# Neurobiology of Early Life Stress: Rodent Studies

*David A. Gutman and Charles B. Nemeroff*

**It is now clear that early experience influences the long-term development of behavioral, neuroendocrine, and cognitive systems in a number of animal species. This article examines the effects of early life stress on the development of the rodent. Postnatal maternal separation is often used as a potent early life stressor, and some of the major findings from these studies are discussed. A majority of these studies have shown that early life stress can lead to a heightened stress response when maternally deprived rodents are tested as adults. The effects of early life stress on the development of brain structures involved in regulating the stress response as adults are also discussed. Finally the influence of both genetics and maternal style are mentioned in relation to their ability to alter the effects of early life stress.**



Early mother-child interactions have long been believed to be crucial for the proper development of the central nervous system (CNS). It is now clear that early experience influences the long-term development of behavioral, neuroendocrine, and cognitive systems in a number of animal species. The importance of the mother-child bond in humans was discussed in detail by Freud over a 100 years ago. However, the critical interaction between environment and behavior was first clearly shown by Harlow in his early studies of maternally deprived rhesus monkeys.[1] Rhesus monkeys who spent the first 6 months of their life in partial isolation (ie, raised with peers in the absence of the mother) exhibited a number of exaggerated oral behaviors, stereotypic movements, heightened fear and aggression, and a reduced ability to deal with daily stressors.[2]

Early work in primate models was soon replicated in other species in the late 1950s and 1960s.[3] Numerous paradigms scrutinizing prenatal stress, neonatal maternal deprivation, and isolation rearing and others have been explored to study the effects of adverse early experience on the development of the CNS. This review is primarily focused on the consequences of neonatal maternal deprivation in the rat.

## Role of Maternal Behavior in Postnatal Development

As in many species, the neonatal rat is completely dependent on its mother for nutrition, grooming, and temperature regulation. Maternal behaviors in rats consists primarily of nest building, retrieval of pups into the nests, anogenital licking and grooming to stimulate urination and defecation, and nursing periods associated with an arched-back posture which facilitates suckling. During this postnatal period, the rat brain is undergoing profound neural development including synaptogenesis, maximal activity at postnatal days (PND) 4-11, hippocampal granule cell neurogenesis and apoptosis, maximal at PND5-7, and dendritic development.[4] The hypothalamic-pituitary-adrenal (HPA) axis is also undergoing development during this period.

Although space constraints prevent a detailed analysis of the physiology of the HPA axis, a brief review is merited. At the apex of the HPA axis is a group of neurons located in the paraventricular nucleus (PVN) of the hypothalamus that contain the peptides corticotropin-releasing factor (CRF) and/or arginine vasopressin (AVP). A variety of sensory inputs conveying information about pain, metabolic imbalances, and higher-order internal and external stimuli relating to actual or perceived stressors converge on the hypothalamus. After stimulation, CRF is released from the median eminence into the hypothalamo-hypophysial portal circulation where it acts on adenohypophysial corticotrophs to stimulate the release of adrenocorticotropin hormone (ACTH) into the systemic circulation. ACTH primarily acts at the adrenal

*From the Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA.*

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*Address reprint requests to Charles B. Nemeroff, MD, Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322.*



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cortex where it stimulates the synthesis and secretion of glucocorticoids (cortisol in humans, corticosterone in rodents), which are critical in mobilizing energy substrates during stress. Circulating glucocorticoid levels are tightly regulated via glucocorticoid-mediated negative feedback on the secretion of ACTH and CRF via activation of cytoplasmic glucocorticoid and mineralocorticoid receptors at the level of the PVN, pituitary, and throughout the CNS. There is also abundant evidence that CRF is, in addition to its endocrine role, the global regulator of the behavioral, autonomic, and immune responses to stress in mammals.[5]

Although a functional HPA axis is essential for survival in adulthood, pronounced fluctuations in the activity of this axis during infancy may be maladaptive to the development of the immature brain. In rodents, the brain is protected from the effects of glucocorticoids due to a reduced sensitivity of the HPA axis to activation during the neonatal period (PND3-16), also known as the stress hyporesponsive period (SHRP). However the reduced HPA axis responsiveness observed during this period is not absolute, and can be surmounted by sufficiently potent stressors, including maternal deprivation.

## Rodent Models of Maternal Deprivation

To study the effects of adverse early experience, specifically maternal separation, several models have been developed. The specific details used in these paradigms vary greatly between research groups, ranging from a single 24-hour deprivation to repeated, but shorter maternal deprivation episodes lasting 12, 8, 6, or 3 hours starting between PND 1 and 2 and extending through PND 14 to 21.[4] Additionally some groups further separate the pups from one another during their separation period, whereas other researchers keep the pups together as a litter during the period of separation.

In the wild, brief maternal separation is common when rodent dams are forced to leave the nest for periods of 15 to 30 minutes to forage for food,[6] though lower ranking females that have burrows farther from food and water sources may spend an even greater amount of time away from their offspring. To model this in a laboratory setting, Plotsky and Meaney have studied the effects of maternal separation in an outbred strain of Long Evans hooded rats. In their paradigm, on PND 2 all pups are removed from their home cage, randomized, and culled to 8 to 10 pups per group, usually consisting of 10 male pups per dam. Each litter is then exposed to 1 of 3 rearing conditions from PND 2-14: (1) animal facility rearing (AFR) which consists of home cage bedding material changes and brief handling twice weekly beginning on PND 5 with no other handling or separation; (2) handled (HMS15) animals which are removed from their home cage daily for a 15 min period; and (3) maternal separation (HMS180) in which pups are removed from their home cage for 180 minutes daily. In some experiments, an additional nonhandled group is included; in this condition the mother and pups are left completely undisturbed for the first 14 days after birth; this also means there are no cage changes during this period. All separations occur between 0800 and 1300 hours. After separation, all litters are returned to their home cage, rolled in their native bedding, and reunited with their dams. Animals are weaned on PND 21 to 23 and group housed (2 to 3 per cage) until adulthood (>PND 60).

## HPA Axis Adaptations

Maternally deprived rats, as adults, exhibit differences in their HPA response to stressors when compared to nondeprived littermates. In a defensive withdrawal test, HMS180 rats showed an increased latency to exit from the "safe" compartment, as well as spending a greater total amount of time in the cylinder as compared with AFR and HMS15 rats.[4] Furthermore, maternally deprived rats spent less time in the open arms in an elevated plus maze, a validated model of anxiety relative to nondeprived animals. Interestingly, animals that were exposed to brief amounts of handling (AFR and HMS15 rats) showed a reduced stress response relative not only to HMS180 animals, but also to nonhandled animals. Indeed, the extant evidence indicates that early life brief handling actually decreases the stress response in adults. These behavioral observations are consistent with the hypothesis that the postnatal environment is able to profoundly influence the developing CNS.

Although basal ACTH and corticosterone plasma trough levels did not differ between rearing groups, maternally deprived rats (HMS180) show exaggerated ACTH and corticosterone responses to psychological stressors. The response

to an airpuff startle (a predominantly psychological stressor)[7] but not controlled hemorrhage (a physical stressor), was greatly enhanced in HMS180 rats.[8] It appears that prolonged maternal separation results in an exaggerated HPA axis response to psychological stressors (eg, novel environment, airpuff startle, restraint), but not to predominantly physiological stressors (eg, cold or hemorrhage; see Fig 1). These results implicate alterations in the corticolimbic pathways coordinating the processing of higher-order sensory stimuli and their transfer to the hypothalamic PVN.

The alterations in HPA axis function are associated with changes in the expression patterns of CRF mRNA. Hypothalamic CRF mRNA, specifically in the PVN, is significantly elevated in maternally deprived and nonhandled rats.[9] HMS180 rats also exhibit elevated CRF and AVP concentrations in the hypophysial-portal circulation relative to handled (HMS15) rats, consistent with the elevated CRF mRNA expression observed in the hypothalamus. In addition hypothalamic CRF receptor binding is increased in maternally deprived rats relative to handled rats. This latter finding suggests increased $CRF_1$ receptor mRNA expression in the PVN as a consequence of the maternal deprivation stress. The increased CRF content along with increased binding demonstrated in these animals would suggest an increased responsiveness of these animals to the effects of CRF. The differences in CRF/AVP synthesis and ACTH responses to stress were associated with altered glucocorticoid negative feedback sensitivity. Administration of dexamethasone or corticosterone resulted in a greater suppression of plasma ACTH responses to

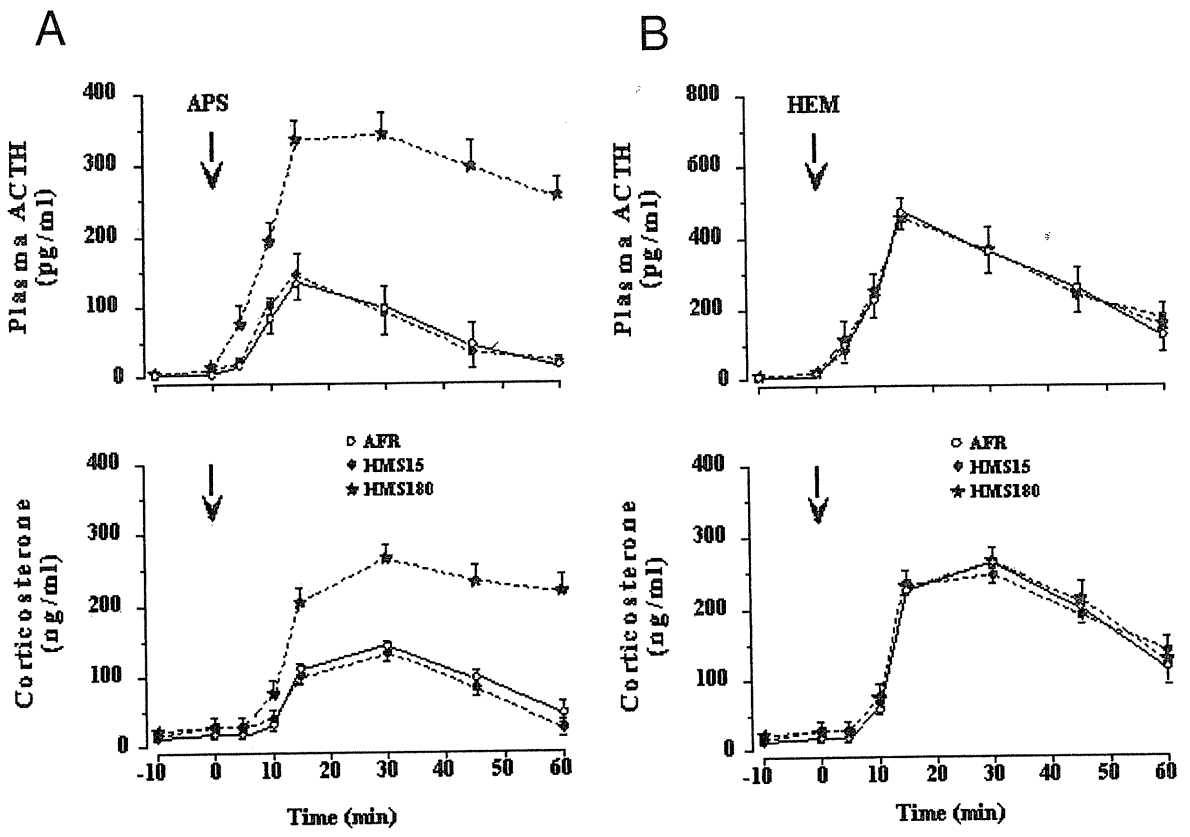


**Figure 1.** Rearing-associated differences in adult responsiveness to psychological (A) and physical stressors (B). In the maternally separated adults (HMS180), the ACTH and corticosterone responses to the psychological stressor of airpuff startle (APS) was enhanced relative to the responses in animal facility reared (AFR) colony controls or handling controls (HMS15). In contrast, no difference in responsiveness was evident among the groups in response to the physical stressor of 15% hemorrhage (HEM). Data shown as mean ± SEM. Reprinted from Ladd et al: Long-term behavioral and neuroendocrine adaptations to adverse early experience. Prog Brain Res 122:81-103, 2000 with permission from Elsevier Science.[8]

stressors in handled when compared with nonhandled animals.[10] Adrenalectomy, which prevents the glucocorticoid negative feedback signal, abolished the group differences in plasma ACTH responses to stress.

There is evidence that maternal deprivation induces changes not only in the HPA axis, but also in various extrahypothalamic sites involved in the coordination and integration of sensory information. Changes in extrahypothalamic CRF systems are of particular interest. CRF mRNA levels in the bed nucleus of the stria terminalis and central nucleus of the amygdala are elevated in HMS180 maternally deprived rats and decreased in HMS15 handled rats relative to nonhandled controls.[4] These CRF pathways project directly to brain stem nuclei, including the locus coeruleus (LC), where CRF directly activates noradrenergic neurons.[11] Because the LC is involved in regulating the autonomic nervous system, these pathways may help enhance vigilance behavior and further drive the HPA axis. In a recent study, Liu et al (2000)[30] showed that maternally deprived rats had a greater noradrenergic response to restraint stress than handled animals, and ACTH release showed a similar response. The rearing conditions did not affect the expression of $\alpha_1$ or $\alpha_2$ adrenergic receptors in the PVN. However $\alpha_2$ receptors in the LC and nucleus tractus solitarius (NTS) were significantly decreased in number in the maternally separated animals. Because $\alpha_2$-receptors are autoreceptors located primarily on noradrenergic neurons, they inhibit norepinephrine (NE) release at terminal sites. This expression pattern would suggest that, once activated, the firing rate of LC neurons may be more difficult to shut off in maternally deprived animals and it provides a mechanism for the differences in stress-induced NE levels in maternally separated versus handled animals. There is also evidence of decreased central benzodiazepine (CBZ) receptor binding in the LC and NTS in HMS180 maternally deprived (HMS180) rats.[12] Thus the increased CRF, and reduced CBZ and $\alpha_2$-adrenergic receptor binding demonstrated in maternally deprived rats provide a general mechanism to explain the observed stress hyperresponsiveness seen in these animals.

Similar results have been obtained with other maternal deprivation protocols. One protocol involved a 6 hour daily separation during PND 2-20. When tested as adults, deprived rats exhibited a marked increase in CRF immunoreactivity in the median eminence, and a reduction in CRF receptor binding in the anterior pituitary.[13] Furthermore, alterations in extrahypothalamic CRF systems were also observed, including an increase in the number of $CRF_1$-receptor binding sites in the raphe and parabrachial nuclei.

The specific details of the maternal deprivation paradigm used, including whether or not the pups are separated from each other during the separation, the time of day the separation is performed, and the duration of the separation period all are critical factors. Van Oers and colleagues, using a single 24-hour period of maternal deprivation, showed that the age at which maternal separation occurs can dramatically alter the functioning of the HPA axis.[14] This group showed that deprivation at PND 3 resulted in a hyperresponsive stress response of the pups at PND 20, whereas deprivation at PND 11 resulted in a hyporesponsive stress response. Clearly more studies are needed to further elucidate the neurocircuits and mechanisms underlying these changes.

## Genetic Variability

Although the field has largely focused on how differences in early environment can produce robust and long-lasting changes in the stress response, the underlying genetic background of the animal also contributes to the differential susceptibility to the effects of behavioral perturbation. The effects of pretest handling on activity in the open-field and elevated plus maze tests showed significant differences when 2 different strains of rats were tested.[15] Similar strain differences in behavioral and endocrine responses to a forced swim test[16] and in stress and immune induced adrenal steroid receptor activation have also been reported.[17] These studies suggest that different strains or species of animals have differing responses to stress, which may be further perturbed by prenatal, maternal deprivation, or other environmental influences.

The results from animal models of mood and anxiety disorders lend validity to a stress-diathesis model in which both genetic and environmental factors interact to regulate complex behaviors, such as those involved in responding to a stressful and changing environment. Although we have focused primarily on the neurobiological sequelae of prolonged periods of maternal

deprivation, short periods of handling during the postnatal period may have neuroprotective or anxiolytic effects in certain instances. Relative to nonhandled animals, rodents handled during infancy spent more time exploring a novel environment when tested as adults,[18] and showed reduced emotional reactivity to handling.[19]

In line with a stress-diathesis model in which different strains or species have different sensitivities to stress, the effects of brief amounts of handling have been examined in several strains of mice (see Anisman[20] for detailed review). These studies showed that the BALB/cByJ strain was most vulnerable to stress induced changes in behavior, whereas the C57BL/6J strain was least affected. For example, BALB/cByJ mice showed heightened anxiety in a plus maze[21] and hypersecretion of corticosterone and ACTH after footshock relative to other strains.[22] However postnatal handling of BALB/cByJ mice was able to attenuate the hypersecretion of ACTH and CORT seen in these animals.[20]

A formal analysis of maternal styles in these 2 mice strains was performed which revealed that BALB/cByJ mothers tended to engage in less arch-backed nursing, licking and grooming of pups, and spent less time in the nest than C57BL/6ByJ mothers.[20] Furthermore, the same authors noticed that BALB/cByJ mice performed more poorly in the Morris water-maze test than did the C57BL/6ByJ mice; however in a cross-fostering study BALB/cByJ mice reared with a C57BL/6ByJ dam exhibited superior performance than when BALB/cByJ were raised with a BALB/cByJ mother. C57BL/6ByJ mice raised with a BALB/cByJ mother however showed performance comparable with C57BL/6ByJ raised with their biological mother.[21] This leads to the compelling conclusion that maternal care may induce behavioral disturbances in susceptible animals, but genetics alone are not always sufficient for the expression of behavioral disturbances, as shown in the cross-fostering paradigm mentioned earlier.

## Maternal Behavior in Rodents

Brief periods of handling or longer periods of maternal deprivation appear to induce changes in maternal behavior that may account for the changes seen in these studies.[23,24] As noted earlier, maternal behavior in rodents consists of a number of stereotypical behaviors associated with feeding that are critical for infant development. During an episode of nursing, the dam may assume a blanket posture or an arched-back posture which is more conducive to suckling. Each nursing bout ends with anogenital licking/grooming which stimulates urination.[4] Studies have shown that suckling stimulates the secretion of growth hormone in rats,[25] and that these maternal behaviors can directly suppress the HPA axis and prevent the pup from mounting an adult-like HPA response to moderate stressors.[26] Feeding and stroking behaviors also desensitize the adrenal glands to circulating ACTH and inhibit the release of ACTH from the anterior pituitary.[26-28]

The dams of pups exposed to the HMS15 protocol exhibited increased licking and grooming of the pups relative to animal facility reared animals (AFR). Also, dams exposed to longer periods of maternal deprivation (HMS180) retrieved their pups with a longer latency on reunion, and took a longer time to begin nursing, licking, and grooming their pups.[4] Liu and Meaney have shown that the frequency of maternal licking and grooming during the first 10 days of life is associated with reduced stress-induced changes in ACTH and CORT, enhanced glucocorticoid feedback sensitivity, and reduced CRF mRNA expression[29]; each measure actually correlated with the degree of licking and grooming. These experiments evaluated naturally occurring differences in maternal behavior in the rat; in these studies a cohort of animals was examined, and mothers that showed a high frequency of licking/grooming and arched-back nursing (LG-ABN) were compared with mothers who had low frequency occurrences of the scored behaviors. Other than these specific differences in maternal behavior, the offspring did not differ in weaning weight or the overall time spent in contact with their dams. Hence it seems reasonable that the observed phenotype seen in maternal deprivation studies may in fact be caused by changes in maternal parenting style induced by separation. Further studies have suggested that maternal behavior per se can increase expression of brain-derived neurotrophic factor (BDNF) mRNA, increase cholinergic innervation of the hippocampus, and enhance spatial learning and memory in their offspring.[30]

The above-cited evidence clearly indicates that early environmental manipulations can result in long-lasting neurochemical and behavioral changes in adult animals. Huot et al has recently

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shown that treatment with the antidepressant paroxetine (a selective serotonin reuptake inhibitor) for 21 days reversed the behavioral consequences of maternal deprivation. In this study, HMS180 rats were tested in a variety of paradigms and showed an increased ACTH and CORT response to air-puff startle, elevated anxiety as measured in the elevated plus-maze, significantly less ingestion of a water-sucrose solution and significantly more ingestion of an ethanol-sucrose solution than AFR or HMS15 rats.[31] These differences were eliminated following paroxetine treatment of the HMS180 animals; paroxetine did not affect these parameters in HMS15 rats.

## Conclusion

A growing body of evidence indicates that adverse early experience can have profound and lifelong effects on the developing brain. Indeed, prominent changes in benzodiazepine, noradrenergic, and CRF neurotransmission have been shown. Although the ultimate source of these effects are unknown, a compelling concatenation of evidence suggests that the maternal-infant interaction may help shape the development of a number of important systems in the developing CNS. Cross-fostering studies and the observation of differences in maternal behavior in nonseparated animals and its consequences provides further evidence that mother-pup interactions are critical in this process. Brief handling and environmental enrichment during the neonatal period can produce opposite changes in stress systems, further showing that the early postnatal period is very susceptible to environmental influences. The fact that antidepressant treatment can reverse some of these otherwise persistent changes in stress mechanisms provides an impetus for further study.

As in young rats, evidence indicates that early adverse experiences in humans can lead to long-term changes in behavioral and stress responsiveness. The exposure to severe childhood stressors including loss of a parent, neglect, or child abuse have been linked to an increased prevalence of mood and anxiety disorders as adults. For example our group has recently reported evidence of HPA axis hyperactivity in adult depressed women who were severely physically or sexually abused as children.[32] It is hoped that maternal deprivation models may help elucidate some of the underlying changes early adverse experiences has on the developing CNS, leading to a better understanding of the psychological and environmental factors involved in depression and anxiety related disorders, and ultimately to improved treatment for these devastating disorders.

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