseptically, under deep anesthesia. The hippocampal removals were made in 2 stages, when the animals were about 1 week of age for the removal in the left hemisphere, and at about 3 weeks of age for the removal in the right hemisphere. All details for surgical procedure as well as pre- and postoperative care were given in detail elsewhere (Bachevalier et al 1990; 1999a).

Briefly, aspiration lesions of the hippocampal formation were made through a ventrolateral approach using a surgical microscope. As shown in Figure 1, the hippocampal lesions were intended to include the dentate gyrus, all Ammon's fields, the subicular complex, as well as a portion of the cortex on the parahippocampal gyrus (i.e., portions of areas TF and TH). Verification of the lesions (via either histological processing or magnetic resonance imaging of the brain) revealed that in all cases the hippocampal removals were virtually complete and included a large portion of temporal cortical areas TH and TF. Minor additional damage was found in the most caudal portion of entorhinal cortex (area 28) as well as in the ventral portion of temporal cortical areas TE and TEO (see for details Figures 3 and 4 in Bachevalier et al 1999a).

### *Rearing Conditions*

All newborn monkeys were laboratory raised and details of their rearing conditions were given elsewhere (Beauregard et al 1995; Bachevalier et al 1999b). Briefly, upon arrival in the primate nursery (NIMH, Bethesda, MD), they were assigned to social groups (dyads or triads) consisting of 1 normal and 1 or 2 operated animals. All infant monkeys were reared in individual wire cages that allowed visual, auditory, and some somatosensory contacts between a pair of animals. They were handled several times per day by the experimenters. In addition, the animals forming each dyad or triad were placed for up to 4–6 hours daily in a playpen, containing toys and towels, and located in the nursery. With these rearing procedures, the animals develop relatively normal social skills and little stereotypies (Rosenblum 1961; Sackett 1982; Schneider and Suomi 1992; Suomi 1997; Ruppenthal et al 1991; Bachevalier et al 1999b), although, as compared to mother-reared monkeys, these peer-reared animals are usually more sensitive to environmental stress, and show behavioral and physiological reactions to social separation (Suomi 1997). It is therefore important to bear in mind that the effects of the neonatal hippocampal lesions on emotional responses and social skills could have differed from those reported here had the monkeys been raised under more natural conditions.

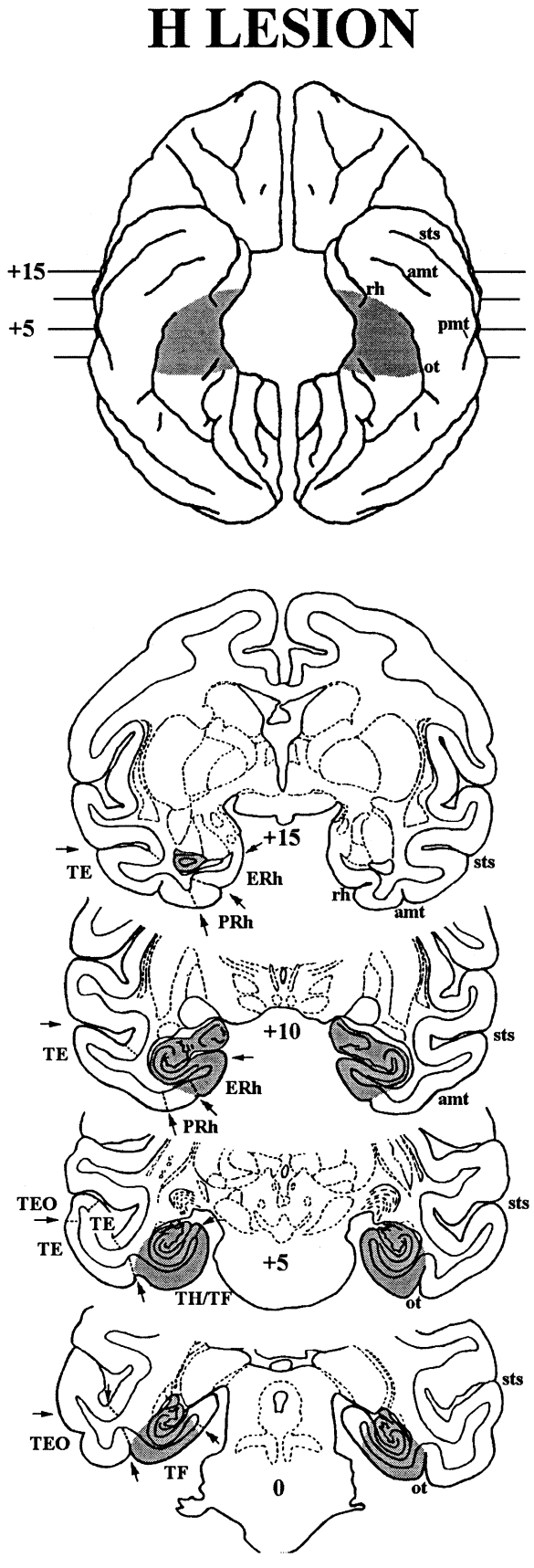


Figure 1. Ventral view and coronal sections through the intended hippocampal lesions (shading). Abbreviations: amt, anterior medial temporal sulcus; ERh, entorhinal cortex; ot, occipitotemporal sulcus; pmt, posterior medial temporal sulcus; PRh, perirhinal cortex; rh, rhinal sulcus; sts, superior temporal sulcus; TE, anterior temporal cortical area; TEO, temporo-occipital cortical area; TH/TF, parahippocampal cortical areas.

## Effects of Neonatal Hippocampal Damage on Memory Processes

At different time points during their maturation, monkeys with neonatal hippocampal lesions and their age-matched controls were tested on a battery of memory tasks that measured discrimination learning (Bachevalier et al 1999a), recognition memory (Bachevalier et al 1999a; Pascalis and Bachevalier 1999), and relational memory (Alvarado et al 1995b). Their performance on these memory tasks as they have reached adulthood will also be compared to that of adult monkeys that had received similar hippocampal lesions in adulthood. Results from this latter group of monkeys are drawn from earlier publications and will be referred accordingly for each task.

### *Concurrent Discrimination Learning*

Object discrimination abilities were measured with a concurrent discrimination task at the ages of 3 months and 4–5 years. A set of 20 pairs of objects was presented once a day, as follows: the first pair of objects, one arbitrarily designated positive (baited with a pellet) and the other negative (unbaited), were presented simultaneously over the lateral wells of a test tray. After the animal made its choice by displacing 1 of the objects, there was a 20 sec interval during which the opaque screen was lowered, following which the second pair of objects was presented for choice, and so on until all 20 pairs had been presented once each. The same series of object pairs was then repeated once every 24 hours. The positive and negative objects within each pair, as well as the serial order of the pairs, remained constant across sessions, but the objects' left-right positions were randomized daily. Testing was continued until the monkeys attained the criterion of 90 correct responses in 5 consecutive daily sessions (100 trials), or for a maximum of 50 sessions. After completing the first set, the animals were trained on 2 new sets of 20 discriminations. Thus, animals were first trained on Sets A, B, and C at the age of 3 months and, then, retested as adults (6–7 years) on the same task, using 3 new sets of 20 discriminations, Sets D, E, and F. Table 1 displays the mean number of sessions and errors to solve the 3 sets by the animals of the present study tested at both age. An analysis of variance of the mean number of sessions revealed no statistical differences between groups [$F(1,$

Table 1. Concurrent Discrimination Learning

| | Neonatal lesions (tested at 3 months) | | Neonatal lesions (tested at 6–7 years) | | Adult lesions[a] (tested at 4–5 years) | |
|---|---|---|---|---|---|---|
| | S | (n) | S | (n) | S | (n) |
| Group C | 9.04 ± 2.76 | (6) | 8.34 ± 2.71 | (5) | 9.33 ± 3.39 | (4) |
| Group H | 11.6 ± 4.36 | (6) | 7.20 ± 3.18 | (5) | 14.0 ± 6.11 | (3) |

Scores are mean number of sessions (S) ± SEM before attainment of criterion across 3 sets of 20 discriminations in monkeys with neonatal lesions tested at 3 months and 6–7 years and in monkeys that sustained lesions between 3–4 years of age and were tested immediately after. *n* = number of animals; Group C = unoperated controls; Group H = animals with ablation of the hippocampal formation for the neonatal lesions and animals with ablation of the hippocampal formation and the amygdaloid complex for the late lesions.

[a]Denotes scores of adult animals tested in Sets A, B, and C and reported in Malamut et al (1984).

Table 2. Object Recognition Memory as Measured by DNMS Task

| | Neonatal lesions (tested at 10 months) | Neonatal lesions (tested at 6–7 years) | Adult lesions[a] (tested at 4–5 years) |
|---|---|---|---|
| Group C | 89.3 ± 1.71 (*n* = 6) | 92.4 ± 1.42 (*n* = 5) | 94.4 ± 0.92 (*n* = 7) |
| Group H | 88.3 ± 2.08 (*n* = 6) | 85.3 ± 1.61 (*n* = 5) | 88.2 ± 2.52 (*n* = 5) |

Scores are percent correct responses (X ± SEM) across the six conditions (delays: 30s, 60s, 120s, and lists: 3, 5, 10 objects) of the DNMS performance test for monkeys with neonatal lesions tested at 10 months and 6–7 years and in monkeys with adult lesions tested at 3–4 years. Group C = unoperated controls, Group H = monkeys with neonatal or adult hippocampal lesions.

[a]Denotes scores of adult monkeys reported in Mishkin (1978), Meunier et al (1993), and Bachevalier et al (1989).

8) = 1.94, NS], between age at testing [$F(1, 8) = 3.69$, NS], or for the interaction Group times Age [$F(1,8) = 2.20$, NS]. The performance of 6–7 year-old monkeys with neonatal lesions was, then, compared to that of 4–5 year-old monkeys that had received large medial temporal lobe lesions (including the hippocampal formation) in adulthood. This latter group of monkeys as well as their unoperated controls were trained in 3 sets of 20 discriminations (Malamut et al 1984, Groups N and L3) in a manner similar to that described above. As shown in Table 1, adult monkeys with either neonatal or adult hippocampal lesions did not significantly differ from each other or from their unoperated controls (all $p_s > .05$), indicating that early damage to the hippocampal formation, like late damage, left object discrimination abilities intact. These findings corroborate those obtained in humans and rodents, suggesting that the hippocampal formation is not critical for this type of memory process (see for review Squire 1992).

### *Recognition Memory*

Object recognition memory was assessed with a delayed nonmatching-to-sample (DNMS) task. In this task, each trial comprised an acquisition phase, in which a baited sample object was presented over the central well of a test tray, followed 10 sec later by a test phase, in which the sample object, now unbaited was paired with a baited novel object, each of which were presented over a lateral well. Thirty seconds later, another set of trials was presented in the same way but with a new pair of objects, the novel object appearing over the right or left well in a pseudorandom order. Twenty trials were given daily, each with a new pair of objects chosen from a pool of several hundreds, until the animals reached a criterion of 90 correct responses in 100 consecutive trials or for a maximum of 1500 trials. A noncorrection technique was used through out. Following mastery on the DNMS task, the animals were given a performance test in which first the delays between sample presentation and choice phase were increased from 10 sec to 30, 60, and finally 120 sec (in blocks of 100 trials each), and then the number of objects to be remembered were increased from 1 to 3, 5, and 10 objects (in blocks of 150 trials each). Monkeys with neonatal hippocampal lesions were tested on this task at the age of 10 months (Bachevalier et al 1999a) and, then, retested on the same task at 6–7 years of age. Performance of animals of the present study at 6–7 years was also compared to that of adult monkeys that had received similar lesions in adulthood and were tested in the same task (Bachevalier and Mishkin 1989; Meunier et al 1993; Mishkin 1978). As shown in Table 2, the neonatal hippocampal removals did not yield significant recognition memory loss when the animals were tested either at 10 months or 6–7 years of age [Groups: $F(1,8) = 3.25$, NS; Age: $F(1,8) = 0.07$, NS; Groups times Age: $F(1,8) = 1.72$, NS]. In addition, the performance of adult animals with neonatal hippocampal lesions did not differ significantly from that of adult animals that had sustained the same lesions in adulthood, and both operated groups did not significantly differ from their unoperated controls (all $p_s > .05$). Thus, both neonatal or adult hippocampal lesions spared visual recognition memory as measured by the DNMS task. These data corroborate recent results in adult monkeys indicating that the medial temporal lobe structures critical for DNMS memory performance are the cortical areas around the rhinal sulcus (i.e., entorhinal and perirhinal cortex) rather than the hippocampus (Alvarez et al 1995; Meunier et al 1993; Murray and Mishkin 1998; Zola-Morgan et al 1989). Although the findings suggest that the hippocampal formation plays a relatively minor role in recognition memory, it is possible that memory tasks, like the DNMS, fail to fully engage the specific memory processing functions mediated by the hippocampus, or that accurate performance at least at the short delays tested can be supported by alternate strategies that are independent of hippocampal

Table 3. Preference for Novelty

| Delays | Group C | Group H |
|---|---|---|
| 10 sec | 60.84 ± 1.99 | 62.31 ± 1.89 |
| 30 sec | 61.46 ± 2.35 | 51.00 ± 3.89 |
| 1 min | 61.83 ± 2.62 | 51.66 ± 2.78 |
| 2 min | 62.31 ± 2.11 | 54.73 ± 2.72 |
| 10 min | 62.38 ± 1.95 | 52.05 ± 2.64 |
| 24 hours | 61.40 ± 2.24 | 52.81 ± 2.30 |

For each delay, scores are average (± SEM) percent looking time at novel stimuli across 10 trials. Group C = adult unoperated controls ($n = 3$); Group H = adult animals with neonatal hippocampal lesions ($n = 3$). From Pascalis et al 1999.

functions. To test this possibility, we recently adapted two new memory tasks to assess memory functions in adult monkeys with neonatal hippocampal lesions and their unoperated controls when they were between 9–11 years of age. One is a preferential viewing task that has been frequently used to test recognition memory in human infants (Fagan 1970) and the other is a transverse patterning task that has been used in rodents to demonstrate the role of the hippocampal formation in relational memory (Alvarado et al 1995a).

### *Preference for Novelty*

A visual paired-comparison task (Bachevalier et al 1993) was used to assess recognition memory in animals with neonatal hippocampal lesions when they reached adulthood (Pascalis and Bachevalier 1999). In this task, the animals were familiarized with a picture of an object for a cumulative 20-sec period. After a delay, which varied from 10 sec, 30 sec, 1 min, 10 min or 24 hours, the picture of the sample object was paired with a picture of a novel object for two retention trials of 5-sec each. In the two retention trials, the left/right position of the familiar and novel objects were reversed. A camera tracked the animal eye movements during testing. Looking time at each of the two stimuli during the retention tests was used to determine the time spent looking at the familiar and novel pictures. In this task, longer looking time to one stimulus (generally the novel one) is indicative of recognition memory. Percent looking at novel stimuli for each delay is given in Table 3. The findings indicated that, whereas normal controls showed strong preference for novelty at all delays tested (>60%), those with early hippocampal lesions showed strong preference for novelty only at the shortest delay of 10 sec (62.3%). Statistical analysis revealed that both main factors were significant [Groups: $F(1,3) = 28.05$, $p < .02$; Delays: $F(5, 15) = 3.37$, $p < .03$], as was their interaction [$F(5, 15) = 4.52$, $p < .01$]. Paired comparisons indicated that neonatal hippocampal lesions significantly abolished preference for novelty at all delays (all $p_s < .05$), except the shortest delay of 10 sec. This visual recognition loss contrasts with the normal performance the same operated animals showed in the DNMS task. The discrepancy between the results obtained in the 2 recognition tasks suggest that, to perform normally on the DNMS task, the operated may have used behavioral strategies that do not depend on the integrity of the hippocampal formation.

### *Transverse Patterning*

To test relational learning in monkeys (Alvarado et al 1995b), monkeys were required to learn 3 concurrent discrimination problems formed from 3 objects, designated A, B and C, as follows: Problem 1) A+ vs. B− (+ indicates correct choice); Problem 2) B+ vs. C−; Problem 3) C+ vs. A−. To perform correctly, monkeys cannot rely solely on the physical qualities of the items of the pairs, but rather must attend to the relationship between the two items (i.e., "if A and B, chose A" and "if A and C, choose C"). Three adult monkeys with neonatal hippocampal lesions and 3 age-matched controls were trained on 2 sets of transverse patterning discriminations. Six objects (A–F) were used to form two sets: Set 1) A+ vs. B−, B+ vs. C−, and C+ vs. A−; and Set 2) D+ vs. E−, E+ vs. F−, and F+ vs. D−. Animals received 5 trials of each problem daily (total: 30 trials) until they reached a criterion of 27 out of 30 correct for 60 consecutive trials on each problem set, or a maximum of 1000 trials on each set. Problems from each set were presented on alternate trials such that a given trial contained no objects from the preceding trial. Whereas unoperated controls learned Set 1 in an average of 300 (SEM: 87.9) trials and Set 2 in an average of 315 (SEM: 71.9), none of the operated animals learned the task in the limit of testing, and received a score of 1000 trials. The findings thus indicated that neonatal hippocampal lesions significantly impaired performance on the transverse patterning task. To further investigate whether the impairment following neonatal hippocampal lesion was due to an inability to use a relational solution, or simply an inability to solve 6 discriminations under conditions of high interference, the task was altered in such way as to permit subjects to use a non-relational solution, but that maintained the conditions of high interference. To achieve this, the following substitution was made in each set: Set 1) A+ vs. B−, B+ vs. C−; and C+ vs. **X−**; and Set 2) D+ vs. E−, E+ vs. F−, and F+ vs. **Y−**. Animals with neonatal hippocampal lesions who had failed the 2 previous sets of relational problems reached criterion on both sets of the transfer test in 5 sessions or 75 trials per set. Thus, the poor performance of animals with neonatal hippocampal lesions seems directly related to their inability to solve nonlinear relational problems, rather than simply a function of the number of problems or interference across problems.

*Summary*

Taken together, the results suggest that, in primates, structures in the hippocampal region play a critical role in specific memory processes, such as those subserving automatic (as opposed to effortful) recognition memory processes and relational learning. Because at the present time the effects of the neonatal hippocampal lesions on these 2 new memory tasks were measured only when the neonatally operated animals reached adulthood, the findings do not indicate whether the memory deficits were already present in early infancy or whether they emerged as the animals matured. In addition, we do not possess data on the effects of hippocampal lesions in adult monkeys on these 2 new tasks to assess whether or not the loss of memory after neonatal hippocampal lesions is comparable to that of adult lesions. Thus, additional studies are therefore needed to clarify these points.

## Effects of Neonatal Hippocampal Damage on Other Behavioral Responses

Aside from its well-documented contribution to learning and memory, the hippocampal formation plays a critical role in the regulation of other behaviors, such as arousal, attention, motivation, emotion, and social behavior. This is not surprising given its widespread anatomical connections with diverse cortical areas, mamillary bodies, anterior thalamic nuclei, septum, amygdala, basal ganglia, and hypothalamus (see for review Rosene and Van Hoessen 1987). Most of our knowledge in this area comes from studies of hippocampal damage in rodents. In a detailed review of the literature, Gray and McNaughton (1983) showed that hippocampal lesions increase activity, reduce spontaneous alternation, retard habituation, attenuate aggressive responses, and prevent the formation of social hierarchies. By contrast, they have no effect on measures of fear and on interactions between conspecifics. Based on its anatomical connections and participation in the analysis of contextual significance, Gray (1995) views the hippocampal formation has a cognitive system controlling goal-directed behavior by linking the multidimensional analysis of an environmental situation to the retrieval of the information appropriate to satisfying the motivational state of the moment. This author also proposed that a dysfunction of such a cognitive process could result in aberrant modulation of affective responses, such as anxiety or schizophrenia (Gray 1995). Therefore, to investigate whether or not early hippocampal lesions could have an effect on cognitive processes other than memory, the socioemotional behavior of the same monkeys with early hippocampal lesions and their controls that had participated in our learning and memory studies was investigated (Beauregard et al 1995).

At the age of 2 months, 6 months, and 5–8 years operated monkeys and their age-matched controls were placed in a play cage containing toys and towels. The behavior of each pair was videorecorded for 2 periods of 5 min each, separated by a 5-min interval, for 6 consecutive days (see for details of the technique Bachevalier et al 1999b). Frequency and duration of behaviors for each animal on the videotapes were recorded independently by 2 observers, who assigned the behaviors to 1 of 9 different behavioral categories. Interobserver reliabilities average 0.83 and 0.82 for frequency and duration respectively, at 2 and 6 months, and 0.89 and 0.91 for frequency and duration respectively, at 5–8 years. The behavioral categories included: *Approach*—social contact initiated by the observed monkey; *Acceptance of approach*—acceptance of social contact initiated by the other monkey; *Dominant approach*—immature forms of aggression, such as snapping at the other monkey, taking toys away from the other monkey, or pushing the other monkey away; *Active withdrawal*—active withdrawal from social approach initiated by the other monkey; *Inactivity*—passive behavior; *Locomotion*—walking, running, jumping, or climbing activities; *Manipulation*—manipulations of toys or parts of the cage with the limbs or mouth; *Locomotor stereotypies*—abnormal motor behaviors, such as circling or doing somersaults; *Self-directed activities*—actions self-administered, such as pressing head or sucking part of the body. For each behavioral category, scores of the operated animals (Group H) were compared to those of the age-matched unoperated monkeys (Group C) that were raised with the operated animals, as well as to those of 6 age-matched normal animals (Group N) raised in triads in the same way as the animals of the present experiment. This latter group of animals was added to provide a measure of normal development of socioemotional responses in our experimental rearing conditions. Thus, behavioral observations were carried out on H + C or N + N dyads.

The results of Group N (Bachevalier et al 1999b) showed that, at both 2 and 6 months of age, pairs of normal animals spent most of their time in social interactions, locomotion, or manipulation. They exhibited virtually no behaviors considered to be abnormal, such as active withdrawal, locomotor stereotypies, or self-directed activities, and almost no inactivity (see Table 4, Group N). Between 2 and 6 months, however, the nature of social interactions between normal animals did change. Whereas at 2 months social behavior consisted primarily of following the other monkey and clinging to it, at 6 months these immature behaviors were replaced primarily by rough-and-tumble play and chasing. As adults, normal monkeys remained mainly in close proximity or physical contact to each other with few episodes of locomotor behaviors and very few stereotypies.

Table 4. Total Social Contacts and Locomotor Stereotypies

| | A Neonatal lesions (tested at 2 months) | B Neonatal lesions (tested at 6 months) | C Neonatal lesions (tested at 5–8 years) | D Adult lesions (tested at 5–6 years) |
|---|---|---|---|---|
| Total social contacts | | | | |
| Dyads C + H | 125.57 ± 29.8 | 76.13 ± 19.54 | 33.4 ± 7.42 | 240.0 ± 28.0 |
| Dyads N + N | 158.36 ± 32.2 | 187.26 ± 38.52 | 270.3 ± 37.61 | 275.0 ± 21.0 |
| Locomotor stereotypies | | | | |
| Group H | 1.64 ± 1.89 | 6.50 ± 6.58 | 54.54 ± 34.59 | 0 ± 0 |
| Group C | 3.72 ± 4.95 | 5.44 ± 5.86 | 31.88 ± 27.03 | 0 ± 0 |
| Group N | 0.12 ± 0.24 | 0.95 ± 1.12 | 3.09 ± 20.81 | 5.4 ± 2.3 |

Scores are mean duration (sec) ± SEM of total social contacts in a dyad and of locomotor stereotypies per recording session (5 min) at 2 months (A), 6 months (B), and 5–8 years (C) of age in animals with neonatal lesions and their controls ($n = 6$ in each group), and at 5–6 years (D) of age in animals with adult hippocampal lesions and their controls ($n = 2$ in each group). Group H = animals with hippocampal lesions; Group C = unoperated controls paired with the operated monkeys; Group N = normal animals paired with another normal animal. Data are from Beauregard et al (1995) and Chaudhuri et al (1996).

By contrast, neonatal hippocampal lesions yielded behavioral disturbances and changes in social interactions that became more pronounced as the animals matured. Thus, at 2 months of age, monkeys with neonatal hippocampal damage displayed significantly less approaches towards their normal controls [$F(2,21) = 6.45$, $p < .01$] and significantly greater passivity [$F(2, 21) = 10.76$, $p < .001$]. These subtle behavioral changes were less evident at 6 months, although at this age, the operated animals displayed more withdrawals in response to an increased aggression from their unoperated peers [Withdrawal: $F(2, 21) = 9.47$, $p < .005$; Aggression: $F(2, 21) = 3.90$, $p < .05$]. In adulthood, as shown in Table 4, the amount of total social contacts in the H + C dyads (compare A, B, and C) was markedly less than that in the N + N dyads [$F(1, 7) = 27.2$, $p < .002$]. Finally, only in adulthood did the operated animals exhibit more locomotor stereotypies than normal controls (Table 4, compare A, B, and C). A statistical comparison across age revealed a significant interaction between groups and age [$F(2,21) = 3.51$, $p < .05$], indicating that although the amount of locomotor stereotypies increased with maturation in all three groups, the increase was greatest in the operated animals. These findings suggest that the behavioral deficits following early hippocampal damage are not always stable throughout maturation and may become progressively more severe as the brain-damaged animals matured. To determine whether these behavioral changes are also found after hippocampal lesions acquired in adulthood, the amount of total social contacts and locomotor stereotypies found in adult monkeys with neonatal hippocampal lesions and their age-matched controls (Table 4C) was compared to that of adult animals raised in the same rearing conditions as the animals of the present experiment, including 2 that were given hippocampal lesions as adults (Table 4D). The socioemotional behavior of animals lesioned as adults was observed 2 and 6 months after the brain surgery when 1 operated animal was paired with an unoperated control. As shown in Table 4 (compare C vs. D), monkeys operated as adults showed only a mild reduction in social contacts and no locomotor stereotypies as compared to controls (Chaudhuri et al 1996). These results show that the loss of social interactions was much greater after the neonatal than after the late hippocampal lesions, and the emergence of locomotor stereotypies were observed only after the neonatal lesions (Beauregard et al 1995).

### *Summary*

Neonatal damage had greater deleterious effects on the maintenance of social interactions as well as on the emergence of disturbed behaviors, such as locomotor stereotypies, than damage incurred in adulthood. More importantly, the abnormalities following neonatal damage appear to remain silent or subtle during infancy but emerge or become more severe as the animals reach maturity.

## Brain Reorganization

Rearrangement of synaptic connections is potentially the most important biological mechanism underlying changes in cognitive and behavioral functions after brain injury in developing and mature rodents and carnivores (see for review Goldman 1974). Much less is known to what degree such neuronal plasticity can occur in the primate brain at maturity or at any stage of development. Primates, including humans, exhibit remarkable sparing of behavioral functions after circumscribed brain injuries, particularly those occurring early in life. Remarkable reorganization of anatomical connections has been shown to occur after early lesions, such as those of the prefrontal cortex (see for review Goldman-Rakic et al 1983) and inferior temporal lobe (see for review Webster et al 1995) and to a lesser extent after late lesions (Jenkins and Merzenich

1987; Nudo and Milliken 1996; Pons et al 1992; Leonard et al 1996). Nevertheless, despite the vast literature on the effects of hippocampal damage on cognitive functions, the impact of such a damage on the reorganization of associated neural systems is relatively unknown. Such information is crucial to further our understanding of the neural substrate for either loss or sparing of cognitive functions after hippocampal damage.

One of the first indications that hippocampal lesions might impact on other neural systems was given by Isaacson et al (1982, 1986). They demonstrated that the hyperactivity found in adult rats with late hippocampal damage was due in large part to disturbances of a secondary nature in the basal ganglia, particularly in the regions to which both the hippocampus and the midbrain dopamine-containing cells project: the medial nucleus accumbens and ventral-medial caudate. These effects were only transient and additional compensatory changes occur to restore an almost normal dopaminergic regulation by 14–28 days after the surgery. More recently, Lipska et al (1993) showed that the behavioral effects of neonatal excitotoxic lesions of the ventral hippocampus in rats depend upon the age that the animals were behaviorally tested. Thus, the levels of motor activity in a novel environment are similar in control and operated animals when tested at 35 days of age, whereas hyperactivity emerges in the operated animals when re-tested later on at 56 days of age. Moreover, rats operated as neonates, unlike those operated as adults, are hyperresponsive to stress, as evaluated with a swim test. The authors concluded that, because the increase in locomotor activity in response to a novel environment or to amphetamine treatment was associated with mesolimbic dopamine transmission and because this hyperactivity can be blocked by haloperidol, an antidopaminergic drug, the emergence of hyperactivity following early hippocampal lesions is presumably due to an increase in mesolimbic dopamine responsivity. This increase in dopamine responsivity appears to be associated with an enhanced postsynaptic sensitivity (Wan et al 1996). These findings suggest that the emergence of locomotor stereotypies in monkeys with neonatal hippocampectomy could likewise be due to an increase in mesolimbic dopamine responsivity.

Although mesolimbic dopamine responsivity was not investigated in the monkeys with neonatal hippocampal lesions, we did find changes in caudate dopamine release in monkeys with early but not late removals of medial temporal lobe region, that included the hippocampal formation. Thus, using an in vivo microdialysis procedure in awake monkeys, the response of dopamine in the caudate nucleus following infusion of *d*-amphetamine into the dorsolateral prefrontal cortex was examined in adult monkeys that had either neonatal or adult MTL lesions, and in normal controls (Saunders et al 1998). In response to *d*-amphetamine challenge, normal animals and those with late MTL lesions showed a reduction in dopamine overflow. By contrast, those with early MTL lesions became hyperdopaminergic. These results suggest that early injury to the primate medial temporal lobe may set the stage for an adult brain to respond to prefrontal cortical stimulation with abnormal striatal dopamine release. This hyperdopaminergic response may well be the cause of enhanced locomotor stereotypies seen in the same animals.

The brain reorganization after neonatal hippocampal lesions might also be widespread, affecting other neural systems associated with the medial temporal lobe region. Although this notion has not yet been directly tested in animals with lesions restricted to the hippocampal formation, recent findings in animals with larger medial temporal lobe lesions that included the hippocampal formation indicated altered development of prefrontal neurons remote from the site of damage. Using proton magnetic resonance spectroscopic imaging (1H-MRSI), an in vivo neurochemical assay technique for measuring signals from metabolites such as *N*-acetyl-aspartate (NAA, a neuronal marker), choline-containing compounds (CHO) and cretonne/phosphocreatine (CRE) in animals with early or late MTL lesions and control animals, significant bilateral reductions of NAA relative signals were found exclusively in the prefrontal cortex of the animals with the neonatal lesions as compared to those with late lesions or unoperated controls (Bertolino et al 1997). Although the physiological role of NAA in neurons has yet to be fully elucidated, it has been regarded as either a marker of neuronal density, of neuronal viability, or of neuronal dysfunction (De Stephano et al 1995; Vion-Dury et al 1995; Brenner et al 1993; Rango et al 1995; Falconer et al 1996). The results thus suggest that the lack of target feedback from the medial temporal structures prevents the prefrontal cortex from undergoing proper neuronal development.

## Conclusion

In sum, these developmental lesion studies in nonhuman primates have shown that neonatal damage to the hippocampal region results in severe deficits in certain types of memory processes, leaving other learning and memory functions intact. Furthermore, the same neonatal damage yielded changes in other behavioral responses, including social interactions and locomotor stereotypies. These behavioral changes were either not present or subtle in early infancy, but became more profound as the animals reached adulthood. Finally, whereas the memory losses following neonatal hippocampal lesions resemble those found after late lesions, only the neonatal hippocampal lesions resulted in a protracted emergence of abnormal behaviors.

These later findings suggested that the neonatal hippocampal lesions impact on neural systems remote from the site of damage, a view that was confirmed by our more recent neurobiological studies on the same animals, demonstrating that neonatal, but not late, damage to the hippocampal region, disrupts the normal behavioral and cognitive processes subserved by the prefrontal cortex and the caudate nucleus. These findings imply that a fixed dysfunction localized to one of the nodes of a neural circuit can influence other areas of the circuit, especially if it occurs early in development.

Whereas the experimental lesions used in the present studies cannot offer an adequate animal model for schizophrenia since this human disease does not result from a brain lesion, they substantiate an earlier proposal from Schneider (1979) that early insult to the structures in the medial temporal lobe may be at the origin of developmental psychosis in humans and provide insights into the neural substrates of debilitating disorders of human neurodevelopment, such as schizophrenia (Schneider 1979; Kovelman et al 1994; Weinberger 1987; Jones et al 1991).

The work discussed here was supported in part by NIMH-IRP, MH-58846, and MH-54167 to JB and by a postdoctoral fellowship MH-10929 to MCA.

This work was presented at the conference, "Schizophrenia: From Molecule to Public Policy" held in Santa Fe, New Mexico in October 1998. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Eli Lilly and Company.

## References

Adolphs R, Tranel D, Damasio H, Damasio AR (1994): Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* 372:669–672.

Adolphs R, Tranel D, Damasio H, Damasio AR (1995): Fear and the human amygdala. *J Neurosci* 15:5880–5891.

Aggleton JP (1992): The functional effects of amygdala lesions in humans: a comparison with findings from monkeys. In: Aggleton JP, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, pp 485–504.

Alvarado MC, Rudy JW (1995a): Rats with damage to the hippocampal-formation are impaired on the transverse patterning problem but not on elemental discriminations. *Behav Neurosci* 109:204–211.

Alvarado MC, Wright AA, Bachevalier J (1995b): Monkeys with early hippocampal formation lesions are impaired in the transverse patterning problems. *Soc Neurosci Abstr* 23:1494.

Alvarez P, Zola-Morgan S, Squire LR (1995): Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. *J Neurosci* 15:3796–3807.

Bachevalier J, Beauregard M, Alvarado MC (1999a): Long-term effects of neonatal damage to the hippocampal formation and amygdaloid complex on object discrimination and object recognition in rhesus monkeys. *Behav Neurosci* (in press).

Bachevalier J, Brickson M, Hagger C, Mishkin M (1990): Age and sex differences in the effects of selective temporal lobe lesion on the formation of visual discrimination habits in rhesus monkeys *(Macaca mulatta). Behav Neurosci* 104:885–899.

Bachevalier J, Brickson M, Hagger C (1993): Limbic-dependent recognition memory in monkeys develops early in infancy. *NeuroReport* 4:77–80.

Bachevalier J, Malkova L, Pettigrew KD, Mishkin M (1999b): Effects of selective neonatal temporal lobe lesions on socioemotional behavior in infant rhesus monkeys *Behav Neurosci* (in press).

Bachevalier J, Mishkin M (1989): Mnemonic and neuropathological effects of occluding the posterior cerebral artery in *Macaca mulatta. Neuropsychologia* 27:83–105.

Bachevalier J, Mishkin M (1994): Effects of selective neonatal temporal lobe lesions on visual recognition memory in rhesus monkeys. *J Neurosci* 14:2128–2139.

Beauregard M, Malkova L, Bachevalier J (1995): Stereotypies and loss of social affiliation after early hippocampectomy in primates. *NeuroReport* 6:2521–2526.

Bertolino A, Saunders RC, Mattay VS, Bachevalier J, Frank JA, Weinberger DR (1997): Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporolimbic lesions: a proton magnetic resonance spectroscopic imaging study. *Cerebral Cortex* 7:740–748.

Brenner RE, Munro PMG, Williams SCR, et al (1993): The proton NMR spectrum in acute EAE: the significance of the change in the Cho:Cre ratio. *Magn Reson Med* 29:737–745.

Chaudhuri JH, Malkova L, Bachevalier J, et al (1996): Socioemotional behavior in adult rhesus monkeys after early versus late lesions of the hippocampus. *Soc Neurosci Abstr* 22:446.

Damasio AR, Eslinger PJ, Damasio H, Van Hoesen GW, Cornell S (1985): Multimodal amnesic syndrome following bilateral temporal and basal forebrain damage. *Arch Neurol* 42:252–259.

DeStefano N, Matthews P, Antel JP, Preul M, Francis G, Arnold DL (1995): Chemical pathology of acute demyelinating lesions and its correlations with disability. *Ann Neurol* 38: 901–909.

Fagan JF (1970): Memory in the infant. *J Exp Child Psychol* 9:217–226.

Falconer JC, Liu SJ, Abbe RA, Narayana PA (1996): Time dependence of *N*-acetyl-aspartate, lactate, and pyruvate concentrations following spinal chord injury. *J Neurochem* 66: 717–722.

Feinberg I (1982): Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiat Res* 17:319–334.

Goldman PS (1974): An alternative to developmental plasticity: heterogeneity of CNS structures in infants and adults. In: Stein DG, Rosen JJ, Butters N, editors. *Plasticity and Recovery of Functions.* New York: Academic Press, pp 149–174.

Goldman-Rakic PS, Isseroff A, Schwartz L, Bugbee NM (1983): The neurobiology of cognitive development. In: Mussen P, editor. *Handbook of Cognitive Development,* Vol. 2. New York: Wiley, pp 282–344.

Gray JA (1995): A model of the limbic system and basal ganglia: applications to anxiety and schizophrenia. In: Gazzaniga MS, editor. *The Cognitive Neurosciences.* Cambridge, MA: MIT Press, pp 1165–1176.

Gray JA, McNaughton N (1983): Comparison between the behavioural effects of septal and hippocampal lesions: a review. *Neurosci Biobehav Rev* 7:119–188.

Isaacson RL (1982): *The Limbic System,* 2nd ed. New York: Plenum Press.

Issacson RL, Springer JE, Ryan JP (1986): Cholinergic and catecholaminergic modification of the hippocampal lesion syndrome. In: Isaacson RL, Pribram KH, editors. *The Hippocampus,* Vol. 4. New York: Plenum Press, pp 127–158.

Jenkins WM, Merzenich MM (1987): Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. *Prog Brain Res* 71:249–266.

Jones PB, Murray RM (1991): The genetics of schizophrenia in the genetics of neurodevelopment. *Br J Psychiatry* 158:615–623.

Kling A, Brothers LA (1992): The amygdala and social behavior. In: Aggleton JP, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, pp 353–377.

Kovelman JA, Scheibel AB (1984): A neurohistological correlate of schizophrenia. *Biol Psychiatry* 19:1601–1621.

Leonard BW, Amaral DG, Squire LR, Zola-Morgan S (1995): Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. *J Neurosci* 15:5637–5659.

Lipska BK, Weinberger DR (1993): Cortical regulation of the mesolimbic dopamine system: implications for schizophrenia. In: Kalivas PW, Barnes CD, editors. *Limbic Motor Circuits and Neuropsychiatry.* Boca Raton, FL: CRC Press, pp 329–350.

Mahut H, Moss M (1986): The monkey and the sea horse. In: Isaacson RL, Pribram KH, editors. *The Hippocampus,* Vol. 4. New York: Plenum Press, pp 241–279.

Malamut BL, Saunders RC, Mishkin M (1984): Monkeys with combined amygdalo-hippocampal lesions succeed in object discrimination learning despite 24-hour intertrial intervals. *Behav Neurosci* 98:759–769.

Malkova L, Mishkin M, Bachevalier J (1995): Long-term effects of selective neonatal temporal lobe lesions on learning and memory in monkeys. *Behav Neurosci* 109:212–226.

Malkova L, Mishkin M, Suomi SJ, Bachevalier J (1997): Socioemotional behavior in adult rhesus monkeys after early versus late lesions of the medial temporal lobe. *NY Acad Sci* 807:538–540.

Meunier M, Bachevalier J, Murray EA, Mishkin M (1993): Effects on visual recognition memory of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J Neurosci* 13:5418–5432.

Mishkin M (1978): Memory in monkeys severely impaired by combined but not separate removal of the amygdala and hippocampus. *Nature (London)* 273:297–298.

Mishkin M, Malamut BL, Bachevalier J (1984a): Memories and habits: two neural systems. In: Lynch G, McGaugh L, Weinberger NM, editors. *Neurobiology of Learning and Memory.* New York: Guilford Press, pp 65–77.

Mishkin M, Petri HL (1984b): Memories and habits: some implications for the analysis of learning and retention. In: Butters N, Squire L, editors. *Neuropsychology of Memory.* New York: Guilford Press, pp 287–296.

Murray EA, Mishkin M (1998): Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J Neurosci* 18:6568–6582.

Nudo RJ, Milliken GW (1996): Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J Neurophysiol* 75:2144–2149.

Pascalis O, Bachevalier J (1999): Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. *Hippocampus* (in press).

Pons TP, Garraghty PE, Ommaya AK, et al (1992): Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 258:1159–1160.

Rango M, Spagnoli D, Tomei G, et al (1995): Central nervous system trans-synaptic effects of acute axonal injury: a H magnetic resonance spectroscopy study. *Magn Reson Med* 33:595–600.

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG (1996): Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J Neurosci* 16:5233–5255.

Rosenblum LA (1961): *The development of social behavior in the rhesus monkey.* Unpublished doctoral dissertation, University of Wisconsin.

Rosene DL, Van Hoesen GW (1987): The hippocampal formation of the primate brain. A review of some comparative aspects of cytoarchitecture and connections. In: Jones EG, Peters A, editors. *Cerebral Cortex,* Vol. 6. New York: Plenum Press, pp 345–456.

Rupenthal GC, Walker CG, Sackett GP (1991): Rearing infant monkeys *(Macaca nemestrina)* in pairs produces deficient social development compared with rearing in single cages. *Am J Primatol* 25:103–113.

Sackett GP (1982): Can single processes explain effects of postnatal influences on primate development? In: Emde RN, Harmon RJ, editors. *The Development of Attachment and Affiliative Systems.* New York: Plenum Press, pp 3–12.

Saunders RC, Kolachana BS, Bachevalier J, Weinberger DR (1998): Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. *Nature* 393:169–171.

Schneider GE (1979): Is it really better to have your brain lesion early? A revision of the Kennard principle. *Neuropsychologia* 17:557–583.

Schneider ML, Suomi SJ (1992): Neurobehavioral assessment in rhesus monkey neonates *(Macaca mulatta):* developmental changes, behavioral stability, and early experience. *Infant Behav Dev* 15:155–177.

Scoville WB, Milner B (1957): Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.

Spence KW (1952): The nature of the response in discrimination learning. *Psychol Rev* 59:89–93.

Squire LR (1992): Memory and the hippocampus: a synthesis

from findings with rats, moneys, and humans. *Psychol Rev* 99:195–231.

Suomi SJ (1997): Long-term effects of different early rearing experiences on social, emotional, and physiological development in nonhuman primates. In: Keshavan MS, Murray RM, editors. *Neurodevelopment and Adult Psychopathology.* Cambridge: University Press, pp 104–116.

Thompson CI (1981): Long-term behavioral development of rhesus monkeys after amygdalectomy in infancy. In: Ben Ari Y, editor. *The Amygdala Complex.* Amsterdam: Elsevier North-Holland Biomedical Press, pp 259–270.

Vion Dury J, Nicoli F, Salvan AM, et al (1995): Reversal of brain metabolic alterations with zidovudine detected by proton localised magnetic resonance spectroscopy. *Lancet* 345:60–61.

Wan RQ, Giovanni A, Kafka SH, Corbett R (1996): Neonatal hippocampal lesions induced hyperresponsiveness to amphetamine: behavioral and in vivo microdyalisis studies. *Behav Brain Res* 78:211–223.

Webster MJ, Bachevalier J, Ungerleider LG (1995): Development and plasticity of visual memory circuits. In: Julesz B, Kovacs I, editors. *Maturational Windows and Adult Critical Plasticity.* Addison: Wesley, pp 1–14.

Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660–669.

Young AW, Hellawell DJ, Van de Wakl C, Johnston M (1996): Facial expression processing after amygdalectomy. *Neuropsychologia* 34:31–39.

Zola-Morgan S, Squire LR (1985): Complementary approaches to the study of memory: human amnesia and animal models. In: Weinberger NW, McGaugh JL, Lynch L, editors. *Memory Systems of the Brain: Animal and Human Cognitive Processes.* New York: Guilford Press, pp 463–477.

Zola-Morgan S, Squire LR, Alvarez-Royo P, Clower RP (1991): Independence of memory functions and emotional behavior: separate contributions of the hippocampal formation and the amygdala. *Hippocampus* 1:207–220.

Zola-Morgan S, Squire LR, Amaral DG (1986): Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci* 6:2950–2967.

Zola-Morgan S, Squire LR, Amaral DG (1989): Lesions of hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *J Neurosci* 9:898–913.