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Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models

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Abstract
Increasing evidence supports the view that the interaction of perinatal exposure to adversity with individual genetic liabilities may increase an individual's vulnerability to the expression of psycho- and physiopathology throughout life. The early environment appears to program some aspects of neurobiological development and, in turn, behavioral, emotional, cognitive, and physiological development. Several rodent and primate models of early adverse experience have been analyzed in this review, including those that "model" maternal separation or loss, abuse or neglect, and social deprivation. Accumulating evidence shows that these early traumatic experiences are associated with long-term alterations in coping style, emotional and behavioral regulation, neuroendocrine responsiveness to stress, social "fitness," cognitive function, brain morphology, neurochemistry, and expression levels of central nervous system genes that have been related to anxiety and mood disorders. Studies are underway to identify important aspects of adverse early experience, such as (a) the existence of "sensitive periods" during development associated with alterations in particular output systems, (b) the presence of "windows of opportunity" during which targeted interventions (e.g., nurturant parenting or supportive–enriching environment) may prevent or reverse dysfunction, (c) the identity of gene polymorphisms contributing to the individual's variability in vulnerability, and (d) a means to translate the timing of these developmental "sensitive periods" across species.

Increasing basic, clinical, and epidemiological evidence supports the thesis that exposure to an adverse early environment may underlie vulnerability to and later expression of physiological changes associated with medical illnesses (Leserman, Drossman, Li, Toomey, Nachman, & Glogau, 1996; Stratakis & Chrousos, 1995) and psychopathology (Ambelas, 1987; Brown, Bifulco, & Harris, 1987; Caldji, Liu, Sharma, Diorio, Francis, Meaney, & Plotsky, 2001; Cui & Valliant, 1996; DeBellis, Chrousos, Dom, Burke, Helmers, Kling, Trickett, & Putnam, 1994; Heim, Owens, Plotsky, & Nemeroff, 1997; Kendler, Kessler, Neale, Heath, & Eaves, 1993; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000; Young, Abelson, Curtis, & Nesse, 1997). Animal models have provided evidence that the experience of an early traumatic event such as maternal stress or illness, as well as postnatal neglect, abuse, or serious medical illness, can alter behavioral and neuroendocrine responsiveness, brain morphology, central levels of gene expression, and neurochemical markers, as well as normal developmental processes that have been implicated in the etiology of psychiatric disorders.

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One of the most salient aspects of the early environment is the interaction between the primary caregiver and the offspring. In most but not all species, this interaction is primarily between mother and infant. This bond is among the strongest social attachments formed by most mammals (Bowlby, 1982). In the case of the rat, maternal cues associated with licking and grooming and with nursing regulate developing systems in the pups (Hofer, 1994), including the limbic–hypothalamic–pituitary–adrenal (LHPA) axis illustrated in Figure 1.

Abundant evidence shows that prenatal stress, as well as postnatal disruption of normal maternal–infant interactions, results in the dysregulation of the developing LHPA and, therefore, concomitant maladaptative changes in the developing neuroendocrine stress response in rodents and in some species of nonhuman primates. Such findings have raised the question of whether a similar cascade occurs in the human infant and, if so, whether it is merely a marker of early stress exposure or whether dysregulation of the LHPA plays a role in the etiology of mood disorders. In an attempt to address this question, we will first briefly review the basic anatomy and regulation of the LHPA axis and then present examples of short- and long-term consequences of the exposure to adverse experiences early in life in a few rodent and primate models that "mimic" maternal separation or loss, abuse or neglect, and social deprivation. We will then discuss how the early environment (including maternal cues) modulates the neurobiological development and, therefore, the normal behavioral, emotional, cognitive, and physiological development. We will discuss how the experience of trauma early in life may increase the vulnerability to psycho- and physiopathology by altering these systems. We will also analyze factors that can determine the individual variability in vulnerability, including the genetic background and prenatal environment. Finally, we will consider potential interventions that may reverse—or at least improve—some of the deficits associated with exposure to early adverse experiences.

Regulation of the Adult Stress Response: The Hypothalamic–Pituitary–Adrenal (HPA) Axis

Any actual or perceived challenge to an organism, including unpredictability or the perception of a loss of control, elicits a complex and coordinated set of behavioral, autonomic, sensory–motor, cognitive, and neuroendocrine responses to the stimulus. Among these responses, the neuroendocrine limb consists of activation of the "fight or flight" sympathetic-adrenomedullary system resulting in the release of catecholamines from sympathetic nerve endings, as well as from the adrenal medulla, and activation of the HPA axis, which results in the release of glucocorticoids (cortisol in primates; corticosterone in the rat) from the adrenal cortex.

The ontogeny of the HPA axis and its regulation has recently been described in detail (Walker, Anand, & Plotsky, 2001). There is wide variation among species in the development of the various components of the HPA axis and the onset of their functional activity. Neonatal rats exhibit a relative inability to mount an adultlike corticosterone response to environmental stimuli from Postnatal Day 4–14 (PND 4-14), which was initially called the stress nonresponsive period (Jailer, 1950). Subsequent studies of this period demonstrated the existence of stressor-specific HPA axis activation that was generally of lower amplitude than observed in adults; thus this period was renamed the stress hyporesponsive period (SHRP; Walker, Perrin, Vale, & Rivier, 1986; Walker, Scribner, Cascio, & Dallman, 1991; Witek–Janusek, 1988). The SHRP has also been described in other species, including the rabbit, guinea pig, and dog, with a duration of only a few days at the most. The presence of such a pituitary–adrenal refractory period in nonhuman primates and humans remains controversial.

The mature HPA axis exhibits a circadian rhythmicity, with a peak around the time of waking and the trough during the quiescent time of the activity cycle. Superimposed upon this diurnal pattern is activation by interoceptive and exteroceptive cues relating to threat,

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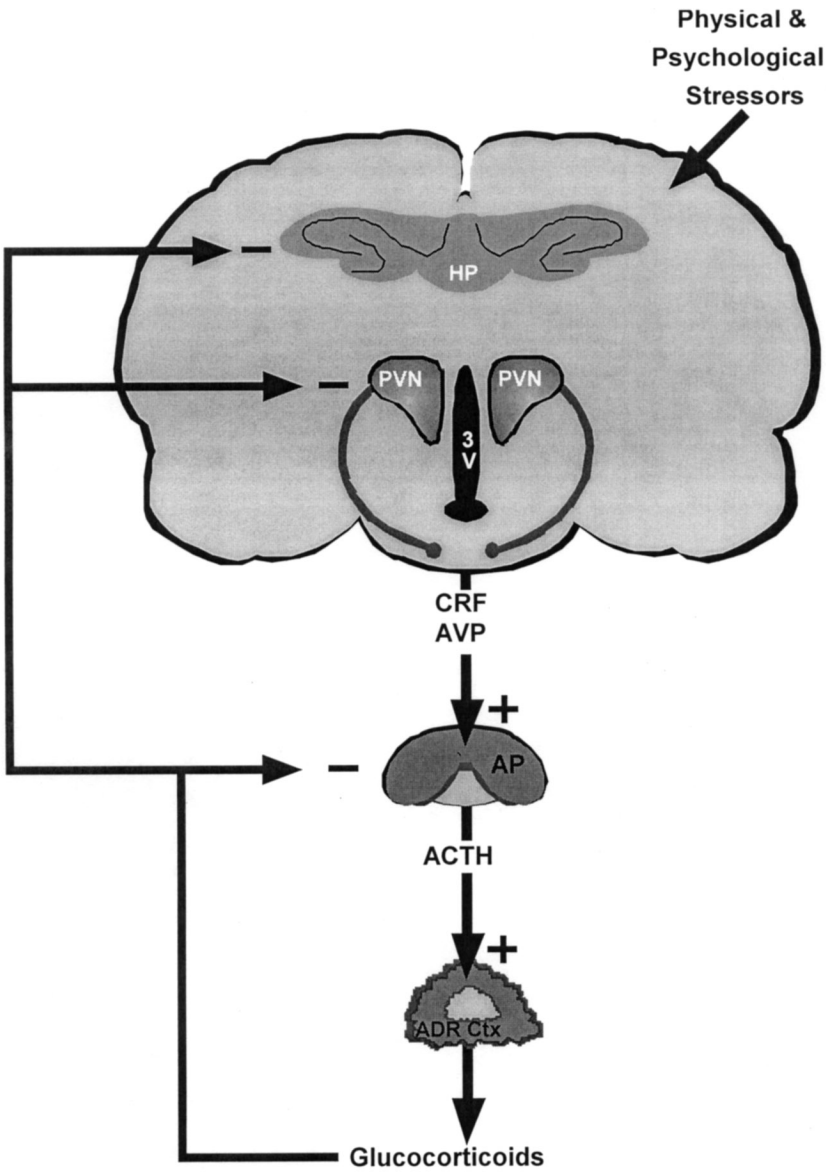


Figure 1. Schematic illustrating the hypothalamic–pituitary–adrenal (HPA) axis. Stressful stimuli of different kinds (systemic, psychogenic) are encoded within different regions in the CNS and funneled to the hypothalamic paraventricular nucleus (PVN), adjacent to the third ventricle (3V), where they stimulate the secretion of corticotropin-releasing factor (CRF) and vasopressin (AVP) from nerve terminals in the median eminence into the hypophyseal–portal vascular system. These neuropeptides are carried to the anterior pituitary (AP), where they stimulate the secretion of ACTH from corticotropes into the systemic circulation. ACTH, in turn, stimulates the de novo synthesis and secretion of glucocorticoids (corticosterone in the rat; cortisol in primates) from the adrenal cortex (ADR Ctx) into the systemic circulation. These circulating glucocorticoids complete a negative feedback loop to shut off the current HPA axis activity and modulate HPA axis activation through their actions at cytoplasmic glucocorticoid receptors distributed at different levels of the axis. HP, hippocampus. *Note:* From "Long-Term Behavioral and Neuroendocrine Adaptations to Adverse Early Experience," by C. O. Ladd, R. L. Huot, K. V. Thrivikraman, C. B. Nemeroff, M. J. Meaney, and P. M. Plotsky, in *Progress in Brain Research: The Biological Basis for Mind Body Interactions* (p. 82), edited by E. A. Mayer and C. B. Saper, 2000, Amsterdam: Elsevier. Copyright 2000 by Elsevier Science. Reprinted with permission.

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unfulfilled expectations, pain, infection, or metabolic crisis that are communicated to the hypothalamus via stressor-specific pathways (for review, see Sawchenko, Imaki, Potter, Kovics, Imaki, & Vale, 1993; Swanson & Sawchenko, 1980; Swanson, Sawchenko, & Lind, 1986; Watts, 1996), where this information is integrated in the paraventricular nucleus (PVN) by parvocellular neurons expressing the 41-amino-acid neuropeptide corticotropin releasing factor (CRF; Merchenthaler, Vigh, Petrusz, & Schally, 1982; Swanson, Sawchenko, Rivier, & Vale, 1983). Secretion of CRF from median eminence nerve terminals into the hypophysial portal circulation stimulates the synthesis of the precursor protein proopiomelanocortin and the release of stored adrenocorticotrophic hormone (ACTH) from the anterior pituitary (Fig. 1). Although CRF is the primary ACTH secretagogue, other neuroactive peptides, such as arginine vasopressin, are coexpressed in parvocellular CRF neurons and act synergistically with CRF to stimulate ACTH release (Plotsky, 1991; Sawchenko et al., 1993). When released into the systemic circulation, ACTH in turn stimulates adrenocortical synthesis and release of glucocorticoids, steroid hormones that mobilize energy substrates during stress and serve as transcriptional regulators.

Prolonged adrenocortical secretion, as can occur during chronic stress or in Cushing syndrome, can lead to pathological states including hypertension, hyperlipidemia, insulin resistance, immunosuppression, and cognitive impairment (McEwen, 1998; Munck, Guyre, & Holbrook, 1984). Normally, this is prevented by glucocorticoid-mediated negative feedback inhibition of further HPA axis activity at pituitary and central sites via two types of corticosteroid receptors (Dallman, Akana, Cascio, Darlington, Jacobson, & Levin, 1987; de Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Jacobson & Sapolsky, 1991). Mineralocorticoid receptors (MR or type I) have a high affinity for glucocorticoids and are believed to modulate the circadian rhythm of glucocorticoid secretion, particularly the diurnal trough. In contrast, the glucocorticoid receptors (GR or type II) have a low affinity for glucocorticoids and are primarily responsible for reactive negative feedback during the circadian peak and following an acute stressor. The central distribution of these receptor types varies in a brain-region and species-typical manner. In the rat brain, GR has a broad distribution, being especially abundant in the PVN, hippocampus, cortex, and cerebellum, whereas MR distribution seems to be circumscribed primarily to the hippocampus and septum.

In comparison with the rat, lower than expected levels of GR have been reported in nonhuman primate hippocampi, whereas a high density of receptors was observed within the PVN, prefrontal and entorhinal cortices, and cerebellar cortex, suggesting that, in the primate, these cortical and hypothalamic areas may be very important targets for GR-mediated effects of glucocorticoids (Sánchez, Young, Plotsky, & Insel, 2000). In addition, the distribution of MR in primates seems to be broader than in rodents, with high levels of expression in the neocortex (López, Akil, & Watson, 1999). The high levels of both MR and GR in primate cortical areas, such as the prefrontal cortex, suggests a potentially important role of glucocorticoids in modulation of cognition, mood, and social behavior and indicates potential differences in the regulation of these output systems between rodents and primates.

Glucocorticoid-mediated negative feedback has been described as having two forms, proactive and reactive (de Kloet et al., 1998). Proactive feedback refers to the maintenance of basal levels of ACTH, whereas reactive feedback refers to the suppression of ACTH increases induced by stress. Although feedback processes are thought to be immature in the neonatal rat, a study by Van Oers, de Kloet, Whelan, and Levine (1998) demonstrated that neonates exhibit both proactive and reactive feedback inhibition of the HPA axis. Interestingly, the sensitivity of these feedback modes to the absence of the mother was differentially expressed in 9- to 12-day-old neonates, with the reactive type being the most impaired by maternal deprivation. Furthermore, there is considerable evidence that even minor perturbations early in life can lead to persistent changes in LHPA axis function (Levine, Huchton, Wiener, & Rosenfeld,

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1991; Meaney, Bhatnagar, Larocque, McCormick, Shanks, Sharma, Smythe, Viau, & Plotsky, 1993; Van Oers, de Kloet, & Levine, 1998). At least some forms of disruption of maternal–infant interaction in nonhuman primates may also lead to long-term changes in LHPA axis activity (Coplan, Andrews, Rosenblum, Owens, Friedman, Gorman, & Nemeroff, 1996; Lyons, Wang, Lindley, Levine, Kalin, & Schatzberg, 1999). However, this phenomenon has not been consistently demonstrated across all species of nonhuman primates or humans.

Regulation of the Adult Stress Response: Extrahypothalamic Corticotropin Releasing Factor

In addition to its major role as ACTH secretagogue, CRF acts as a neurotransmitter within the central nervous system (CNS; for review, see Owens & Nemeroff, 1991). CRF-containing neurons and CRF receptors are widely distributed in cortical, limbic, and brain stem regions (De Souza, Insel, Perrin, Rivier, Vale, & Kuhar, 1985; Sawchenko et al., 1993). Central CRF neurocircuits, specifically those projecting from the hypothalamus and amygdala to medullary noradrenergic nuclei, have been implicated in the behavioral and autonomic expression of stress (for reviews, see Fisher, 1993; Heinrichs, Menzaghi, Pich, Britton, & Koob, 1995).

Increasing anatomical and functional evidence suggests that the amygdala may play a pivotal role in central CRF neurotransmission. Activation of the amygdala is modulated via peptidergic and aminergic projections from numerous limbic and midbrain structures, which in turn receive reciprocal CRF projections from the central nucleus of the amygdala (Gray & Bingaman, 1996). For example, CRF-containing neurons in the PVN receive CRF projections from the central nucleus of the amygdala, some of them involved in the activation of the HPA axis, both directly and indirectly via the bed nucleus of the stria terminalis (BNST) and brain stem nuclei (Feldman & Weidenfeld, 1998; Gabr, Birkle, & Azzaro, 1995; Marcilhac & Siaud, 1997). It is interesting to note that, unlike in the PVN, GR activation in the amygdala enhances CRF mRNA expression (Makino, Schulkin, Smith, Pacak, Palkovits, & Gold, 1995). Thus, repeated or chronic elevations in plasma corticosterone may result in increased CRF expression within the amygdala.

The amygdala also appears to mediate fearful behavior via CRF projections to brain stem nuclei, particularly the locus coeruleus (LC). In various behavioral tests, activation of amygdala CRF neurocircuits appears to mediate the acoustic startle reflex (Lee & Davis, 1997), stress-induced freezing (Swiergel, Takahashi, & Kalin, 1993), defensive withdrawal (Takahashi, Kalin, Vandenburgt, & Sherman, 1989) and stress-induced emotionality in an elevated plus maze (Heinrichs, Pich, Miczek, Britton, & Koob, 1992). It is important to note that the LC is the largest of seven brain stem nuclei from which noradrenergic projections in the brain emerge and accounts for approximately 75% of all noradrenaline in the forebrain. Ultrastructural studies have demonstrated that CRF terminals from central amygdala efferents synapse onto catecholamine dendrites in the rostral LC (Van Bockstaele, Colago, & Valentino, 1996; Van Bockstaele, Colago, & Valentino, 1998), supporting previous physiological evidence that acute stressors sequentially activate CRF and noradrenergic neurotransmission in this region (for review, see Valentino, Curtis, Page, Pavcovich, & Florin–Lechner, 1998). Recent studies have shown that previous exposure to stress can modulate CRF neurotransmission in the LC (Curtis, Pavcovich, Grigoriadis, & Valentino, 1995), as can chronic antidepressant treatment (Curtis & Valentino, 1994). Finally, central blockade of CRF receptors prevents upregulation of tyrosine hydroxlase mRNA in the LC following acute stress (Jezova, Ochedalski, Glickman, Kiss, & Aguilera, 1999).

CRF acts via adenylate cyclase linked receptors. To date, two CRF receptors have been cloned, CRF_1 and CRF_2, that display a heterogeneous distribution in the adult rat (Grigoriadis, Lovenberg, Chalmers, Liaw, & De Souza, 1996; Lovenberg, Liaw, Grigoriadis, Clevenger, Chalmers, De Souza, & Oltersdorf, 1995). The CRF_1 receptor is localized to the neocortex, cerebellum, olfactory bulb, and anterior pituitary (De Souza et al., 1985),

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while the CRF_2 receptor is concentrated in discrete subcortical regions, including the ventromedial hypothalamus, lateral septum, amygdaloid nuclei, and the dorsal and caudal raphe nuclei (Chalmers, Lovenberg, & De Souza, 1995). Urocortin, a CRF-like neuropeptide related to fish urotensin, has a much higher affinity for the CRF_2 receptor than CRF, suggesting that urocortin may be the CRF_2 endogenous ligand in the mammalian brain (Lovenberg et al., 1995; Vaughan, Donaldson, Bittercourt, Perrin, Lewis, Sutton, Chan, Turnbull, Lovejoy, Rivier, Rivier, Sawchenko, & Vale, 1995). However, the relationship between receptor distribution and either CRF or urocortin distribution remains the primary determinant of which peptide serves as the ligand at a particular site. In the normal adult rat, abundant expression of urocortin is limited to the Edinger Westphal nucleus and the lateral superior olive. The function of urocortin-CRF_2 receptor neural networks remains speculative, but recent studies suggest that they may modulate ingestive behaviors (Spina, Merlo–Pich, Chan, Basso, Rivier, Vale, & Koob, 1996) or counter the actions of CRF-CRF_1 receptor neurocircuits (Eghbal–Ahmadi, Hatalski, Avishai–Eliner, & Baram, 1997; Skelton, Nemeroff, Knight, & Owens, 2000).

Work by our group has demonstrated that in the primate the CRF_2 receptor subtype is more broadly distributed in CNS and pituitary than in the rat (Sánchez, Young, Plotsky, & Insel, 1999a). Thus, CRF_2 as well as CRF_1 receptors were found in the neocortex, pituitary, amygdala, and hippocampal formation of the rhesus monkey, suggesting that both receptor subtypes may be mediating the effects of CRF on HPA function, as well as in affective regulation and cognitive function in the nonhuman primate, unlike what has been previously described in the rat.

Early Adverse Experience as a Risk Factor for the Development of Psychopathology: Evidence From Rodent Models

Effects of a single 24-hr maternal separation period in the neonatal rat

It has been postulated that the SHRP observed in neonatal rats evolved to shield the developing brain from the catabolic and other effects of exposure to excess glucocorticoids (Walker, Perrin, Vale, & Rivier, 1986; Walker et al., 1991; Witek–Janusek, 1988). In fact, this period may be necessary for normal brain development in rodents (Gould, Woolley, Cameron, Daniels, & McEwen, 1991; Gould, Woolley, & McEwen, 1991). Accumulating evidence from preclinical studies supports the thesis that while recruitment of the neuroendocrine stress response is adaptive and even essential to survival in adulthood, it can cause immediate and persistent alterations in neuroendocrine functioning in the neonate. Since a major factor maintaining the quiescence of the preweaning rat pup HPA axis appears to be contact with the mother, especially licking and grooming (Suchecki, Mozaffarian, Gross, Rosenfeld, & Levine, 1993; Van Oers, de Kloet, Whelan, & Levine, 1998; Van Oers, de Kloet, & Levine, 1999), an effective method of investigating the effects of early stress on the developing HPA axis has been to preface acute stressors with varied periods of single or repeated maternal separation.

Several groups have examined the acute and persistent developmental effects of a single 24-hr period of maternal separation (Eghbal–Ahmadi, Avishai–Eliner, Hatalski, & Baram, 1999; Pihoker, Owens, Kuhn, Schanberg, & Nemeroff, 1993; Sutanto, Rosenfeld, de Kloet, & Levine, 1996; Van Oers, de Kloet, & Levine, 1998, 1999). The persistent effects of 24-hr maternal separation on HPA axis activity appear to be dependent on the age at which maternal separation occurs. Animals separated on PND3 and PND11 are hyper- and hyporesponsive to stress, respectively, when tested just prior to weaning on PND20, while animals separated on PND7 were relatively unaffected when tested on PND20 (Van Oers, de Kloet, & Levine, 1998, 1999). Measures in these experiments included hypothalamic CRF and c-*fos* mRNA, as well as plasma ACTH responses to acute saline injection. These investigators have offered several hypotheses accounting for this apparent age of exposure dependence. They have postulated that maternal behavior toward pups varies with age and that the absence of specific time-dependent maternal cues alters HPA axis functioning both acutely and persis-

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tently (Van Oers, de Kloet, & Levine, 1999). Alternatively, these authors postulate that maternal separation may "alter the density or 'synaptic weight' of specific inputs to the PVN" according to the age at which it is experienced (Van Oers, de Kloet, & Levine, 1998, p. 249). Finally, reactive negative feedback could restrain the HPA axis more effectively in older pups exposed to maternal separation (Van Oers, 1998).

A major task remaining is to determine those factors that underlie the marked changes in HPA axis functioning following a single 24-hr period of maternal separation. Given that pups are exposed to elevated glucocorticoids for at least 16 hr during the separation procedure (Stanton, Gutierrez, & Levine, 1988; Van Oers, de Kloet, Whelan, & Levine, 1998), coupled with the inherent plasticity of central corticosteroid receptors (de Kloet et al., 1998), the most obvious hypothesis is that LHPA alterations are secondary to prolonged glucocorticoid exposure during the separation procedure. However, it has recently been demonstrated that these HPA axis changes are independent of the separation-induced corticosterone response and are instead associated with the absence of maternal care (Van Oers, de Kloet, Whelan, & Levine, 1998; Van Oers, de Kloet, & Levine, 1999). Remarkably, all of the HPA axis changes noted above, both immediate (Van Oers, de Kloet, Whelan, & Levine, 1998) and persistent (Van Oers, de Kloet, & Levine, 1999), can be prevented by mimicking behaviors associated with nursing in the infant rat, especially stroking of the anogenital region or feeding. Anogenital stroking with a fine, moistened brush for approximately three 45-s sessions simulates maternal licking of this region and stimulates the micturition reflex. That a series of such short manipulations can prevent activation of parvocellular PVN neurons during this prolonged period of maternal separation is truly remarkable. Furthermore, these data suggest the involvement of viscerosensory and somatosensory pathways associated with suckling behavior, licking and grooming, and the micturition reflex in the development of the LHPA axis in the rat (Van Oers, de Kloet, Whelan, & Levine, 1998).

Only a few studies have examined the long-term effects of a single 24-hr maternal separation experience on HPA axis function and behavior. It is worth noting that the persistence of effects from this model is variable. Rots and colleagues (Rots, De Yong, Workel, Levine, Cool, & de Kloet, 1996) found that 24-hr maternal separation on PND3 was associated with reduced PVN CRF mRNA, while basal plasma ACTH and corticosterone concentrations were significantly elevated on PND60 as compared to nonhandled rats. No differences in hippocampal GR or MR mRNA were noted, although GR mRNA levels in the PVN and anterior pituitary were reduced. The separated rats also showed enhanced apomorphine-induced stereotypic gnawing behavior. When hippocampal cytosolic GR binding was assessed at PND48 in rats exposed to 24-hr maternal separation on PND3 followed by saline or ACTH1-21 injection, a gender and treatment specific effect was observed (Sutanto et al., 1996). In the male rats, separation resulted in a reduction of GR and MR binding, while separation plus ACTH only reduced GR binding as compared to nonhandled rats. In female rats, separation plus saline or ACTH injection increased GR binding saline without effect on MR binding. In another study, Morris water maze acquisition and reversal learning trials (for assessment of learning and perseveration, respectively) were performed on 3-, 12-, 24-, and 30- to 32-month-old Brown Norway rats exposed to 24-hr maternal separation on PND3 (Oitzl, Workel, Fluttert, Frosch, & de Kloet, 2000). The general conclusions of this study were that (a) the mean performance of senescent rats in the water maze did not differ between the groups, while the individual performance was strikingly different within each group; (b) senescent deprived rats were either nonimpaired or impaired with only a few animals showing an intermediate performance; (c) approximately 40% of animals are resistant to the effect of maternal deprivation; (d) maternal deprivation has long-term consequences for behavior culminating at senescence in amplification of individual differences rather than in a generalized deterioration of cognitive function. In our own studies using 24-hr maternal separation applied on PND3, we found that approximately 20% of adult animals displayed HPA

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axis hyperresponsivity as compared to either nonhandled or animal facility reared (AFR) animals when tested with a mild psychological stressor at PND90 (P. M. Plotsky, unpublished observations). Furthermore, few of these separated animals exhibited dexamethasone feedback resistance and even fewer showed increased anxiety-like behavior in either the elevated plus maze or in a novel open field test. Thus, the majority of effects in this model appear to be confined to a several week period immediately following the date of 24-hr maternal separation.

Long-term consequences of repeated 3-hr neonatal maternal separation in rats

Currently, the most well characterized model of the long-term consequences of adverse early experience has been obtained from studies of Long Evans hooded rats exposed to brief handling and neonatal maternal separation for 180 min/day (HMS180) on PND2-14 as compared to either briefly handled rats separated for 15 min on each day from PND2-14, or to AFR rats. This model, an adaptation of that developed by Levine and colleagues (see below), is based the observation that dams often leave the nest to forage for 15- 30-min periods (Calhoun, 1962; Jans & Woodside, 1990; Leon, Croskerry, & Smith, 1978), although low-ranking females may have to forage for up to 2–3 hr. These manipulations are performed between 8:00 and 12:00 each morning, with the pups removed to an incubator and the dams removed to an adjacent cage. Beginning on Day 15, pups are reared normally with weaning at PND21 and testing beginning after PND60.

It is important to note that neonatal rat pups are almost entirely dependent upon their mothers for thermoregulation, nutrition, stimulation of micturition, and protection for at least the first 10 days of life. Furthermore, as far as can be determined, brain development in rat pups at birth is roughly equivalent to a human gestational age of 23–24 weeks (Plotsky, Bradley, & Anand, 2000).

Measurements of maternal behavior upon reunion, as well as of maternal and pup pituitary–adrenal hormone levels, has been revealing. Upon reunion of the dams with her pups, the HMS180 dams displayed a delay in retrieving pups to the nest as well as to initiation of licking, grooming, and nursing relative to HMS15 or AFR dams (Huot, Smith, & Plotsky, 1997). No significant elevations in maternal ACTH or corticosterone were observed in dams of the HMS15 or HMS180 litters during either the period of separation or following reunion with their pups. In contrast, pups in the HMS180 litters displayed elevations in circulating ACTH and corticosterone within 5 min of reunion with their dams that appeared to be derived from the pup pituitary–adrenal system rather than from the dam via transfer through the milk (Huot, Smith, & Plotsky, 1997). The apparent disruption of maternal behavior in the HMS180 groups is reminiscent of previous observations of an inverse correlation between maternal licking and grooming behavior and adult pituitary–adrenal responsiveness or PVN levels of CRF mRNA (Caldji, Diorio, & Meaney, 2000; Liu, Tannenbaum, Caldji, Francis, Freedman, Sharma, Pearson, Plotsky, & Meaney, 1997). These observations support the maternal-mediation hypothesis (Denenberg, 1964). In short, it appears that the quality of maternal behavior encountered upon reunion plays a significant role in determining individual differences in stress responsiveness of the progeny. However, what appears as disrupted maternal behavior may indeed be the dam's adaptive attempt to find a safe location to which to move her nest and pups after they had been disturbed. Finally, it must be stressed that in other species and, perhaps, even in rodents, social buffering may play an important role in moderating the outcome of adverse experiences. Maternal behavior can be normalized by providing the dams with an age- and gender-matched litter during the period of separation. Furthermore, cross-fostering studies demonstrate the importance of maternal behavior as a regulator of the development of regulatory systems in their pups.

Long-term alterations in HPA axis function and behavior have been recently reviewed (Caldji et al., 2001; Ladd et al., 2000). Offspring exposed to neonatal maternal separation exhibited hyperresponsiveness to psy-

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chological stressors as compared to AFR or HMS15 progeny when tested as adults (after PND60). For instance, when adults that had been exposed to different rearing conditions were exposed to the mild stressor of airpuff startle, the HMS180 animals displayed a 2- to 3-fold increase in ACTH and corticosterone secretion, as well as a delayed shutoff of secretion of these hormones, as compared to AFR or HMS15 rats. The adult HMS180 animals exhibited resistance to glucocorticoid-mediated negative feedback as evident from the inability of dexamethasone administration at noon to inhibit the circadian elevation of endogenous corticosterone at 7:00 and 8:00 PM. In contrast to the 24-hr separation model, no rearing differences were found in adrenal sensitivity to ACTH, corticosterone metabolism, serum concentrations of corticosterone binding globulin, or pituitary sensitivity to CRF and AVP. Of particular noteworthiness is the observation that this pattern of HPA axis hyperresponsiveness persists for the remainder of these animals' lives. Behaviorally, the HMS180 progeny exhibit increased anxiety-like behavior, development of a depression-like syndrome, anhedonia, and a proclivity for increased ethanol intake.

While we have not undertaken a comprehensive ontogenetic study of the development of HPA axis hyperresponsiveness in these rats, we have observed enhanced ACTH and corticosterone responses to stressors (e.g., restraint, cat odor) by PND14 in the HMS180 pups versus HMS15 or AFR pups. Underlying these neuroendocrine outcomes are changes in the characteristics and function of multiple neurocircuits, including the CRF, norepinephrine (NE), and gamma-aminobutyric acid (GABA) systems. The neuroendocrine changes were associated with (a) up-regulation of CRF gene expression in the hypothalamic PVN with a consequent increase in CRF peptide content in terminal fields of these neurons located in the median eminence, (b) a 33% down-regulation of CRF receptor binding in the anterior pituitary gland, (c) 40–50% down-regulation of hippocampal GR binding and mRNA levels as well as up-regulation of hippocampal MR binding and mRNA levels, and (d) decreased GR mRNA expression in the medial prefrontal cortex (Caldji et al., 2001; Ladd et al., 2000; Liu et al., 1997; Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji, Sharma, Seckl, & Plotsky, 1996; Plotsky & Meaney, 1993).

In association with increased anxiety-like behavior, hypervigilance, development of a preference for ethanol, anhedonia, and mild cognitive impairment, we—and others—found (a) up-regulation of CRF gene expression in the BNST and the central nucleus of the amygdala (CeA) with a consequent increase in CRF peptide content in terminal fields of these neurons, (b) decreased GR mRNA expression in the medial prefrontal cortex, (c) increased expression of tyrosine hydroxylase mRNA in the locus coeruleus, (d) increased basal and stress-induced norepinephrine release in LC terminal fields, (e) down-regulation of alpha-2 adrenergic receptors in the locus coeruleus, (f) alterations in electrophysiological characteristics of the locus coeruleus and the ventral tegmental area, (g) changes in GABA/benzodiazepine receptor binding as well as in receptor subunit composition in selected brain regions, (h) reduced mossy fiber density, and (i) reductions in oxytocin receptor binding in the basomedial nucleus of the amygdala (Caldji, Diorio, & Meaney, 2000; Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Cirulli, Alleva, Antonelli, & Aloe, 2000; Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Huot, Thrivikraman, Meaney, & Plotsky, 2001; Ladd et al., 2000; Liu, Caldji, Sharma, Plotsky, & Meaney, 2000).

HMS180 rearing was also associated with a 4-fold increase in CRF_1 receptor binding in the PVN and the Pen-LC and a robust decrease in the frontal, parietal, and piriform cortices, as well as in the basolateral amygdala (Ladd, Huot, Thrivikraman, & Plotsky, 1998, 1999). This opposing effect on CRF receptors in PVN and LC versus cortex and amygdala is interesting. Cortical and amygdala CRF_1 receptor binding could be down regulated by increased CRF release in these areas. In the PVN, CRF_1 receptor expression is virtually undetectable under basal conditions but increases dramatically following chronic stress (Makino et al., 1995). Alter-

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ations in the normal developmental patterns of CRF receptor expression following maternal separation could explain these opposite effects, as it has been reported that CRF receptors are expressed in a distinct pattern in the neonate compared to the adult (Avishai–Eliner, Yi, & Baram, 1996). It should be noted that the CRF_1 receptor up-regulation in the LC and PVN would potentially be able to sensitize these regions to extracellular CRF, which may already be elevated in these terminal fields. These observations support our hypothesis that one primary consequence of maternal separation in the HMS180 animals would be the enhanced CRF neurotransmission within and from the amygdala: in the PVN, CeA, and LC, providing evidence that the neurocircuits connecting these three regions are sensitive to the effects of early experience.

Overall, animals experiencing 3 hr of daily maternal separation on PND2-14 displayed a fundamental reorganization of neurocircuits involved in neuroendocrine regulation (hypothalamic PVN, hippocampus, frontal cortex), regulation of arousal and vigilance behavior (LC), regulation of autonomic nervous system tone (LC, nucleus of the solitary tract), and regulation of fear- or contextual-conditioning (CeA, BNST). Alterations in other cortical and dopaminergic circuits, perhaps correlating with anhedonia, are also apparent in these animals, although these changes remain less well defined at the current time. Interestingly, Stout, Mortas, Owens, Nemeroff, and Moreau (2000) recently reported elevations of CRF mRNA in the CeA of anhedonic rats, while Weiss and colleagues reported increased CRF release in this area under conditions of noxious stimuli and drug withdrawal (Pich, Lorang, Yeganeh, Rodriguez de Fonseca, Raber, Koob, & Weiss, 1995; Richter & Weiss, 1999). Neither the precise factors mediating these changes nor the order of the cascade of changes has yet been determined. Unraveling this cascade may have profound implications for our understanding of factors involved in organizing coping ability, stress responsiveness, and of factors determining health and disease.

Studies in our laboratory have demonstrated multiple methods for ameliorating the effects of these changes associated with adverse early experience. Gonzalez, Ladd, Huot, Owens, and Plotsky (1999) have shown that providing an age-matched foster litter to dams while their own pups were separated prevented the development of a "separation phenotype" in terms of behavior, neuroendocrine changes, and CNS changes. Similarly, cross-fostering of pups subjected to HMS180 conditions to dams whose pups were only separated for 15 min prevented development of the "separation phenotype," while fostering HMS15 pups to dams whose pups were separated for 180 min yielded progeny appearing to have experienced maternal separation. In addition, treatment of adult offspring expressing the "maternal separation phenotype" with antidepressants such as the serotonin reuptake inhibitor paroxetine or the norepinephrine reuptake inhibitor reboxetine for 21–28 days reversed most aspects of neonatal maternal separation (Huot, Thrivikraman, Meaney, & Plotsky, 2001; Ladd et al., 1999, 2000; Plotsky, Ladd, Huot, Thrivikraman, & Nemeroff, 1997). However, these pharmacological treatment effects were transient, with "symptoms" returning within 10–14 days after cessation of treatment. These observations suggest opportunities for early intervention as well as later treatment.

The diathesis–stress model postulates the interaction between a genetic predisposition and adverse life events in the genesis of mood disorders. Not only is there a significant correlation between environmental stress and the subsequent onset of an affective episode (Ambelas, 1987; Anisman & Zacharko, 1982; Brown, Bifulco, & Harris, 1987; Dunner, Patrick, & Fieve, 1979), but considerable research suggests that adverse early experience or exposure to major trauma are precipitating factors as well (Francis, Caldji, et al., 1999; Heim et al., 1997; Kendler et al., 1993).

Although several theories regarding the primary pathophysiology of depression have been postulated, much recent research has focused on theories citing dysregulation of the central glucocorticoid receptor (Holsboer, Grasser, Friess, & Wiedmann, 1994; Holsboer, Lauer, Schreiber, & Krieg, 1995) or

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CRF (Heit, Owens, Plotsky, & Nemeroff, 1997; Nemeroff, 1996) systems. The etiology of depression and the neurochemical adaptations associated with it have been difficult to determine for lack of appropriate laboratory animal models (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen, & Kendler, 1994). On the basis of preclinical research with early adverse experience, we believe that the neonatal maternally separated rat provides an initial model of depressive-like syndrome meeting most criteria. These animals exhibit dysregulation of the HPA axis similar to that observed in a subset of depressed patients, including increased CRF expression (Caldji et al., 2001; Heit et al., 1997; Ladd et al., 2000) and cortical CRF receptor down-regulation (Ladd et al., 1998; Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988), decreased corticotrope CRF receptor signaling (Amsterdam, Maislin, Winokur, Berwish, Kling, & Gold, 1987; Amsterdam, Maislin, Winokur, Kling, & Gold, 1998; Ladd, Owens, & Nemeroff, 1996), dexamethasone resistance (Evans, Burnett, & Nemeroff, 1983a, 1999b; Ladd et al., 1998, 2000), enhanced anxiety-like behavior (Caldji et al., 2000), and anhedonia (Ladd et al., 2000). Many of the symptoms observed in major depressive disorder and in animal models can be elicited in normal rats by central administration of CRF (Heinrichs et al., 1995; Holsboer, 1999). Importantly, many of the neurocircuits postulated to mediate the pathophysiology observed in major depressive disorder exhibit stable changes in function in the adult HMS180 animal, and various classes of antidepressants, when administered to adults for at least 21 days, at least temporarily normalize these systems (for reviews, see Ladd et al., 2000, and Caldji et al., 2001).

Fitting the jigsaw puzzle together into a coherent vulnerability model

Numerous groups have identified neurocircuits linking CRF-expressing systems with brain stem noradrenergic and serotonergic circuits (Kirby, Rice, & Valentino, 2000; Koob, 1999; Pavcovich, Yang, Miselis, & Valentino, 1998; Valentino et al., 1998; Van Bockstaele, Peoples, & Valentino, 1999). Recently, Baram and colleagues (Eghbal–Ahmadi et al., 1999) outlined a putative CRF dependent neuronal circuit relaying sensory cues associated with feeding, grooming, and micturition to limbic and hypothalamic nuclei. At the heart of this neurocircuit is the amygdaloid complex, including the basomedial nucleus, central nucleus, and medial nucleus. Somatosensory cues associated with licking and grooming and with suckling behavior may reach the central nucleus of the amygdala via pedunculopontine and lateral dorsal tegmental nuclei, acetylcholine-containing cell groups receiving substantial somatosensory inputs from the spinal cord. Alternatively, the CeA may receive integrated sensory information from the medial amygdala, which contains a subset of CRF neurons and projects to the CeA, basomedial amygdala, and paraventricular thalamus. Viscerosensory cues associated with micturition are relayed via the nucleus of the solitary tract to Barrington's nucleus, the micturition center that expresses CRF abundantly and projects monosynaptically to the thalamic PVN. The CeA and paraventricular thalamus relay sensory and micturition information, respectively, to the basomedial amygdala, a putative sensory integration center that projects to hypothalamic and medullary nuclei either directly or back through the CeA.

Baram's group postulated that following grooming- or handling-induced micturition, the paraventricular thalamus is activated by CRF pathways from Barrington's nucleus (Eghbal–Ahmadi et al., 1999). Subsequent activation of paraventricular thalamus efferents to the CeA might increase CRF stimulation of the VMH and basomedial amygdala. We further hypothesize that separation-induced activation of the CeA through these pathways enhances HPA activity and fearful behavior via CRF efferents to the PVN and LC (Pihoker et al., 1993). As a central site of CRF neurocircuitry that mediates both the autonomic and behavioral responses to stress, the CeA is in a unique position to coordinate the complex array of maternal separation effects on extrahypothalamic CRF systems and HPA axis reactivity. Furthermore, expression of CRF mRNA (Keegan, Herman, Karolyi,

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O'Shea, Camper, & Seasholtz, 1994) and translation of CRF_1 receptor mRNA (Avishai–Eliner, Yi, & Baram, 1996; Insel, Battoglia, Fairbanks, & De Souza, 1988) appears to be delayed in the amygdala, allowing a developmental window of plasticity in CRF neurotransmission within this limbic structure. Finally, expression of both CRF (Pihoker et al., 1993) and its receptors (Hatalski, Guirguis, & Baram, 1998) in the amygdala are sensitive to separation stress in the neonate. Reviewing this collection of data, we postulate that amygdala CRF neurocircuits are a primary target of maternal separation, which we believe alters activity-dependent CRF synaptic development between the amygdala and the PVN, LC, frontal cortex, and hippocampus, ultimately causing dysregulation of the behavioral and neurendocrine stress response.

Another postulated site of separation-induced neuroendocrine dysregulation is the glucocorticoid inhibitory system, which causes a decrease in regional corticosteroid receptor expression that leads to impaired glucocorticoid feedback and subsequent enhancement of HPA activity. Meaney's group has postulated a cascade by which handling alters neonatal serotonin release in the hippocampal region, thus altering GR expression (Meaney, Diorio, Francis, Larocque, O'Donnell, Smythe, Sharma, & Tannenbaum, 1994; Meaney, Diorio, Francis, Weaver, Yau, Chapman, & Seckl, 2000; Meaney, Viau, Bhatnagar, Betito, Iny, O'Donnell, & Mitchell, 1991; Mitchell, Betito, Rowe, Boksa, & Meaney, 1992; Mitchell, Iny, & Meaney, 1990; Smythe, Rowe, & Meaney, 1994). Corticosterone-induced upregulation of CRF expression in the CeA and BNST may further enhance neuroendocrine stress responsiveness, initiating a self-perpetuating cascade of events that has been postulated to underlie not only the maternal separation phenotype but also major depressive episodes (Holsboer et al., 1994, 1995).

Other possible targets include descending corticolimbic and ascending noradrenergic hypothalamic afferents, pathways activated by processive stimuli. Compared to pathways activated by systemic stressors, these hypothalamic afferents appear immature in the preweaning rat and may be responsible for the stressor specificity observed during the SHRP. Interestingly, it is these immature pathways that appear to be sensitized both immediately following and several months after maternal separation. Thus, it is plausible that the "synaptic weight" of these developing hypothalamic afferents is increased as a consequence of decreased maternal sensory cues relayed through the specific amygdaloid nuclei mentioned above (Van Oers, de Kloet, & Levine, 1998). This hypothesis is supported by the observed increase in noradrenergic drive of the HPA axis in maternally separated adult rats (Liu et al., 2000).

Finally, we postulate that insufficient GABAergic inhibitory tone on the aforementioned excitatory neurocircuits (CRF, noradrenergic) may precede these changes in the maternally separated rat (Caldji et al., 2000). Specifically, we believe that reduced GABA–benzodiazepine receptor activation in the amygdala–BNST complex or brain stem noradrenergic nuclei fails to properly inhibit ascending noradrenergic hypothalamic afferents.

A synthesis of these postulates, presented in Figure 2, is that removal of maternal cues associated with feeding and grooming disinhibits ascending pathways relaying somatosensory information to amygdala nuclei and PVN by reducing GABAergic inhibitory tone in the LC and nucleus of the solitary tract. Subsequently, CRF synthesis within the CeA and PVN is increased, as is CRF neurotransmission between amygdala efferents and the LC, nucleus of the solitary tract, PVN, and BNST, all nuclei involved in the collective neuroendocrine stress response. Ascending noradrenergic and descending corticolimbic hypothalamic afferents, coursing through the amygdala–BNST complex, are sensitized to processive stimuli by a combination of decreased inhibitory GABAergic tone and enhanced facilitatory modulation by CRF. Simultaneous reduction of hippocampal and cortical corticosteroid receptor expression further enhances CRF expression in the PVN and subsequent HPA activation. The resulting increase in glucocorticoid load may further increase CRF expression in the CeA and BNST, perpetuating fearful states and stress hyperre-

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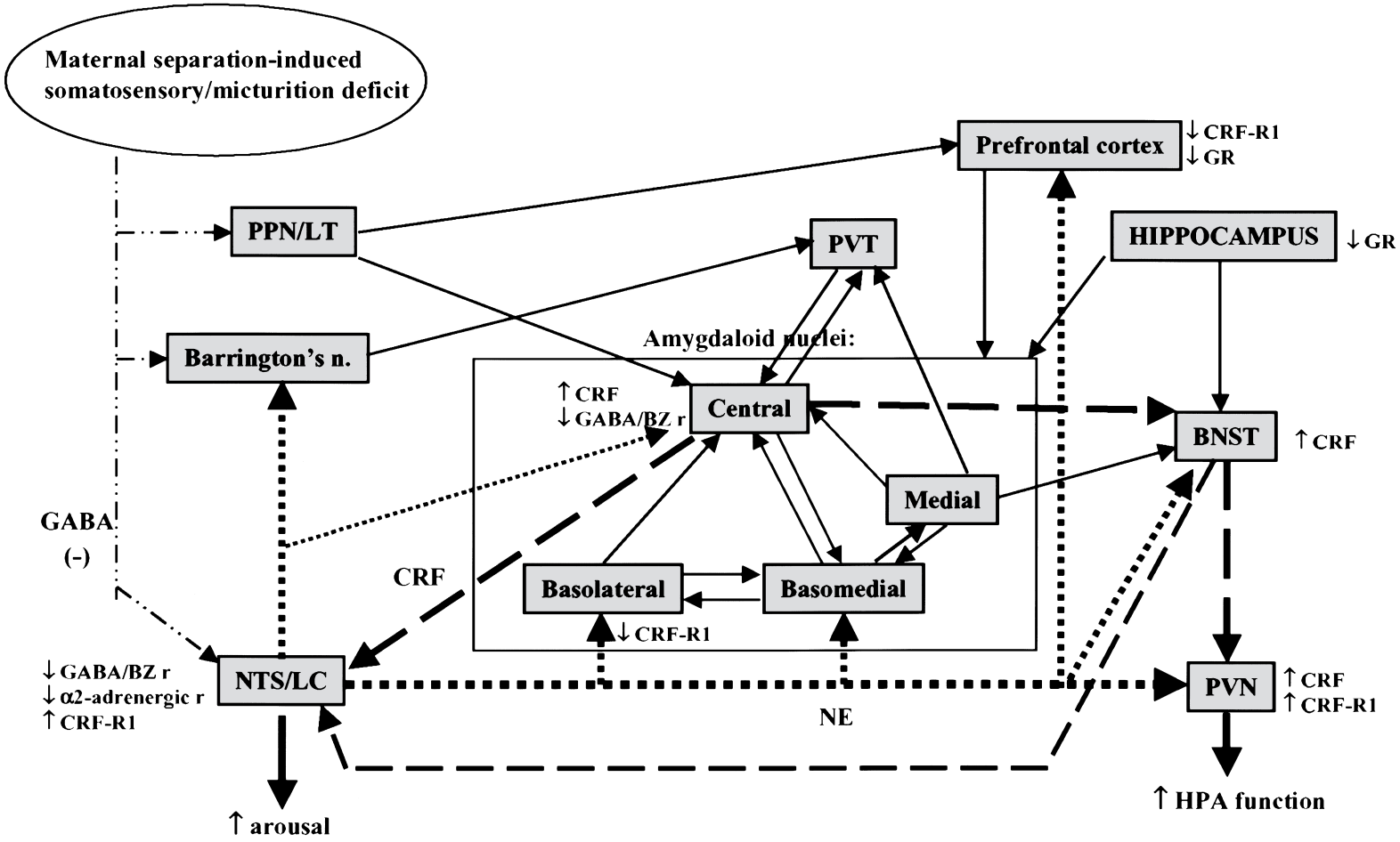


Figure 1. See caption on following page.

sponsiveness. These collective changes result in a robust increase in the neuroendocrine stress response that is present immediately following separation and persists well into adulthood.

Early Weaning Followed by Social Isolation: Opposite Effects On HPA Function When the Early Adverse Experience Takes Place at Different Developmental Times

The development of the LHPA axis in the rat is regulated by factors of maternal origin but is also dependent on social interactions with littermates (Rosenfeld, Suchecki, & Levine, 1992; Stanton, Gutierrez, & Levine, 1988; Suchecki, Rosenfeld, & Levine, 1993). Thus, acute episodes of maternal deprivation and separation from littermates during the preweaning period, when the PVN-stimulating pathways are in a developing stage (Stanton, Gutierrez, & Levine, 1988; Vazquez & Akil, 1992), produce alterations in HPA activity of rat pups (Stanton, Gutierrez, & Levine, 1988; Hennessy & Weinberg, 1990). The long-term effects of prolonged social deprivation after an early weaning (at PND15-16) on the adult rat HPA function, however, are different from those of repeated brief periods of maternal separation. Whereas the early weaning and isolation also results in a behaviorally hyperreactive adult, more aggressive and anxious than the control animal, it provokes a hypofunctional LHPA axis, which includes low basal plasma corticosterone levels but is particularly evident in response to acute stress (Sánchez, Aguado, Sánchez–Toscano, & Saphier, 1998), which is in sharp contrast with the hyperresponsive adult HPA axis of animals that experienced daily maternal separation from either PND2-14 (Plotsky & Meaney, 1993) or PND2-20 (Ladd, Owens, & Nemeroff, 1996). The neuroendocrine alterations found in the early weaned and deprived animals have been related to the reduced activity detected by electrophysiology in specific limbic–hypothalamic pathways, particularly from the medial amygdala to BNST–medial preoptic area and then to the PVN (Sánchez, Aguado, Sánchez–Toscano, & Saphier, 1995). Interestingly, this pathway from amygdala to BNST to PVN, which is involved in the control of the neuroendocrine response to psychogenic stress and becomes "hyporesponsive" in the early weaned and deprived animals, also appeared to be altered in the animals exposed to a few hours of daily maternal separation described above, but in this case it became "hyperresponsive." This interesting "inconsistency" between long-term neuroendocrine, but sometimes also behavioral, effects of different postnatal manipulations, such as maternal separation, has been discussed recently (Lehmann & Feldon, 2000). The developmental "state" of the LHPA system at the mo-

Figure 2. A schematic diagram of acute and persistent central changes in response to neonatal maternal separation in rats. Sensory deprivation associated with suckling or grooming may disinhibit ascending noradrenergic facilitatory hypothalamic and amygdala afferents by reducing the GABAergic tone in the NTS and LC (dashed lines). Enhanced noradrenergic drive of the amygdaloid complex and PVN would lead to elevated CRF expression in the central nucleus of the amygdala, BNST, and PVN and modulation of regional CRF receptor expression. Following sensory deprivation, the GABAergic tone may also be impaired in the micturition circuit or PPN/LTN cholinergic projections to the amygdala. Simultaneous reduction of GR expression in the hippocampus and frontal cortex could enhance HPA activity, thus perpetuating the altered extrahypothalamic expression of CRF via elevated glucocorticoid exposure. As a result, corticolimbic and ascending hypothalamic afferents relaying emotional and sensory stimuli, respectively, could be persistently sensitized to subsequent stimuli, leading to enhanced HPA axis, behavioral, and autonomic responses to psychological stressors. The full complexity of the connectivity is not represented in order to achieve clarity. See text for further details. The dashed lines represent the CRF overactive pathways, and the dotted lines represent the NE overactive pathways. BNST, bed nucleus of the stria terminalis; NTS, nucleus of the solitary tract; LC, locus coeruleus; PPN/LT, pedunculopontine nucleus/lateral tegmental area; PVN, hypothalamic paraventricular nucleus; PVT, thalamic paraventricular nucleus.

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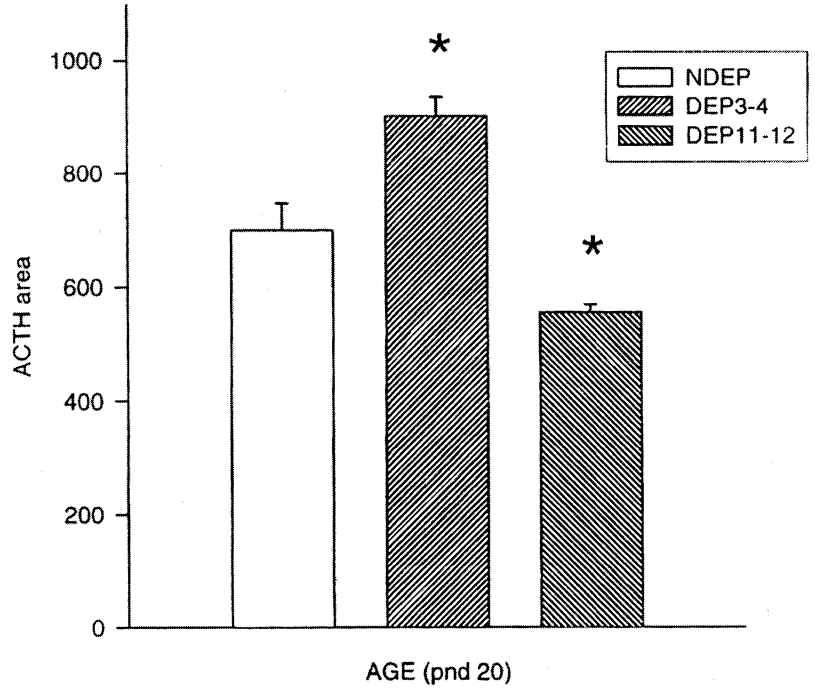


Figure 3. Integrated ACTH responses (area under the curve) to a mild stress in the 20-day-old animals deprived either at PND3-4 (DEP3-4) or at PND11-12 (DEP11-12), in comparison to control nondeprived animals (NDEP). *Note:* From "Early vs. Late Maternal Deprivation Differentially Alters the Endocrine and Hypothalamic Responses to Stress," by H. J. J. Van Oers, E. R. de Kloet, and S. Levine, 1998, *Developmental Brain Research, 111,* p. 249. Copyright 1998 by Elsevier Science. Reprinted with permission.

ment of the insult could be a factor determining the opposite effects of different early disruptions of maternal or social bonds on the functionality of the adult system. For example, 24 hr of maternal separation at PND3 results in increased levels of plasma ACTH and CORT in adulthood (Rots et al., 1996), as well as in increased ACTH response to stress at PND20 and PND30, in parallel to elevated levels of mineralocorticoid receptor in the hippocampus, whereas separation at PND11 has the opposite effect: a blunted ACTH response to stress and a down-regulation of GR mRNA in the hippocampus at 20 and 30 days of age (Van Oers, de Kloet, & Levine, 1998), as summarized in Figure 3. In summary, although the long-term outcomes can be different (even opposite) depending on the developmental state of the LHPA axis at the time of the insult or trauma, on the duration and frequency of the insult, as well as on the level of maternal–social and sensorial deprivation, all the models described above indicate the importance of the primary caregiver and social environment as factors regulating the development of the LHPA system in the rat pup. Therefore, the experience of trauma early in life results in behavioral and emotional alterations, as well as in the dysregulation of the adult LHPA function.

Early Adverse Experience as a Risk Factor for the Development of Psychopathology: Evidence From Primate Models

The Old World rhesus monkey (*Macaca mulatta*) is the primate species most frequently used to study the developmental effects of the early social environment. The rhesus monkey is native to northern and central India. It lives in a wide variety of habitats, from forests to large cities, adapting successfully to different complex environments. Rhesus monkeys are

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highly social animals, living in troops with moderately stable social organization and clear dominance hierarchies. Apart from the relative physical maturity of the rhesus infant at birth (e.g., at the age of 2 or 3 days an infant rhesus monkey can locomote), a difference between the early development of infant humans and rhesus monkeys is the amount of physical contact between mother and neonate (Seay & Gottfried, 1975). The macaque infant remains closely attached to the mother's ventral surface almost constantly for several weeks and it sleeps in close ventral contact with the mother for nearly a year, when weaning occurs. Apart from warmth and nutrition, the mother provides the infant with a sense of security and reassuring comfort, training her young to understand social clues (facial expressions, vocalizations) and proper ways to interact with other members of the group, including the regulation of early play with peers (Mears & Harlow, 1975), which will help the youth to develop important relationships with conspecifics, as well as sensory–motor coordination and social skills. Therefore, for the infant primate, the primary social relationship is between the mother and infant. Another function of this relationship appears to be to enable the infant to control and modulate its physiological and behavioral responses to stress and its arousal levels by means of maintaining contact and proximity to the mother. Along with the social interactions, a developing primate maintains an intimate and ongoing relationship with its daily environment, which provides with sensory stimulation and motor experiences that are crucial for the proper development and correct wiring of the primate's neural circuitry (Hubel, Wiesel, & LeVay, 1976). If any of these important relationships are disrupted, the long-term consequences are dramatic.

The closest model of human child maltreatment—and, therefore, for the effects of this kind of early adverse experience on the normal development—is the spontaneous occurrence of infant physical abuse and neglect among nonhuman primates. Apart from the clear risk of injuries and death, child maltreatment can have multiple short- and long-term consequences, such as insecure attachment with caregivers, difficulties in peer relations, cognitive delay, and even alterations in the neuroendocrine responsiveness to stress in parallel with depressive symptoms, as well as conduct disorders and drug abuse (Cicchetti & Toth, 1995; Hart, Gunnar, & Cicchetti, 1995, 1996). Within large social groups of rhesus monkeys and pigtail macaques, 2–10% of the infants born are subjected to physical abuse or neglect by their mothers (Maestripieri, 1999). Examples of infant physical abuse in monkeys include violent behaviors such as hitting, biting, dragging the infant on the ground by the tail or legs, and throwing or stepping on it (Troisi & D'Amato, 1983; Troisi, D'Amato, Fuccillo, & Scucchi, 1982). The fact that abuse is more likely to occur within certain families of rhesus monkeys, pigtail macaques (*M. nemestrina*), and sooty mangabeys (*Cercocebus atys;* Maestripieri & Carroll, 1998; Maestripieri, Wallen, & Carroll, 1997a, 1997b) suggests that infant abuse "traits" can be transmitted along the maternal line for generations. However, it is not clear if this transmission is due to heritability in temperament characterized by the anxiety, impulsivity, and low threshold for aggression that have been related to low serotonergic function (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Higley, King, Hasert, Champoux, Suomi, & Linnoila, 1996; Higley, Mehlman, Higley, Fernald, Vickers, Lindell, Taub, Suomi, & Linnoila, 1996), or to repetition of learned behaviors. Although a very interesting model of child maltreatment, the developmental effects of such early adverse experiences on the nonhuman primate have not yet been characterized.

The imposition of stringent and, sometimes, unpredictable foraging demands has also been studied as a paradigm to disturb the normal social and maternal behavior of bonnet macaques (*M. radiata*). Interestingly, animals confronted with a variable foraging demand (VFD; i.e., unpredictable alternation of periods of strenuous foraging with others in which free access to food is provided) had the most profound effects on the mothers and their infants, suggesting that *unpredictability* may represent an important factor in the out-

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comes. The VFD manipulation altered the social behavior of females and also reduced the amount of time they respond to infant solicitations for contact and attention, thus resulting in insecure patterns of attachment behavior (Rosenblum & Andrews, 1994). Although VFD allowed for apparently normal physical and social development of the offspring, as they matured they became less socially competent, more fearful, and hyperresponsive to stressful stimuli (both behaviorally and physiologically). In addition, the animals exhibited persistent alterations in CSF levels of CRF, somatostatin, and biogenic amines (Coplan et al., 1996; Coplan, Trost, Owens, Cooper, Gorman, Nemeroff, & Rosenblum, 1998), as well as a reduced growth hormone response to the alpha-adrenergic agonist clonidine, which is inversely correlated with the increases observed in CRF CNS activity (Coplan, Smith, Trost, Scharf, Altemus, Bjornson, Owens, Gorman, Nemeroff, & Rosenblum, 2000) and is sometimes observed in mood and anxiety disorders.

As described above for the rodent, the early separation from the mother and conspecifics has been the manipulation most widely used to study how early adverse experiences increase the vulnerability for later psycho- and physiopathology on the nonhuman primate. Monkey and human infants exhibit similarities in their reaction to episodes of maternal separation. The rhesus infant's initial reaction to maternal separation consists of "protest," characterized by increased activity and vocalization, and physiological reactions such as defecation (Harlow, Harlow, & Suomi, 1971) and increased HPA function (Bayart, Hayashi, Faull, Barchas, & Levine, 1990). The ethological value of this "protest phase" consists of increasing the probability that the mother finds the infant; if this does not happen, however, the calls can attract predators and deplete the infant's physiological resources (Kraemer, 1992). Therefore, the infants settle down after 1 or 2 days, but their activities levels are then reduced and they do not exhibit interest in playing with other infants; shortly after, they exhibit "despair-like" behavior. This "despair phase" actually allows the infant to conserve energy and survive as long as possible under usually hostile conditions. Pigtail macaques respond even more intensely to maternal separation than rhesus monkeys (Kaufman & Rosenblum, 1967), pointing out species-specific differences in macaque social behavior. After reunion with the mother, the intensification of the mother–infant relationship is evident for days or even months.

New World infant squirrel monkeys (*Saimiri sciureus*) also respond to maternal separation with an increase in distress vocalizations and elevations in plasma levels of cortisol, suggesting that this is a common response in both Old and New World monkeys. The magnitude of the infant plasma cortisol elevations is directly proportional to the time separated from the mother, although in comparison to the Old World monkey the cortisol response to separation does not appear to habituate in this species (Levine, 1993). Following reunion, the infant spends most of the time in direct contact with the mother or in very close proximity. Reunion seems to terminate the cortisol response. Interestingly, there seems to be no systematic relationship between distress vocalizations and the hormonal response to separation, suggesting that the behavioral and endocrine responses to maternal separation are controlled by independent neural mechanisms (Wiener, Coe, & Levine, 1988).

Apart from the behavioral and neuroendocrine responses, the acute disruption of the mother–infant relationship also affects neurochemical systems and general brain activity. Elevations in the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol, but not of serotonin or dopamine metabolite concentrations in CSF, have been detected in rhesus monkeys in response to maternal separation (Gunnar, Gonzalez, Goodlin, & Levine, 1981). In a recent study, Rilling et al. (Rilling, Winslow, O'Brien, Gutman, Hoffman, & Kilts, 2001) demonstrated by positron emission tomography imaging that maternal separation in rhesus monkeys provokes a robust activation of the right frontal cortex and deactivation of the left frontal cortex in parallel to the expected cortisol response to separation. Further analyses demonstrated that the activity in these regions was positively or negatively cor-

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related with the levels of cortisol, respectively. These results are very interesting, especially considering the long-term effects that maternal separation can have in prefrontal cortex function. In fact, adult rhesus monkeys that exhibit higher cortisol levels and fearful temperament have more pronounced frontal lobe electroencephalogram (EEG) asymmetries favoring the right hemisphere (Kalin, Larson, Shelton, & Davidson, 1998). These results are particularly interesting in light of data from EEG studies on human infants. Thus, infants showing more distress in response to maternal separation had greater right frontal and less left frontal resting activity (Davidson & Fox, 1989), a pattern of activity that could be correlated with anxiety traits.

This data gives rise to several important questions: (a) Can prolonged maternal separation affect prefrontal cortex activity in a chronic way, permanently increasing the activity of the right and decreasing the activity of the left prefrontal lobe? and (b) Are these changes in prefrontal activity a consequence of the cortisol response to the separation or is it the other way around? Excessive exposure to cortisol can specifically affect prefrontal cognitive abilities, including inhibitory control of behavior (Lyons, Lopez, Yang, & Schatzberg, 2000), and is presumed to be mediated by the high levels of glucocorticoid receptors present in the primate prefrontal cortex (Sánchez, Young, Plotsky, & Insel, 2000).

Some of the early demonstrations that chronic disruption of the maternal–infant bond and social deprivation affect primate development and leads towards psychopathology came from studies carried out at the University of Wisconsin Primate Laboratory in the 1960s and 1970s (Harlow, Dodsworth, & Harlow, 1965; Harlow, Harlow, & Suomi, 1971; Mason, 1960; for review, see Seay & Gottfried, 1975). When rhesus monkey infants are separated from their mothers, peers, and social group at birth and reared in "partial social isolation" (with auditory, visual, and olfactory, but not tactile, contact with conspecifics) for at least 6–12 months, there are tremendous long-term behavioral alterations, including the occurrence of autistic-like behaviors (stereotyped movements, compulsive nonnutritional sucking, and self-mutilatory behavior when animals reach puberty), lack of recognition of social cues and inability to develop normal social relationships, hyperaggresiveness, and disoriented sexual behavior. Under more severe social limitations (i.e., "total social isolation" for the 1st year of life), the effects are even more severe, with a much higher degree of autistic-like self-clasping, self-orality, rocking, and huddling, as well as lack of exploration and social interaction. In this case, though, the animals are extremely fearful and anxious, and they freeze in reaction to aggression from other animals. The closest human situation to these social deprivation studies can be found in poorly run orphanages where children are reared with low rates of human contact and little sensory stimulation (Chisholm, 1998; Kaler & Freeman, 1994; Rosenberg, Pajer, & Rancurello, 1992). Children reared in these deprived environments develop abnormal behavioral patterns and cognitive deficits referred to as *anaclitic depression* by Spitz in the 1940s (Spitz, 1945) and that appear very similar to the characteristics of nonhuman primates reared under similar conditions.

Other studies from the same laboratories included less dramatic manipulations of the early rearing environment, including situations in which singly housed animals were allowed to play with conspecifics for either 15–30 min or for 2 hr per day, or were peer-reared from birth, or reared with only their mother for 6 months (with no interaction with other animals). This variety of manipulations resulted in less aberrant behaviors, such as delay in developing social contact or rough-and-tumble play, more aggressiveness, and inadequate sexual behavior.

If animals are exposed to a social environment soon enough (before or at 6 months of age), the species-typical repertoire of social and nonsocial behaviors can develop, even in the infants reared in total isolation (Harlow & Suomi, 1971). This seems to be due to the fact that the first 6 postnatal months in a rhesus monkey (equivalent to 24–30 months in a human infant) are crucial for the normal development of social attachment and cognitive abilities, which happen in parallel to very

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important phases in neurobiological development (see Kraemer, 1992, for review), including changes in neurochemical systems, synaptogenesis, remodeling of synapses, and myelination. The "reversibility" of certain gross alterations if "therapy" is applied at the right developmental age in humans has been the focus of a recent discussion (Schaffer, 2000). As reported by the author, the "age at the time of move from adverse to beneficial environment is clearly an important consideration and sets limits to the extent of the recovery" (p. 7) and seems to apply for both human and nonhuman infants.

Summarizing the long-term behavioral effects consistently observed in nonhuman primates subjected to prolonged periods of early maternal or social deprivation, these animals exhibit increased fearfulness and anxiety, social and sexual dysfunction, and aberrant stereotypic and self-directed behaviors. Other long-term effects consist of alterations of ingestive behaviors (polydipsia and polyphagia) without affecting body weight (Miller, Mirsky, Caul, & Sakata, 1969); decreased preference for sucrose, which could be indicative of anhedonia—frequently associated with depressive states—but that together with increased preference for quinine points to a likely insensitivity to gustatory stimuli (Paul, English, & Halaris, 2000); alterations of immune function (Lubach, Coe, & Ershler, 1995); and altered sympathetic response to stressful stimuli (Martin, Sackett, Gunderson, & Goodlin–Jones, 1988).

Despite the compelling evidence from experimental studies of rodents that maternal separation or social isolation produces dramatic alterations in the adult LHPA axis, if and how the HPA function is affected in nonhuman primates after exposure to early adverse experiences is still not clearly understood. Although higher basal levels of plasma cortisol have been reported in singly reared rhesus monkeys at 19 months of age (Champoux, Coe, Schanberg, Kuhn, & Suomi, 1989; Sackett, Bowman, Meyer, Tripp, & Grady, 1973), no differences in the HPA axis response to stressful stimuli or in general HPA function in 4-year-old animals have been detected (Meyer & Bowman, 1972). Similarly, either reduced (Clarke, 1993; Meyer, Novak, Bowman, & Harlow, 1975) or increased (Higley, Hasert, Suomi, & Linnoila, 1991; Higley, Suomi, & Linnoila, 1991, 1992) basal HPA function has been reported in peer-reared rhesus macaques. Interestingly, when increased HPA function was detected in peer-reared young rhesus monkeys, either in basal conditions (Higley, Hasert, et al., 1991) or in response to separation stress (Fahlke, Lorenz, Long, Champoux, Suomi, & Higley, 2000), the levels of plasma cortisol were positively correlated with alcohol consumption. Using a different manipulation, monkeys reared on cloth surrogate mothers exhibited low early morning cortisol levels and alterations in the normal circadian rhythm of cortisol when they were 5–7 months old (Boyce, Champoux, Suomi, & Gunnar, 1995).

There is little information on the long-term effects of early life adverse events on New World monkeys. However, repeated intermittent separations of squirrel monkey infants from the natal group can result in blunted increases in cortisol and fewer vocalizations in response to later maternal separation or brief social isolation (Levine, Lyons, & Schatzberg, 1997; Lyons, Martel, Levine, Risch, & Schatzberg, 1999). These infants also spent significantly more time near peers during a maternal absence, suggesting that nonmaternal forms of social support can "buffer" stress-induced anxiety in infant primates, in a similar way that the presence of familiar conspecifics can modulate the adrenocortical response to stressors in adults (Levine, 2000; Levine & Coe, 1988). The reported blunting in the cortisol response to maternal separation does not seem to be due to changes in the pituitary CRF receptors (Lyons, Yang, Mobley, Nickerson, & Schatzberg, 2000), unlike reported alterations in some patients with major depression or posttraumatic stress disorder (Chrousos & Gold, 1992; Holsboer, von Bardeleben, Buller, Heuser, & Steiger, 1987; Plotsky, Owens, & Nemeroff, 1998; Yehuda, 1998). However, the greater glucocorticoid suppression of the CRF-stimulated ACTH response detected after glucocorticoid administration in the infants that had experienced repeated intermittent separations supports

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clinical reports of differences in negative feedback of glucocorticoids on the HPA axis of those patients. This parallelism provides support for the thesis linking the experience of early life trauma, the alteration of normal neural development, and the increased vulnerability for development of psycho- and physiopathologies (including affective disorders) in adulthood.

Although stress-related states have been associated with increased activity of the LHPA axis, recent studies in humans suggest that exposure to adverse conditions early in life can actually result in hypofunctionality of this system, with lower basal levels of plasma cortisol and a flattening in the circadian rhythm, either in adulthood or during development, as has been reviewed by Gunnar and Vazquez (2001) in another article of this Special Issue. Interestingly, some animal models described above display blunted HPA activity as a result of the early adverse experience, although no information regarding the effects on the HPA circadian rhythm is available except for the study by Boyce et al. (1995). Either hypo- or hyperresponsiveness of the LHPA axis would have dramatic consequences for the development and health of the individual (Heim, Ehlert, & Hellhammer, 2000), as has previously been proposed for a hyperresponsive system (Gold, Goodwin, & Chrousos, 1998).

Although there is compelling evidence from rodent and primate studies for the impact of an early life trauma on the later development of psychopathology, the vulnerability may also be, at least in part, heritable. Studies in squirrel monkeys demonstrated that paternal half-siblings that exhibit prolonged adrenocortical and vocalization responses to maternal separation are the ones that spend more time near the mother in the undisturbed groups (Lyons et al., 1999), indicating that the individual variability in "coping" and "recovering" from the adverse experience has both a genetic and experiential component, in agreement with human twin studies (Goldsmith & Gottesman, 1981; Kendler & Karkowski–Shuman, 1997; Silove, Manicavasagar, O'Connell, & Morris–Yates, 1995). Additional evidence for a diathesis–stress or gene–environment model explaining why similar early adverse experiences may differentially affect individuals is provided by studies performed in rhesus monkeys with genetically high- or low-reactive behavioral profiles (Suomi, 1987, 1997). Interestingly, maternal and peer interaction seem to modulate the genetic risk for serotonergic dysfunction and, therefore, the temperamental differences associated with different serotonergic "tone" (such as impulsivity, aggression, and propensity to substance abuse). As previously described in the rodent models of early adverse experience, exposure to effective or nurturing parenting styles can reduce the genetic risk for psycho- or physiopathology in highly reactive nonhuman primates. In addition, there seems to be a behavioral mode of intergenerational transmission of "nurturing" maternal behaviors. For instance, when highly reactive female rodents are reared by intensely nurturant foster mothers, not only are their behavioral profiles improved but they are also effective mothers, a characteristic that seems to be passed on to the next generation (Liu et al., 1997; Francis, Diorio, Liu, & Meaney, 1999).

Early adverse experiences can also take place prenatally. Although the experience of prenatal stress has been associated with adverse birth outcomes and problems in human development, a reliable chain of causality has not yet been established (for review, see Lobel, 1994). In nonhuman primates, exposure of pregnant females to stressful situations increases the risk of miscarriage (Sackett, 1981) and dermatoglyphic asymmetry, which is indicative of altered fetal development and is associated with increased perinatal mortality (Newell–Morris, Fahrenbruch, & Sackett, 1989). Daily exposure to stressors during rhesus monkeys mid-to-late gestation resulted in lower birth weights, impaired neuromotor development, and attention deficits in the offspring (Schneider, 1992c), as well as delays on learning tasks (Schneider, 1992a), less motor and exploratory behavior in a novel environment (Schneider, 1992b), enhanced behavioral responses to stress, higher levels of abnormal behavior and deficits in social behavior (Clarke & Schneider, 1993), long-term effects on HPA function (Clarke, Wittwer, Abbott, & Schneider, 1994), and changes

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in CSF concentrations of biogenic amines (Schneider, Clarke, Kraemer, Roughton, Lubach, Rimm–Kaufman, Schmidt, & Ebert, 1998). Although interesting, some of these results have to be interpreted with caution. In some of these studies both the control and prenatally stressed groups of infants were separated from the mother on PND2, nursery-reared until 30 days old, and then peer-reared until 6 or 12 months, when they were tested. Therefore, factors such as maternal separation and peer rearing could be interacting with the effects of prenatal stress in the offspring. Independent of this possibility, there seem to be periods of higher vulnerability to the exposure to prenatal stress in nonhuman primates. Schneider et al. (Schneider, Roughton, Koehler, & Lubach, 1999) have demonstrated that, although exposure to mild psychological stress during any point of gestation resulted in deficits of attention and neuromotor maturation in macaque infants of 4–22 days of age, exposure during early days of gestation (E45–E90) had more pronounced and pervasive motor effects than did exposure during mid-to-late gestation (E90–E145) and resulted in infants with lower weights.

Neurobiological Underpinnings of the Long-Term Consequences of Adverse Early Experience in Primates

Dysregulation of monoaminergic systems has been reported in isolate- or peer-reared primates. Animals reared in partial-isolation exhibit decreased levels of NE in CSF during their postnatal development, and this neurochemical difference has been related to the self-directed, self-injurious, and stereotypic behavior described above (Kraemer, Ebert, Schmidt, & McKinney, 1989). Interestingly, peer rearing seemed to produce the opposite effect (i.e., increased NE concentrations in CSF) and also affected 5-hydroxyindoleacetic acid (5-HIAA) CSF levels during the 1st year of age in a gender-specific (decreased in females, but increased in males) manner (Higley, Suomi, & Linnoila, 1992). Low levels of 5-HIAA in CSF are associated with higher incidence of impulsive risk-taking behavior, as well as with excessive alcohol consumption and aggression in rhesus macaques (Higley & Bennett, 1999; Higley, Mehlman, Taub, Higley, Fernald, Vickers, Suomi, & Linnoila, 1996; Westergaard, Suomi, Higley, & Mehlman, 1999).

Long-term alterations in central dopaminergic function have also been detected in isolation-reared rhesus monkeys and related to the stereotypic and self-injurious behavior present in these animals (Lewis, Gluck, Beauchamp, Keresztury, & Mailman, 1990). In particular, the decreased dopaminergic innervation observed in the basal ganglia could contribute to the psychomotor alterations consistently found in these deprivation studies (Martin, Spicer, Lewis, Gluck, & Cork, 1991). In addition, either excessive or insufficient dopamine neurotransmission can impair prefrontal cognitive functions involving working memory, as well as behavioral inhibition (Arnsten & Goldman–Rakic, 1998; Brozoski, Brown, Rosvold, & Goldman, 1979; Collins, Roberts, Dias, Everitt, & Robbins, 1998).

Consistent with the lack of clear effects on HPA function, no differences have been reported so far in either levels of CRF expression (Ginsberg, Hof, McKinney, & Morrison, 1993a; Sánchez, Young, Plotsky, & Insel, 1999b) or in noradrenergic innervation (Ginsberg, Hof, McKinney, & Morrison, 1993b) in the hypothalamic PVN in 1.5- to 2.5-year-old isolate-reared monkeys. It appears, however, that some limbic areas regulating HPA function may be more affected, as demonstrated by the increased expression of neurofilament protein in the hippocampal dentate gyrus (Siegel, Ginsberg, Hof, Foote, Young, Kraemer, McKinney, & Morrison, 1993), although no differences in gross morphology or total hippocampal volume, as measured by MRI (Sánchez, Hearn, Do, Rilling, & Herndon, 1998), have been detected.

Early maternal and social deprivation also interferes with the normal cognitive development of primates (Beauchamp & Gluck, 1988; Beauchamp, Gluck, & Lewis, 1991; Gluck, Harlow, & Schiltz, 1973; Gluck & Sackett, 1976; Sánchez et al., 1998b). The cognitive impairments have been partially attributed to the strong perseverative response tendencies exhibited by the deprived animals, which re-

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flect a failure of systems involved in the cessation and inhibition of ongoing behavior. They have also been attributed to attentional or motivational deficits.

However, the neurochemical and neuroanatomical changes underlying such impairments are still unclear. Many of the cognitive deficits described above involve impaired response inhibition, which could be due to prefrontal cortex dysfunction. Recent evidence suggests that some prefrontal cognitive deficits may arise from disruptions in forebrain dopamine neurotransmission induced by excessive exposure to cortisol (Lyons et al., 2000). It might be possible that the initial cortisol response to prolonged exposure to early life adverse conditions alter the normal development of dopamine neurotransmission in the prefrontal cortex; however, this remains to be formally tested.

Some of the plastic events observed in the CNS have been actually attributed to somatosensory deprivation and restriction of movement, such as the decreased dendritic branching of Purkinje cells in the cerebellum (Floeter & Greenough, 1979) or in cells of the somatosensory and motor cortex (Struble & Riesen, 1978). Abnormal electrical recordings from hippocampus, frontal cortex, and sensory relay nuclei for vestibular and propriocepytive function in the cerebellum and somatosensory thalamus have also be reported in rhesus monkeys reared in social isolation (Heath, 1972), which may underlie abnormal forms of emotion and perception in these animals.

Structural MRI has also been used as a tool to detect gross neuroanatomical changes in rhesus monkeys separated from the mother at 2 months of age and singly housed until 12 months old (Sánchez et al., 1998b). The scans performed at 18 months of age detected a reduction in the midsagittal size of the corpus callosum, in parallel to a decrease in white (but not gray) matter content in the parietal and prefrontal cortices in the deprived animals. The different rearing conditions did not affect, however, the total brain, cerebellar or hippocampal volumes, or the size of the anterior commissure, another structure containing interhemispheric fibers, therefore suggesting specific reductions in cross-hemispheric projections probably resulting from a reduction in the number of callosal axons (or in their myelination and growth) from the same number of neurons. These alterations were not reversed by introduction of the isolates into a peer group for 6 months and occurred in parallel with cognitive impairments.

Conclusions

The evidence reviewed above from rodent and nonhuman primate studies supports the thesis that the perinatal environment is a very important factor modulating neurobiological development and, thus, behavioral, emotional, cognitive, and physiological development. The developing brain must be viewed as overlapping sets of moving targets that external stimuli may influence or "program," with the outcome based on their developmental state. This gives rise to a system that may respond differently to the same stimulus in an age-dependent manner. As a corollary, the impact of adverse experiences will vary in different species depending on the relative developmental stage at the time of exposure. Despite these caveats, some of the long-term behavioral effects of adverse early experience are intriguingly similar in rodents and nonhuman primates, including the increase in fearfulness and anxiety-like behavior and the deficits in social behavior, sexual behavior, and cognitive performance. There are, however, some notable differences, including the observation that nursery rearing (maternal separation) does not appear to drastically affect HPA axis function in the nonhuman primate, in contrast to the strong effects on this axis in rat models of maternal separation.

In comparison to the abundant and sophisticated information provided by rodent models on how, when, and in what direction early adverse experiences alter CNS development, as well as information concerning alterations in neural systems involved in the behavioral and neuroendocrine responses to stress, further research is necessary both in human and nonhuman primates. At the current time, we have not identified the critical neural pathways underlying stimulus processing of maternal and social cues in the progeny. It is likely that these pathways are involved in pro-

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gramming CNS substrates regulating emotionality (including arousal, fear, and anxiety), as well as the LHPA axis responses to stress throughout life. We do not even know what behaviors in nonhuman primates and humans are equivalent to maternal licking and grooming in the rat, maternal behaviors that are closely correlated with stress responsiveness and coping style in the offspring. In human and nonhuman primates maternal contact with the infant (sometimes not even physical, but the mere maternal presence) and the presence of familiar cohorts are known to buffer both the behavioral and physiological responses of the infant to stressful stimuli; however, the neural pathways underlying these effects and how adverse experiences such as abuse and neglect, maternal separation, or social deprivation can affect their development have not been characterized.

Although early adverse experiences have dramatic effects on primate behavior and emotional regulation, the effects on LHPA function are unclear and inconsistent, relative to the alterations described in rodents. Perhaps the fact that the primate CNS is more mature at birth than the rat results in a LHPA axis that is "more resilient" to early life stress; however, there is not enough normative information on the development of the central components of LHPA system in primates or how they are regulated by stimuli to prove this point. In addition, although there is tantalizing evidence, there is no clear information regarding the existence of a stress hyporesponsive period in nonhuman or human primates.

As outlined below, multiple factors may determine the outcome of exposure to early adverse experience and should be the focus of future investigation:

1. *The developmental stage at which the trauma occurs*. The existence of "sensitive periods" is postulated and needs to be identified for each system.
2. *Important characteristics of the insult*. The nature, severity, frequency, chronicity, and "predictability" of the insult may represent critical variables that need to be systematically evaluated; it appears that a major attribute of adverse early experience is the inability of the infant (or mother) to predict the environment or exert any sense of control over events.
3. *The individual's variability in vulnerability and coping mechanisms*. This involves interaction of the experience with the genetic background or prenatal experience; in the case of human infant maltreatment, this is very often happening on top of prenatal exposure to maternal stress, malnourishment, and even drugs of abuse, experiences that by themselves can negatively affect development of the primate CNS.
4. *Translation of developmental stages across species*. In order to develop valid animal models, we need to be able to translate equivalent developmental stages of the brain across rat, monkey, and human.

Only when we amass this information will we fully understand the balance and interaction between nature and nurture in sculpting individual differences in perception of processing and responsiveness to external stimuli. From a therapeutic viewpoint, this information will permit the development of effective early interventions and later remediative therapies to prevent or reverse the negative consequences of adverse early experience.

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