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The effects of neonatal stress on brain development: Implications for psychopathology

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Abstract
Recent studies have focused on the behavioral and neurobiological sequella of exposure to early adverse events. We hypothesize that early adverse experiences result in an increased sensitivity to the effects of stress later in life and render an individual vulnerable to stress-related psychiatric disorders. This vulnerability may be mediated by persistent changes in corticotropin-releasing-factor (CRF)-containing neurons, the hypothalamic–pituitary–adrenal axis, and the sympathetic nervous system. We therefore present an overview of the CRF system and its role as a mediator in the development of the stress response, major depression, and posttraumatic stress disorder. The literature pertaining to behavioral and neurobiological alterations associated with exposure to early adverse life events in rodents, nonhuman primates, and humans is reviewed. We focus on animal models that precipitate depressive and anxiety symptoms while producing neuroendocrine alterations that mimic those seen in adults with those disorders. The literature integrating neurobiological and behavioral consequences of early life stress is also reviewed, focusing primarily on infants born to mothers with depression and on infants who were abused or neglected.

Early trauma, abuse, neglect, loss of a parent, and inadequate parenting are stressors that confront some children. Because children differ on behavioral, cognitive, and affective functioning at different stages of development, it is likely that the impact of adverse events may vary at different stages. The neonatal period may be an especially high risk period given the continued proliferation of neuronal cells and development of neural pathways, and the greater dependency on caregivers. Findings show that infants experience early behavioral and neurobiological changes in response to maternal depression, and that the effects of early inadequate parenting may be long lasting (e.g., Jones, Field, Davalos, & Pickens, 1997). Given the high rates of depression in women of childbearing age (Garrison & Earls, 1986; O'Hara, Zekoski, Phillips, & Wright, 1990), it is not surprising that researchers have accumulated substantial evidence on the impact of maternal depression on child attachment, development, and later risk for psychopathology.

It is now relatively well established that stress often precipitates episodes of affective disorders (Dunner, Patrick, & Fieve, 1979) or is related to its development (Hammen, Davila, Brown, Ellicot, & Gitlin, 1992). Indeed, major depression has been shown to be a frequent sequelae of maltreatment and abuse in childhood (Browne & Finkelhor, 1986). Childhood abuse and other early traumas may also result in posttraumatic stress disorder (PTSD) in children and adolescents, and to the development of syndromal PTSD in re-

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sponse to subsequent stressors in adulthood (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Green, 1994; Lynch & Cicchetti, 1998). Since changes in the hypothalamo–pituitary–adrenal (HPA) axis have been correlated with major depression and PTSD in adults (Yehuda, Giller, Southwick, Lowy, & Mason, 1991), it is important that we understand the neurobiological alterations associated with neonatal stressors and how they may render one vulnerable to the later emergence of stress-induced psychopathology, such as major depression and PTSD.

There have been compelling reports of neurobiological findings which support dysregulation of the HPA axis as a result of early adverse life events in rodents and nonhuman primates. Events such as early maternal separation, early handling, having variable access to the mother, and being reared by a parent with varying foraging demands have been associated with neurobiological changes in offspring (e.g., Albeck, McKittrick, Blanchard, Nikulina, McEwen, & Sakai, 1997; Coplan et al., 1996; Ladd, Owens, & Nemeroff, 1996) which mimic those changes seen in adult humans with PTSD and depression, and produce behavioral changes in rodents and nonhuman primates that resemble fear, anxiety, and depression as well (Butler, Weiss, Stout, & Nemeroff, 1990; Kalin & Takahashi, 1988; Weiss, Stout, Aaron, Owens, & Nemeroff, 1994). Furthermore, in rodents these neurobiological alterations have been shown to persist into adulthood (Meaney, Aitken, & Bhatnagor, 1991; Meaney, Aitken, & Sapolsky, 1988) and to be reversed by treatment with a selective serotonin reuptake inhibitor (SSRI; Nemeroff, 1996). If found to be valid models for the development of depression and PTSD in adults, these animal findings present important treatment implications for the population of neonates exposed to major stressors.

The importance of the corticotropin-releasing factor (CRF) system warrants review in our effort to integrate neurobiological and behavioral changes, and therefore we will begin with a discussion on the ontogeny and morphology of CRF and CRF receptors. We next focus on developmental differences in the capacity of animals and humans to respond to stress. We then review behavioral sequella associated with alterations in the HPA axis and CRF system as a result of stress, giving special attention to the development of behaviors consistent with depression and anxiety in animals, and the diagnosis of major depression and PTSD in humans. A detailed review of neurodevelopmental adaptation to specific early life stressors in rodents, nonhuman primates, and humans will be presented, as well as the implication for the development of subsequent psychopathology. We will conclude with a discussion on the relevance of this material and directions for future research.

Neurobiology of the Stress Response

In this section we will review the ontogeny and function of CRF, as well as the localization of CRF receptors. Although identified in a crude form in 1955, CRF was not structurally characterized as a peptide containing 41 amino acids until 1981 (Chen, Lewis, Perrin, & Vale, 1993). The peptide is extensively distributed in both hypothalamic and extrahypothalamic brain areas. CRF-containing neurons, abundant in the paraventricular nucleus of the hypothalamus, project nerve terminals to the median eminence (Stout, Kilts, & Nemeroff, 1995). CRF is released from these nerve terminals into the hypothalamo–hypophysial portal system and transported to the anterior pituitary gland, where it stimulates the secretion of adrenocorticotropin (ACTH) into the general circulation (Heim, Owens, Plotsky, & Nemeroff, 1997). ACTH then stimulates the release of glucocorticoids (cortisol in primates and corticosterone in most rodents) in response to stress (Heim et al., 1997; see Figure 1).

Thus CRF is the prime regulator of the endocrine stress response, and is also believed to coordinate the behavioral, immunological, and autonomic responses of mammalian organisms to stress (Owens & Nemeroff, 1991). There is considerable evidence that CRF-containing neurons innervate noradrenergic, serotonergic, and dopaminergic systems (Austin, Rhodes, & Lewis, 1997). CRF is believed to modulate the release of norepinephrine from cells originating in the locus coeruleus and to

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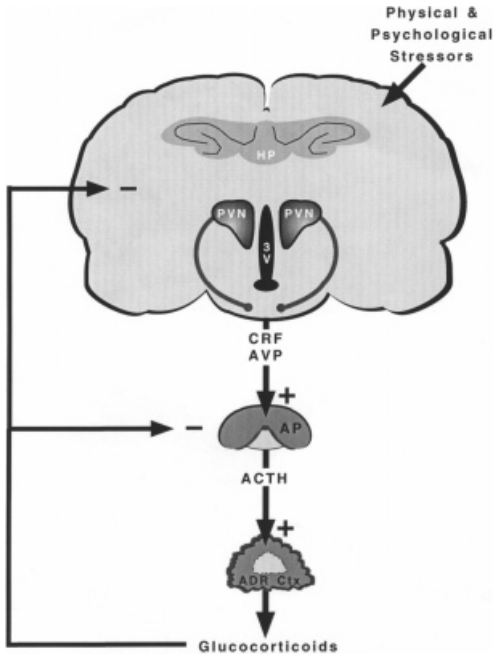


Figure 1. Neurobiological effects of physical and psychological stress on the CRF system and the HPA axis. HP, hippocampus; AP, anterior pituitary; ADR Ctx, adrenal cortex.

mediate arousal and vigilance (Dunn & Berridge, 1990). Given the high concentrations of CRF in the locus coeruleus in humans, these CRF axons may modulate noradrenergic neurotransmission to the hippocampus and hypothalamus, two structures integral to emotional regulation. Interactions of CRF with these noradrenergic systems in the human brain stem may play a significant role in the pathophysiology of stress-induced psychiatric disorders.

The localization of CRF-receptor subtypes provides insight into their role as mediators in emotional responsiveness. There have been two distinct CRF-receptor subtypes identified in rat (Lovenberg, Liaw, et al., 1995; Lovenberg, Chalmers, Liu, & DeSouza, 1995; Potter et al., 1994) and human brains (Chen, Lewis, Perrin, & Vale, 1993; Liaw, Lovenberg, Barry, Oltersdorf, Grigoriadis, & DeSouza, 1996): CRF_1 and CRF_2. These subtypes differ both functionally and in their regional distribution (Primus, Yevich, Baltazar, & Gallager, 1997). The CRF_1-receptor is comprised of 415 amino acids and mediates CRF-induced ACTH release. CRF_1 receptor mRNA has been found in abundance in the cerebellum, pituitary, cerebral cortex, and olfactory bulb, while CRF_2 binding sites are most abundant in the cerebellum, frontoparietal, and temporal cortices (Chalmers, Lovenberg, Grigoriadis, Behan, & DeSouza, 1995; Potter et al., 1994).

CRF-receptor subtypes likely have very distinct functional roles given their differential distribution (Primus et al., 1997). In rodents there are two forms of the CRF_2 receptor: $CRF_{2\alpha}$ (consisting of 411 amino acids) and $CRF_{2\beta}$ (consisting of 431 amino acids; Lovenberg, Chalmers, et al., 1995). CRF_2-receptor mRNA is abundant in the ventromedial nucleus of the hypothalamus, entorhinal cortex, amygdala, and lateral septal nucleus, consistent with CRF_2 binding sites in the limbic–hypothalamic regions (Primus et al., 1997). Localization of CRF_2 receptors to limbic–hypothalamic brain regions suggests that this receptor may also be involved in the regulation of emotional behavior.

The localization and distribution of CRF receptors has provided insight into their role as mediators of the stress response. Animal studies have provided insight into the location and distribution of these stress mediators and their receptors, allowing us to hypothesize about changes in distribution in humans as a result of stress (Austin et al., 1997). More selective radiolabeled ligands for CRF-receptor subtypes are needed to quantify their localization, and for the development of ligands that can be used in conjunction with positron-emission tomography (PET) to allow for visualization in humans and nonhuman primates. This will allow for further distinction between the effects of different stressors and forms of psychopathology associated with them.

Behavioral Effects of CRF

The role of CRF has been revealed through a series of experiments in which CRF was injected into various neuroanatomical regions and found to produce distinct behavioral patterns. In the locus coeruleus, administration of CRF in rats alters the firing rate of noradrenergic cells, simulates fear reactions, and decreases exploratory behavior (Valentino,

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Foote, & Aston–Jones, 1983; Weiss et al., 1994). Similar behavioral changes are seen when CRF is injected into the amygdala (Butler et al., 1990). These behavioral changes are also seen in rodents and nonhuman primates exposed to early adverse life events (Butler et al., 1990; Kalin et al., 1988; Weiss et al., 1994) and are associated with elevated CRF concentrations.

Injection of CRF into the locus coeruleus or parabrachial nucleus has an anxiogenic effect in rodents, inducing a pronounced decrease in exploratory behavior in a novel environment (Butler et al., 1990), and an increase in fearful behaviors when exposed to a conflict test (Weiss et al., 1994). Injection of CRF into the locus coeruleus of rodents also increases the firing rate of noradrenergic neurons that project to the amygdala, a brain area which is involved in encoding emotional responses (Butler et al., 1990), increases tyrosine hydroxylase activity (Melia & Duman, 1991), and induces the release of excitatory amino acids (Singewald, Zhou, Chen, & Philippu, 1996).

Injection of CRF directly into the amygdala produces a decrease in exploratory behavior and an increase in fear-related behaviors (Liang & Lee, 1988; Stout et al., 1995), consistent with neuroantomical links between the locus coeruleus and the amygdala. Lesioning studies reveal that the amygdala plays a seminal role in the HPA-axis response to stress (Beaulieu, DiPaolo, & Barden, 1986); in fact, amygdala lesions completely block CRF-induced potentiation of the startle response (Hitchcock & Davis, 1996) and may be involved in encoding emotional responses. There has also been documentation of neuroanatomical changes in areas such as the amygdala and hippocampus associated with PTSD and depression (Bremner et al., 1993; Sheline, Wang, Gado, Csernansky, & Vannierr, 1996). Thus, the behavioral sequella associated with injection of CRF into the amygdala and locus coeruleus supports the hypothesis that these two structures are integral to the development of PTSD and depression.

Direct injection of CRF into the central nervous system (CNS) in rodents results in behavioral changes that resemble depression (see Table 1)—for example, decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations (Kalin et al., 1988). Prolonged increases in CRF activity has been posited to underlie many symptoms of depression, such as sleep disruption, alterations in arousal, and loss of appetite and libido. The behavioral changes seen in rodents who received centrally administered CRF supports this hypothesis. Furthermore, numerous symptoms of anxiety or PTSD, including hypervigilance, increased autonomic reactivity, avoidance behavior, and potentiated startle responses, are consistent with increased CRF activity (Heim, Owens, Plotsky, & Nemeroff, 1997).

Chappell et al. (1986) demonstrated that both acute and chronic stress leads to a 2-fold increase in CRF concentrations in the locus coeruleus, and a 50% decrease in CRF concentrations in the median eminence in rodents. A comparable dysregulation of stress-responsive neuronal systems may underlie the remarkable symptom overlap and frequent comorbidity between major depression and PTSD (Heim et al., 1997). Thus, we are beginning to understand neurobiological connections between CRF, the locus coeruleus, amygdala, early adverse events, and the development of PTSD and depression.

Neurobiological Alterations Associated with PTSD and Depression

Now that we have explored the behavioral changes in animals in response to injection of CRF, and their similarity to depression and anxiety in humans, we will examine neurobiological changes in humans that have been associated with major depression and PTSD.

Using cortisol concentrations in plasma and urine as an index of HPA-axis activity, major depression results in a hyperactive HPA axis, whereas PTSD results in the opposite, a hypoactive HPA axis (Yehuda et al., 1991). Thus both diseases are stress related and apparently alter an individual's CNS. Understanding the neurobiology of the stress response may lead to the development of biological and behavioral interventions to

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Table 1. *Behavioral effects of corticotropin-releasing factor*

Behavior following CRF Administration	Behavior following CRF-Receptor Antagonism or CRF Passive Immunization
Increased locomotor activity in familiar environments	Reversed stress- and drug-induced anorexia
Decreased exploration of unfamiliar environments	Decreased stress-induced fighting
Decreased response to operant conflict	Reversed defensive withdrawal (induced by stress, drugs, or genotype) and restored exploratory
Enhanced stress-induced freezing behavior	
Decreased food intake	Attenuated stress-induced freezing
Disrupted sexual behavior	Blocked fear-potentiated startle
Enhanced acoustic startle response	Decreased acquisition of conditioned emotional response
Conditioned fear and aversion	
Disrupted sleep rhythms	Reduced defensive burrowing
Increased frequency of grooming and defensive burrowing	Prevented stress-induced sensitization
Induced seizures at high doses	

Note: Adapted from Anand and Nemeroff (1996).

decrease an individual's vulnerability for developing affective disorders.

HPA-axis hyperactivity in major depression is characterized by hypercortisolemia, decreased number of glucocorticoid receptors in lymphocytes, nonsuppression of cortisol after administration of dexamethasone, decreased ACTH responses to intravenously administered CRF, increased CSF concentrations of CRF, decreased density of CRF binding sites in the frontal cortex, and enlargement of both the pituitary and adrenal gland (Gold, Goodwin, & Chrousos, 1988; Nemeroff, Owens, Andorn, & Stanley, 1988). These findings all support the hypothesis of increased hypothalamic release of CRF. The findings of a blunted ACTH but normal cortisol response to CRF suggests a downregulation of adenohypophyseal CRF receptors (secondary to CRF hypersecretion) or increased feedback of cortisol on pituitary corticotrophs (Heim et al., 1997).

Support for CRF hypersecretion is indirectly provided by the finding of increased pituitary and adrenal volumes in patients with major depression (Krishnan et al., 1991; Nemeroff, Krishnan, Reed, Leder, Beam, & Dunnick, 1993). Our group has repeatedly demonstrated that drug-free depressed patients exhibit increased CSF CRF concentrations (Nemeroff et al., 1984; Owens, Plotsky, & Nemeroff, 1996) when compared to normal controls and patients with other psychiatric disorders. CRF has been measured in cisternal CSF collected postmortem from suicide victims and found to be elevated (Arato, Banki, Bissette, & Nemeroff, 1989; Nemeroff et al., 1988). Postmortem studies of depressed patients have revealed large increases in the density of CRF neurons and CRF mRNA expression in the paraventricular nucleus of the hypothalamus (Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994; Raadsheer, Van-Heerikhuize, Lucassen, Tilders, & Swaab, 1995).

In contrast to depressed patients, PTSD patients demonstrate low urinary cortisol levels, increased CSF somatostatin concentrations, enhanced sensitivity of cortisol to low-dose dexamethasone, increased number of glucocorticoid receptors in lymphocytes, and increased ratio between nadir and peak cortisol levels during the diurnal cycle (Heim, Owens, Plotsky, & Nemeroff, 1996). The HPA axis in PTSD appears to be hyperresponsive in some respects, allowing for a maximal stress response that is effectively controlled by negative-feedback inhibition. Similar to findings in major depression, increased CSF CRF concentrations, and a blunted ACTH but normal cortisol response to both stress and CRF administration, has been reported in Vietnam

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veterans and sexually abused girls (Bremner et al., 1993; Smith et al., 1989). Kaufmann et al. (1997) however observed an exaggerated ACTH response with normal cortisol responses to stress in sexually abused girls with major depression. Thus PTSD patients, like depressed patients, demonstrate increased CSF CRF levels and a blunted ACTH, yet normal cortisol response to exogenously administered CRF (Bremner et al., 1993; Smith et al., 1989). Patients with PTSD, however, differ in demonstrating hypocortisolemia, suppression to low doses of dexamethasone, and increased numbers of cytosolic glucocorticoid receptors (Yehuda et al., 1991). This suggests fundamental differences in the neurobiological alterations of PTSD and major depression. Though PTSD patients demonstrate hypocortisolemia, there have been similar findings of hippocampal atrophy in combat veterans with PTSD (Bremner et al., 1995; Gurvits et al., 1996). Potential mechanisms may involve toxic effects of high cortisol levels at the time of the trauma or an increased vulnerability of the hippocampus due to increased glucocorticoid number or sensitivity.

As noted earlier, Bremner et al. (1998) observed smaller right hippocampal volumes in Vietnam veterans with PTSD and hypothesized that alterations in hippocampal function may be associated with neuronal hypersecretion of CRF. Although we failed to detect atrophy of the hippocampal–amygdaloid complex in depressed patients in an early study using relatively crude methods (Axelson et al., 1993), Sheline et al. (1996) detected significant reductions in hippocampal volumes in women with a history of recurrent depression. Furthermore, there was a correlation between the total duration of depressive episodes and the degree of atrophy. Gurvits et al. (1996) also documented decreases in volume in both right and left hippocampi in combat veterans with PTSD, compared to combat veterans without PTSD and to normal controls. A correlation was found between combat exposure and hippocampal volume. A destructive cycle may be initiated whereby damage to the hippocampus leads to increased CRF secretion, increased cortisol secretion, and further damage to the hippocampus. An alternative theory is that smaller hippocampal volumes (perhaps as a result of previous stressors) predispose individuals to the development of PTSD in respose to traumatic exposure.

Somatostatin is another neuropeptide implicated in the stress response. Somatostatin is widely distributed in hypothalamic regions, with high concentrations in the median eminence, amygdala, hippocampus, cerebral cortex, and nucleus accumbens (Krisch, 1981). When administered centrally it produces some behavioral changes in rodents that resemble depression—alterations in food consumption, sleep patterns, locomotor activity, and memory (Aponte, Leung, Gross, & Yamada, 1984; Rezek, Havlicek, Hughes, & Freisen, 1976). Somatostatin appears to be released in response to CRF release in rodents (Rivier & Vale, 1985).

In human normal controls, CRF and somatostatin concentrations are positively correlated; however, in depressed patients CSF somatostatin concentrations are reduced relative to CRF (Bremner et al., 1993). In PTSD patients, CSF CRF and somatostatin are both elevated and significantly correlated (Bremner et al., 1993). There was no correlation between CSF CRF and somatostatin concentrations in PTSD patients with comorbid depression, regardless of level of combat exposure (Bremner et al., 1993). Increased peripheral glucocorticoid concentrations are associated with low CSF somatostatin levels (Rivier & Vale, 1985). Because depressed patients have high circulating peripheral glucocorticoids, this may explain the dissociation of CRF and somatostatin concentrations in this population. The increased CSF CRF levels in PTSD patients is consistent with the hypothesis of CRF neuronal hypersecretion in PTSD. PTSD patients may indeed have two distinct processes contributing to the increased CSF somatostatin concentrations: reduced peripheral glucocorticoiod secretion and increased CRF secretion.

In a study of bonnet macaques, there was no significant correlation between CSF CRF and CSF cortisol in adult animals reared under a chronically stressful environment (variable foraging demand [VFD]) compared to controls (Coplan et al., 1996). VFD animals

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demonstrated significantly elevated CSF CRF concentrations but reduced CSF cortisol concentrations (Coplan et al., 1996). These findings are identical to those observed in PTSD patients. Simultaneous measurement of HPA-axis activity and CSF CRF concentrations has provided evidence that the two systems are asynchronous (Coplan et al., 1996), and thus highlights the distinction between the neuroendocrine and neurotransmitter functions of CRF. Infants reared under VFD also demonstrated increased CSF somatostatin, serotonin, and dopamine metabolite concentrations during adulthood (Coplan et al., 1998). Taken together, these findings suggest that the extrahypothalamic CRF systems and the HPA axis may function quite independently, and moreover that CSF CRF levels largely reflects extrahypothalamic CRF neuronal system activity.

The Development of the Stress Response in Animals and Humans

Thus far we have concentrated on the neurobiology of the stress response and how that relates to the development of certain behaviors in animals and psychiatric syndromes in humans. We will now consider the development and maturation of stress-responsive systems in animals and humans, and what inferences may be drawn.

A plethora of research has emerged focusing on the developmental consequences of early stress. Indeed, the plasticity of the brain after birth may be protective, or alternatively render one vulnerable later in life through persistent alterations in developing neurobiological systems. Our group and others have demonstrated that maternal deprivation, one form of neonatal stress, may predispose to the development of depressive-like symptoms in adulthood in both rodents and nonhuman primates (Owens & Nemeroff, 1994). We next briefly describe this critical period of neurobiological development and the consequences that early stress may have on predisposed individuals to developing subsequent psychopathology.

CRF and CRF binding sites in the brain and pituitary appear prenatally in several species—as early as Day 16 in the rat fetus (Insel, Battaglia, Fairbanks, & DeSouza, 1988), Day 100 in the sheep fetus (Challis & Brooks, 1989), and Weeks 12–13 in the human fetus (Ackland, Ratter, Bourne, & Rees, 1986; see Table 2). These receptors become sensitive to glucocorticoid-feedback inhibition during late gestation. The stress-hyporesponsive period in rats, characterized by low baseline levels of corticosterone, lower numbers of CRF receptors, and decreased POMC mRNA gene expression occurs from Postnatal Days (PND) 4–14 (Grino, Burgunder, & Eskay, 1989a; Sapolsky & Meaney, 1986; Walker, Perrin, Vale, & Rivier, 1986). During this period, stress induced upregulation of CRF synthesis does not occur in response to chronic cannula implantation and abolishing the negative-glucocorticoid-feedback mechanism; upregulation has, however, been demonstrated consistently in rats older than 2 weeks (Baram, Yi, Arishai–Eliver, & Schultz, 1997). Stress-induced upregulation of CRF gene expression does not occur in rats until PND 9 (Baram et al., 1997). This period may be protective because glucocorticoids can exert an adverse effect on growth and neuronal myelination. High circulating levels of glucocorticoids have been reported to accelerate death of hippocampal neurons, which may predispose to cognitive and memory impairments, stress, and perhaps affective disorders in adulthood (McEwen, 1994; Sapolsky & Meaney, 1986). Glucocorticoid hypersecretion is also associated with glucocorticoid Type 2 receptor loss in rodents (Sapolsky & Meaney, 1986).

The stress hyporesponsive period can be conceptualized in rodents as one in which there is decreased sensitivity to CRF stimulation (Walker, Sapolsky, & Meaney, 1986) and greater corticosteroid inhibition of the HPA axis, including inhibition of the expression of CRF mRNA expression in the paraventricular nucleus (PVN) neurons (Grino et al., 1989, 1989). Although rat pups do not respond to a variety of stressors during this stress-hyporesponsive period, they do respond to maternal separation (Pauk, Kuhn, Field, & Schanberg, 1986; Plotsky & Meaney, 1993; Schanberg, Evoniuk, & Kuhn, 1984).

Evidence for a stress hyporesponsive pe-

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Table 2. *Correlation of rat and human brain development*

Developmental Feature	Rat	Human	References
Morphology of the spinal cord	E15	6 weeks	Marti et al. (1987)
	E17	8 weeks	Marti et al. (1987)
Ingrowth of afferent fibers	E14–15	7–10 weeks	Okado et al. (1982)
Substantia gelatinosa cells born	E16	14 weeks	Marti et al. (1987)
			Nornes & Das (1974)
Lamination of the spinal cord	E17	13 weeks	Rizvi et al. (1987)
			Marti et al. (1987)
First movements	E16	7–8 weeks	Narayanan et al. (1971)
			DeVries et al. (1982)
Motoneurone death	E15–P1	11–25 weeks	Nornes & Das (1974)
			Oppenheim (1987)
Nociceptive neurotransmitters	E16–18	8–10 weeks	Marti et al. (1987)
Increased neurotransmitter and receptor expression	E20–21	26–30 weeks	Charney et al. (1984)
		36–40 weeks	Loizou (1972)
			Okado et al. (1984)
Exaggerated cutaneous reflexes	Up to P10	up to 1 year	Fitzgerald & Gibson (1984)
			Prendergast & Shusterman (1982)
Corticospinal tract maturation	P7–10	1–2 years	Schreyer & Jones (1982)
			Prendergast & Shusterman (1982)

Note: E, embryological day; P, postnatal day. Adapted from Anand and Nemeroff (1996). See their review for the cited references.

riod in human neonates has not been documented; the CNS maturity of a 24-week-gestation premature infant would correspond with the CNS maturity of a newborn rat pup (Anand & Aynsley–Green, 1988). If newborn rat pups are protected against certain stressors (e.g., physical) but not others (e.g., maternal separation), then infants in utero, as early as 24 weeks gestation, may also be sensitive to certain stressors. ACTH can be detected as early as 7 weeks in the fetus (Kaplan, Grumbach, & Aubert, 1976), and at 26 weeks gestation the concentration of ACTH in the fetus corresponds to levels seen in newborn infants (Pavlova, Pronina, & Skebel'skaya, 1968). This may indicate early maturity of the ACTH system in human fetuses with a functional-feedback mechanism, given the relatively low concentrations of cortisol throughout gestation. Cortisol measures in human infants reveal that free cortisol is greatest in term infants immediately following birth, levels drop dramatically by Days 3–5 of life, and then they gradually rise to adult levels by age 3 months (Robicki, Forest, Loras, Bonnet, & Bertrand, 1990). Levels are elevated in infants delivered by natural birth compared to cesarean delivery (Kaplan et al., 1976). Premature infants demonstrate higher cortisol levels than term infants until Days 3–5 of life (Robicki et al., 1990); then they demonstrate the same pattern of reduction in cortisol (Kraiem, 1985). Kraiem (1985) has also reported transiently elevated cortisol levels after birth which decline within 48 hr and remain low for the next 3–10 days.

Infants less than 4 weeks old who are physically ill with respiratory distress, whether term or premature, demonstrate the highest overall cortisol levels when compared to controls (Economou, Andronikou, Cholevas, & Lapatsanis, 1993), indicating the capacity of the HPA axis to respond to physical stress in early infancy. Infants have also demonstrated elevations in cortisol (in term infants) and in the precursor hormones (in preterm infants) in response to surgical procedures early in life (Anand et al., 1988; Anand,

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Sippell, & Aynsley–Green, 1987). Again, we may find that the first few days of life are relatively protective for infants, but that they are capable of responding to physical stressors.

Thus, it appears that both animals and humans are capable of responding to stress early in life, which may be protective in some aspects but detrimental developmentally. The potential damage of high circulating levels of glucocorticoids on developing neurons in response to acute and prolonged stress may induce susceptibility to the effects of future stressors.

Effects of early adverse life events on neurodevelopment in rodents and nonhuman primates

Now that we have explored the neurobiological basis for this discussion, we will focus on the actual effects of stress in target populations. There have been multiple paradigms utilized in assessing the effects of stress in animals, including maternal separation, peer isolation, early handling, and exposure to unpredictable environments. There is currently a wide body of literature pertaining to the effects of early life stressors in rodents and various stressors have been correlated with strikingly similar neurobiological alterations.

The most widely accepted criteria for evaluating animal models of behavioral disorders was proposed by McKinney and Bunney in 1969, and summarized by Weiss and Kilts (1995). The validity of the model is based on the extent to which the animal model "1) is produced by etiological factors similar to those that produce the human disorder, 2) resembles the human disorder in manifestations or symptomatology, 3) has an underlying pathophysiological basis similar to that of the human disorder, and 4) responds as does the human disorder to the appropriate therapeutics treatments." Studies in rodents and nonhuman primates have demonstrated that exposure to early untoward life events alters the neurobiology of the stress response and that these alterations persist into adulthood (Benes, 1994; Meaney et al., 1991; Meaney et al., 1988). This has important clinical implications for the identification and treatment of individuals who have been exposed to early life stress.

Prenatally, exposure to stress has been associated with changes in various excitatory amino acids in rats. These rats demonstrate changes in the activity of GABA-receptor-gated chloride-ion channels and increased benzodiazepine-receptor binding activity in the dentate gyrus and septal nuclei (Winslow & Insel, 1991). Rats prenatally exposed to stress demonstrate a reduction in hippocampal pyramidal neurons (Uno, Tarara, Else, Suleman, & Sapolsky, 1989), persistent hyperactivity of their HPA axis (Takahashi & Kalin, 1991), and a vulnerability toward later sensitivity to stressful stimuli (Fride, Dan, Feldon, Halvey, & Weinstock, 1986). Prenatal exposure to stress appears to be unique in predisposing rodents to impaired neuronal maturation and a potentiated stress response later in adulthood (Benes, 1994).

Rats postnatally exposed to mild foot shock exhibit marked arousal and agitation, presumably through diminished GABAergic activity (Cordia & Biggio, 1986). Thus, stress may contribute to arousal and anxiety through influencing the GABA system, perhaps at the receptor level. Mild foot shock and restraint has also been associated with increases in dopamine concentrations (Thierry, Tassin, Blanc, & Glowinski, 1976) and tryptophan hydroxylase activity (Boadle–Biber, Corley, Graves, Phan, & Rosecrans, 1989) in specific brain regions. These increases are reversed by various benzodiazepines, suggesting that the GABA system also serves an important role in modulating the stress response.

In infant rodents, maternal separation has been used reliably as an early stressor. Indeed, maternal separation in rodents results in HPA-axis alterations similar to those seen in depressed adults (Coplan et al., 1998; Pihoker, Owens, Kuhn, Schanberg, & Nemeroff, 1993), behavioral changes which mimic depression and anxiety (Ada et al., 1969; Levine, 1962; Levine, Haltmeyer, & Karas, 1967), and a reversal of the HPA-axis alterations occurs after treatment with SSRIs (Plotsky et al., personal communication, 1998), thus qualifying it as an appropriate

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model for evaluating the precipitation of psychopathology by early loss or separation. Also, nonhuman primates who are allowed visual but not physical access to their mothers demonstrate behavioral changes observed in abandoned and neglected children (Albeck et al., 1997).

Ten-day-old rat pups acutely separated from their mothers exhibited increased plasma corticosterone and decreased growth hormone concentrations, decreased CRF concentrations in the median eminence (likely due to increased release), and an unchanged number of pituitary CRF receptors (Pihoker et al., 1993). The magnitude of reduction of CRF (46%) resembles that of adult rats following acute stress. In 12-day-old rat pups separated from their mothers for 24 hr, an increase in CRF-receptor density in certain brain regions—the frontal cortex, amygdala, and bed nucleus of the stria terminalis—was observed. In response to a saline-injection stressor, these pups had greater ACTH and corticosterone responses than controls. In 18-day-old rat pups undergoing maternal separation, downregulation of CRF receptors in the anterior pituitary was observed, likely secondary to CRF hypersecretion; the longer the separation period, the more pronounced was the decrease in CRF concentrations in the median eminence (Pihoker et al., 1993).

As adults, rats who underwent maternal separation for 6 hr a day between Days 10 and 21 demonstrated persistent alterations in their HPA-axis response to stress—enhanced ACTH and corticosterone responses, increased basal and stress induced corticosterone responses, decreased CRF-receptor density in the anterior pituitary, and increased CRF concentrations in the median eminence, as well as increased CRF mRNA expression in the paraventricular nucleus of the hypothalamus (Ladd et al., 1996). Maternal separation is not the only reliable stressor; early handling of rat pups has produced similar results.

Rats who were handled during the 1st week after birth (15 min/day) demonstrated decreased behavioral inhibition in response to a novel environment and decreased ACTH and corticosterone responses to a variety of stressors compared to nonhandled rats (Ada et al., 1969; Levine, 1962; Levine et al., 1967). Rats separated for 180 min/day between Days 2 and 14 demonstrated, as adults, marked increases in ACTH and corticosterone responses, marked increases in hypothalamic PVN CRF mRNA expression, increases in CRF concentrations in the median eminence, and early escape from dexamethasone suppression, thus suggesting an alteration in response at the level of the hypothalamus (Plotsky, Thrivikraman, & Meaney, 1993). Meaney et al. (1988, 1991) found that these changes persisted over the life span of these animals. Glucocorticoid-receptor density was reduced in the frontal cortex, hypothalamus, and hippocampus of the animals who were exposed to neonatal stress (Meaney et al., 1988, 1991). These rats also exhibited a marked increase in cocaine and alcohol craving as a result of maternal deprivation, both of which have high rates of comorbidity with mood and anxiety disorders.

Another model for early life stress is being allowed visual access to the mother but not physical access, a model of chronic stress designated as a visible burrow system (VBS). Albeck et al. (1997) studied a group of rats (dominant and subordinate) who were placed in a VBS. All rats exposed to the VBS demonstrated increased plasma cortisol levels, suggesting tonic activation of the HPA axis, and they had significantly higher levels of amygdala CRF mRNA expression. A subgroup of these rats exhibited impaired cortisol release following stress, and were designated as stress-nonresponsive (NRS). The NRS group appeared to be the most severely stressed, as evidenced by the greatest degree of body-weight loss, adrenal hypertrophy, basal cortisol levels, and lowest levels of corticosterone-binding globulin (CBG). These changes occurred quite gradually, suggesting an adaptive response to chronic stress. The hippocampal glucocorticoid Type 1 and 2 receptor subtypes are believed to be downregulated by the high circulating concentrations of glucocorticoids in these rats.

The rats who were exposed to the VBS but still capable of mounting a cortisol response to stress (designated stress-responsive systems [SRS]) demonstrated elevations in CRF

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mRNA in the PVN as well as the amygdala, whereas the more severely stressed rats (NRS) had decreased PVN CRF mRNA (Albeck et al., 1997). This combination of decreased CRF mRNA in the PVN and impaired cortisol responses to stress was postulated to be the result of enhanced inhibitory input to PVN neurons (i.e., increased glucocorticoid feedback or increased inhibitory neural input).

Bonnet macaques reared by mothers exposed to variable foraging conditions demonstrated persistently elevated CSF CRF concentrations (Coplan et al., 1996). These elevations persisted after the mothers were allowed a predictable diet. This suggests that early untoward life events, at least in nonhuman primates, leads to long-standing CRF neuronal hyperactivity through sensitization of the CRF neuron by upregulating its gene expression and chronically increasing the rate of CRF synthesis. Increases in the activity of one or more subsets of CRF neurons appear to be a common sequella of early life stress, depression, and PTSD.

There have also been reports of immunologic changes associated with early life stress in rodents and nonhuman primates. Premature weaning of rats has resulted in suppression of lymphocyte proliferation, increases in opportunistic infections, and premature deaths (Keller, Ackerman, & Schleifer, 1983). Monkeys who experience maternal separation during infancy display initial agitation, accompanied by increases in heart rate and body temperature; this is followed by a behavioral response that resembles depression, and persistent dysregulation of heart rate, body temperature, circadian rhythm, and nocturnal sleep patterns (Reite, 1987). During adulthood these monkeys also demonstrated slightly elevated total white blood cell counts and a significant suppression of lymphocyte proliferation in response to B-cell and T-cell mitogens, indicating impaired immune function (Reite, 1987). This corroborated previous findings of immunological changes in nonhuman primates as a result of maternal separation in infancy (Laudenslager, Capitanio, & Reite, 1985), and is an area that warrants further study in human infants.

Thus, we see that early life stress in animals leads to persistent changes in the CRF system, HPA axis, and markers of immune function. Next we shall examine the effects of stress in human infants.

Effects of early adverse life events on neurodevelopment in humans

Effects of maternal depression on child development. Postpartum depression does not translate directly to bad mothering, but it does interfere with optimal mothering. The result of maternal emotional unavailability can be devastating to the infant and can serve as a significant early life stress. Infancy is an especially high risk period because depressed mothers will have extensive contact with their infants, while the infant's contact with healthy others may be limited. There has been a plethora of reports documenting the effects of maternal depression on their developing offspring; however, few of these studies have attempted to integrate neurobiological findings with alterations in temperament, attachment, cognition, and development.

We will first review reports of other measures of biological functioning (e.g., changes in noreepinephrine, heart rate, and sleep) in infants exposed to maternal depression, and then present a brief overview of recent disturbances in EEG functioning associated with infants of depressed mothers. Newborns of depressed mothers have been reported to spend more time in indeterminate sleep, a less mature sleep state, and to have elevated levels of norepinephrine (Jones et al., 1997). This is an interesting finding, since indeterminate sleep has been reported to be inversely related to IQ 12 years later (Sigman & Parmalee, 1989). Dysregulation in infants of depressed mothers has also been characterized by Field (1998) to include elevated stress hormones during the neonatal period (e.g., norepinephrine and cortisol), excessive periods of indeterminate sleep, decreased vagal tone, right frontal EEG activation that remains stable from 1 week to 3 years of age, neurologic delays at 6 months, inferior scores on the Bayley Scale of Infant Development, and growth delays up to 12 months.

The literature suggests that infants born to

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mothers with depression demonstrate irritability and flattened affect early in life (Cohn, Matias, Tronick, Lyons–Ruth, & Connell, 1986), decreased scores on the Bayley Scale of Infant Development (Whiffen & Gotlib, 1989), and have higher rates of insecure attachments (Radke–Yarrow, Cummings, Kuczynski, & Chapman, 1985). Insecure attachment during infancy has been associated with behavioral inhibition and elevations in cortisol during the Strange Situation task (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). These infants also demonstrate lower levels of positive affect during play, behavioral disorganization during the Strange Situation task, lower levels of distress and longer latencies to onset of distress in response to maternal separation, and reduced right frontal electroencephalogram (EEG) activity (Dawson, Klinger, Panagiotides, Hill, & Speiker, 1992; Dawson, Klinger, Panagiotides, Speiker, & Frey, 1992).

In older, behaviorally inhibited children, hyperactivity of hypothalamic and amygdala-mediated responses to novel situations has been demonstrated (Kagan, 1982; Kagan, Reznick, & Snidman, 1988). We will show the relevance of this finding, given the ability of researchers to identify inhibited children during infancy. Increased activity of the sympathetic nervous system to unfamiliar events correlated with high morning salivary cortisol levels in these children as well. Rosenbaum et al. (1993) studied Kagan's longitudinal cohort of children initially identified as inhibited during infancy, and a separate "at-risk" clinical population, and concluded that "children identified as having behavioral inhibitions have high rates of childhood onset anxiety disorders themselves, and children of parents with panic disorder with agoraphobia, either alone or comorbid with major depressive disorder, are at increased risk for behavioral inhibition." At 3-year follow-up the differences in behaviorally inhibited children became more robust; they were significantly more likely to be diagnosed with four or more psychiatric disorders, and two or more anxiety disorders based on the DSM-III (Rosenbaum et al., 1993). Behavioral inhibitions often persist in the form of anxiety and mood disorders (Hirshfeld et al., 1992) and frequently lead to impairment in functioning. CRF hypersecretion may cause behavioral inhibition and pathological responses of the HPA axis in response to stress, suggesting a common mechanism for the development of behavioral inhibitions in infants and children and depression and anxiety in adults (Gold et al., 1988). The ability to detect neurobiological changes that appear stable over time in early infancy as a result of exposure to stress has been enhanced with the consistency of recent EEG findings.

The literature documenting EEG changes in infants born to mothers with depression has provided valuable insight into the sensitivity of the infant brain to early life stress. The most consistent findings have been in the frontal lobe. This is not surprising given the frontal lobe's rapid development in the first 2 years of life and its role in the regulation of emotion and affect (Chugani & Phelps, 1986). As early as 1 month of age, infants of depressed mothers exhibit greater relative right frontal EEG assymetry and more negative facial expressions (Jones et al., 1997). This pattern of right frontal EEG assymetry due to left frontal activation has been previously reported in depressed adults and teenagers (Davidson & Fox, 1989; Field, Fox, Pickens, & Nawrocki, 1995). EEG findings in this population at 1 month were significantly correlated with EEG findings at 3 months (Jones et al., 1997), suggesting stability in the system.

A separate study of 3- to 6-month old infants of depressed mothers also demonstrated right frontal EEG assymetry compared to controls. Furthermore, these changes were found to be associated with depressed affect in these infants (Field et al., 1995). Three years later, over 75% of these mothers continued to report elevated depressive symptoms, and their infants continued to demonstrate right frontal EEG asymmetry (Jones et al., 1997). As preschoolers, these children were observed to be more inhibited during play and less empathic during maternal distress. Indeed, greater relative right frontal EEG assymetry has been documented in children with behavioral inhibition (Fox et al., 1995). Left frontal EEG activation has been reported to reflect approach emotions such as joy (Fox, 1991). Left frontal

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hypoactivation (resulting in right frontal assymetry) may reflect a predisposition towards negative emotions, such as distress, or a diminution of approach emotions, predisposing one to behavioral inhibition.

Not only do these EEG changes in early infancy parallel those seen in their depressed mothers, they have also been found to be highly predictive of an infant's response to stress, such as maternal separation (Davidson & Fox, 1989). Several studies have confirmed that infants of depressed mothers demonstrate lower levels of distress in response to maternal separation and fail to activate the expected response of right frontal EEG activity (Dawson, Klinger, Panagiotides, Hill, & Spieker, 1992; Dawson, Klinger, Panagiotides, Spieker, & Frey, 1992). These infants also demonstrate reduced left frontal brain activity and longer periods of neutral affect during play, perhaps reflecting their diminished capacity to experience joy, or vulnerability towards experiencing negative emotions.

Whether right frontal EEG assymetry can be viewed as a state or a trait marker poses an interesting question given the stability of EEG changes in infants of depressed mothers across time. The work of Henriques and Davidson (1990) demonstrates that in depressed adults this pattern of EEG assymetry remains even after remission of symptoms suggesting a trait condition, independent of current depressed state. Davidson's group theorizes that relative right frontal EEG assymetry may be used as a marker for current depressed state and a predisposition for future depression. Certainly, the ability to utilize noninvasive measures, such as EEG, to identify high-risk infants would be a valuable tool in directing early intervention.

The ability to detect early alterations in HPA-axis functioning in infants as a result of exposure to maternal depression or other early adverse life events, and the ability to follow those changes longitudinally, would provide further insight into the vulnerability of developing neurological systems. Our group is currently addressing this deficit in the literature by following infants of depressed mothers over the 1st year of life, obtaining behavioral measures, as well as measurements of salivary cortisol during baseline conditions and in response to maternal separation. This will provide novel information while addressing the effect of treatment by comparing findings before and after the mother's recovery from depression. We also plan to explore the area of prenatal exposure to maternal depression through the measurement of neuroendocrine indices in cord blood of neonates born to mothers with current depression.

As mentioned previously, maternal depression is but one form of early life stress that infants are exposed to. In the next section we will explore other adverse events, such as abuse and neglect.

Effects of early abuse and neglect on infant development. Early adverse life events in humans have long been postulated to increase an individual's vulnerability toward the development of psychopathology in adulthood (Brown, Harris, & Eales, 1993). Recent studies emphasize the importance of these early negative interactions or deprivations in the development of early childhood conflicts that lead to adult psychopathology (Egeland, Sroufe, & Erickson, 1983; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Styron & Janoff–Bulman, 1997). There have been a plethora of studies examining the role of early psychosocial stress in the pathogenesis of affective and anxiety disorders (Fergusson, Horwood, & Lynskey, 1996; Mullen, Martin, Anderson, Romans, & Herbison, 1994). Although a genetic contribution has clearly been established in the development of affective disorders (Musselman et al., 1998), there is unequal penetrance, suggesting a genetic-stress diathesis where environment plays a preeminent role. Other factors such as age of onset, chronicity and frequency of abuse, the way a child perceives a situation (McEwen, 1998), and the presence of "enduring protective factors" or "transient buffers" (Cicchetti, 1993) may play equally important roles. Indeed, early life stress likely renders an individual vulnerable to subsequent life stressors, resulting in an increased risk for stress-induced psychopathology.

As described in detail previously, persistent changes in CRF neuronal systems have

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been implicated as one of the underlying mechanisms for increased vulnerability to psychopathology as a consequence of exposure to early life stressors (Ladd et al., 1996). Because CRF-containing neurons have a wide distribution in the CNS and play a role as the primary regulator of the endocrine, immune, behavioral, and autonomic stress response (Owens et al., 1991), this system represents a logical candidate to mediate this vulnerability. Moreover CRF neurons are believed to mediate cognitive and affective responses to stress, perhaps in part by modulating monoaminergic neurotransmitter systems (Dunn et al., 1990).

Within the past decade, several studies have revealed that childhood abuse and neglect predispose individuals to the development of both anxiety and affective disorders in adulthood (Brown et al., 1993; McCauley et al., 1997). Although a number of studies have characterized the behavioral and neuroendocrine consequences of early life stress in rodents and nonhuman primates, little data of a controlled type are available in human infants.

We have reviewed the neurobiological changes associated with major depression and PTSD in adults previously. We have also reviewed animal literature documenting early changes in the CRF system and HPA axis as a result of early adverse life events. It is likely that early abuse or neglect, especially chronic exposure, activates the HPA axis of infants, perhaps leading to permanent changes in their developing neurobiological systems. Findings have recently emerged from the study of children in orphanages which shed light on the impact of early deprivation in infants.

Gunnar (in press), in collaboration with Elinor Aimes in British Columbia, studied a group of infants who were adopted out of Romanian orphanages either prior to 4 months of age or after 8 months of age. Children adopted prior to 4 months of age did not differ behaviorally from other children reared in British Columbia who were matched for age, sex, and socioeconomic status. Not only did children who remained in orphanges beyond 8 months differ behaviorally during infancy, but 6–7 years later they demonstrated higher cortisol levels, especially during evening hours when one would expect the nadir levels. Carlson et al. (1995, 1999) conducted a longitudinal study on Romanian orphans ages 9–22 months who initially received a therapeutic intervention. When studied 2–3 years later these children lacked a strong circadian rhythm, showing a cortisol peak at noon instead of early morning. In addition, those children who lived at home with their parents but attended a funded day-care program showed normal cortisol rhythms while at home during weekends, but blunted circadian rhythms while attending the day-care program. Thus, it appears that infants with even limited exposure are sensitive to the effects of stress. Whether neglect differs from other forms of early life stressors requires closer scrutiny.

The perpetrator of abuse or neglect on an infant is often one of its primary caregivers (Basta & Peterson, 1990; Ernst, Angst, & Foldenyi, 1993), altering the development of appropriate attachments and impeding regulation of affect. Infants who have been physically abused demonstrate high levels of negative affect, while those who have been neglected show a predominantly flattened affect (Gaensbauer & Hiatt, 1984). This difficulty in regulating affect appears to persist into childhood, affecting social competence and peer relations. Several studies have confirmed high percentages of disorganized attachments in babies who are maltreated (Barnett, Ganiban, & Cicchetti, 1992; Carlson, Cicchetti, Barnett, & Braunwald, 1989; Main & Solomon, 1990), and elevated cortisol responses to maternal separation and approach by a stranger in infants with disorganized attachments (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; Spangler & Grossman, 1993). These early disturbances in cortisol regulation suggest involvement of the same systems implicated in adulthood depression and PTSD. We will now briefly review the available literature on early abuse.

While there is no body of literature addressing the effects of sexual and physical abuse during infancy, children who were maltreated as toddlers were followed longitudinally and rated as being more angry and noncompliant, hyperactive, distractable, inattentive, and aggressive during their preschool

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and kindergarten years (Erickson, Egeland, & Pianta, 1989). They used fewer "internal state" words to describe themselves, engaged in less symbolic play, evidenced lower self-esteem (Egeland et al., 1983), and perceived themselves to be less competent. To date, studies of HPA-axis alterations as a result of maltreatment have focused primarily on preschool and school-aged children. Salivary cortisol measurements in preschool children revealed that maltreated children scored lower in social competence, higher in shy–internalizing behaviors and acting out–externalizing behaviors, and demonstrated lower cortisol reactivity (Hart, Gunnar, & Cicchetti, 1995, 1996). It is likely that the CRF system and HPA axis is vulnerable to early physical or sexual abuse, given early changes associated with other types of stressors in infants. Future studies are needed to examine whether maltreatment during infancy predisposes one to transient or permanent alterations in HPA-axis functioning and ability to respond to stress.

Summary

In this paper we reviewed the neurobiological alterations in animals and humans that have been associated with exposure to a variety of early life stressors. These changes have been reported as early as the prenatal period in animals and the neonatal period in humans. Although changes in HPA-axis functioning as a result of early life exposure to stress appears reversible in animals, there is no documentation of reversibility in infants. Indeed, reports on EEG findings in infants reflect stability over time. Maternal depression and neglect are but two examples of maternal unavailability during the critical neonatal period of development; whether early sexual or physical abuse or abandonment results in similar neurobiological alterations has yet to be determined. Also, the specific contribution of individual stressors needs to be examined.

Through the process of allostasis, the HPA axis adapts to protect the body from a variety of internal and external stressors. Having a high allostatic load with multiple stressors, resulting in chronic overactivity of the HPA axis, can have deleterious effects on the individual (McEwen & Stellar, 1993). One example of this is the damaging effects of high glucocorticoid levels to hippocampal neurons, causing hippocampal atrophy. Atrophy of the hippocampus appears reversible if the stress is short-lived, but permanent if the stress continues for months or years (Sapolsky, 1992; Uno et.al., 1989).

Animal studies have shown that infant rodents and nonhuman primates develop neurobiological alterations in the HPA axis and CRF system in response to a variety of early life stressors. Documentation of frontal lobe EEG changes in infants of depressed mothers helps us to understand the dysregulation of affect and behavior in these infants, while studies of infants who were neglected or abused help to clarify the effects of those stressors on developing systems in humans.

Conclusions

Although considerable advances have been made, much remains obscure regarding the timing and magnitude of changes of components of the HPA axis, and of specific CRF neuronal systems, as a result of exposure to early life stressors. Future research should be directed towards longitudinal characterization of neuroendocrine function in children who are abused or neglected beginning at various ages. Measurement of hippocampal (and other brain regions), pituitary, and adrenal volumes, controlling for other risk factors for depression, twin studies to help evaluate the impact of genetics versus environment, and the impact of early identification and treatment (psychotherapeutic and somatic) in these vulnerable individuals deserves further scrutiny.

There may be important treatment implications of this work. Antidepressants will likely play a seminal role in the treatment of psychopathological states associated with early life stress. Adult rats maternally deprived as neonates demonstrated attenuation of the exaggerated HPA-axis response after chronic treatment with paroxetine, an antidepressant that is an SSRI (Nemeroff, 1996). SSRI treatment resulted in normalization of the ACTH and corticosterone response, CRF mRNA expres-

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sion in the PVN, amygdala, and bed nucleus of the stria terminalis, as well as basal and stress-induced CSF CRF concentrations. Treatment of rhesus monkeys with venlafaxine, a 5HT/NE reuptake inhibitor, reduced CRF mRNA expression in rats and CSF CRF concentrations in nonhuman primates (Ned H. Kalin, University of Wisconsin, unpublished observations). Preliminary studies by Plotsky et al. (personal communication, 1999) reveal that cessation of SSRI treatment results in a return of the exaggerated HPA stress response in the maternally deprived rats.

Tricyclic antidepressants, SSRIs, and venlafaxine have all been shown to reduce CRF mRNA expression (Brady, Gold, Herkenham, Lynn, & Whitfield, 1992; Brady, Whitfield, Fox, Gold, & Herkenham, 1991; Grigoriadis, Yearsall, & DeSouza, 1989). Treatment with fluoxetine reduces CSF CRF concentrations in depressed patients (DeBellis et al., 1994), as does desipramine treatment of normal controls (Veith, Lewis, & Langhor, 1992), and venlafaxine treatment of rhesus monkeys (Ned H. Kalin, University of Wisconsin, unpublished observations). SSRIs have also been shown to be effective in the treatment of PTSD (Friedman & Southwick, 1995). There is evidence that victims of childhood abuse appear to respond more favorably to fluoxetine than combat victims (Van derKolk et al., 1994). Our group has recently shown in rats that chronic paroxetine treatment reverses the effect of early maternal separation on CRF neurons (Nemeroff, 1996).

Thus, SSRIs and dual 5HT/NE reuptake inhibitors may have clinical utility in the treatment of abused individuals with depression or PTSD in part by reversing the neurobiological consequences of early life stress. Whether prophylactic antidepressant treatment can prevent or substantially reduce the risk for development of depression or PTSD, and whether the reversal of the neurobiological alterations persists posttreatment, remains unknown. The development of selective CRF-receptor-subtype antagonists represent a potential novel class of antidepressants or anxiolytics in the treatment of individuals exposed to traumatic events or early adverse life events, and developmental efforts are being pursued.

References

Ackland, J., Ratter, S., Bourne, G., & Rees, L. (1986). Corticotropin-releasing factor-like immunoreactivity and bioactivity of human fetal and adult hypothalami. *Journal of Endocrinology, 108*, 171–180.

Albeck, D., McKittrick, C., Blanchard, R., Nikulina, J., McEwen, B., & Sakai, R. (1997). Chronic social stress alters levels of corticotropin-releasing factor and arginine vasopressin mRNA in rat brain. *Neuroscience, 17*, 4895–4903.

Ada, R., & Grota, L. (1969). Effects of early experience on adrenocortical reactivity. *Physiology and Behavior, 4*, 303–305.

Anand, K., & Aynsley–Green, A. (1988). Measuring the severity of surgical stress in newborn infants. *Journal of Pediatric Surgery, 23*, 297–305.

Anand, K., & Nemeroff, C. (1996). Developmental Psychoneuroendocrinology. In M. Lewis (Ed.), *Textbook of child and adolescent psychiatry* (pp. 64–86). Baltimore: Williams & Wilkens.

Anand, K., Sippell, W., & Aynsley–Green, A. (1987). Randomized trial of fentanyl anesthesia in pre-term babies undergoing surgery: Effects on the stress response. *Lancet, 1*, 243–248.

Aponte, G., Leung, P., Gross, D., & Yamada, T. (1984). Effects of somatostatin on food intake in rats. *Life Science, 35*, 741–746.

Arato, M., Banki, C. M., Bissette, G., & Nemeroff, C. B. (1989). Elevated CSF CRF in suicide victims. *Biological Psychiatry, 25*, 355–359.

Austin, M., Rhodes, J., & Lewis, D. (1997). Differential distribution of corticotropin-releasing hormone immunoreactive axons in monoaminergic nuclei of the human brainstem. *Neuropsychopharmacology, 17*, 326–341.

Axelson, D., Doriswamy, M., McDonald, W., Boyko, O., Tuper, L., Patterson, L., & Nemeroff, C. (1993). Hypercortisolemia and hippocampal changes in depression. *Psychiatry Research, 47*, 163–173.

Baram, T., Yi, S., Arishi–Eliver, S., & Schultz, L. (1997). Developmental neurobiology of the stress response: Multi-level regulation of corticotropin-releasing hormone function. *Annals of the New York Academy of Sciences, 814*, 252–265.

Barnett, D., Ganiban, J., & Cicchetti, D. (in press). Maltreatment, negative expressivity, and the development of Type D attachments from 12- to 24-months of age. *Monographs of the Society for Research in Child Development*.

Basta, S., & Peterson, R. (1990). Perpetrator status and the personality characteristics of molested children. *Child Abuse and Neglect, 14*, 555–566.

Beaulieu, S., DiPaolo, T., & Barden, N. (1986). Control of ACTH secretion by the central nucleus of the amygdala: Implication of the serotonergic systems and its relevance to the glucocorticoid delayed negative feedback mechanism. *Neuroendocrinology, 44*, 247–254.

Benes, F. (1994). Developmental changes in stress adap-

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press

tation to psychopathology. *Development and Psychopathology, 6,* 723–739.
Boadle–Biber, M., Corley, K., Graves, L., Phan, T., & Rosecrans, J. (1989). Increases in the activity of tryptophan hydroxylase from cortex and midbrain of male Fisher 344 rats in response to acute or repeated sound stress. *Brain Research, 482,* 306–316.
Brady, L., Gold, P., Herkenham, M., Lynn, A., & Whitfield, H. (1992). The antidepressants fluoxetine, idazolam, and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: Therapeutic implications. *Brain Research Reviews, 572,* 117–125.
Brady, L., Whitfield, H., Fox, R., Gold, P., & Herkenham, M. (1991). Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineral corticoid receptor gene expression in rat brain. *Journal of Clinical Investigation, 87,* 831–837.
Bremner, J., Randall, P., Scott, T., Bronen, R., Seibyl, J., Southwick, S., Delaney, R., McCarthy, G., Charney, D., & Innis, R. (1995). Magnetic resonance imaging-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *American Journal of Psychiatry, 152,* 973–981.
Bremner, J., Randall, P., Vermetten, E., Staib, L., Bronen, R., Mazure, C., Capelli, S., McCarthy, G., Innis, R., & Charney, D. (1998). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—A preliminary report. *Biological Psychiatry, 41,* 23–32.
Bremner, J., Southwick, S., Johnson, D., Yehuda, R., & Charney, D. (1993). Childhood abuse and combat-related posttraumatic stress disorder in Vietnam veterans. *American Journal of Psychiatry, 150,* 235–239.
Brown, G., Harris, T., & Eales, M. (1993). Aetiology of anxiety and depressive disorders in an inner city population. *Psychological Medicine, 23,* 155–165.
Browne, A., & Finkelhor, D. (1986). Impact of childhood sexual abuse. *Psychological Bulletin, 99,* 66–77.
Butler, P., Weiss, J., Stout, J., & Nemeroff, C. (1990). Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus ceruleus. *Neuroscience, 10,* 176–183.
Carlson, V., Cicchetti, D., Barnett, D., & Braunwald, K. (1989). Disorganized/disoriented attachment relationships in maltreated infants. *Developmental Biology, 25,* 525–531.
Carlson, M., Dragomir, C., Earls, F., Farrell, M., Gunnar, M., Mocovei, O., Nystrom, P., & Sparling, J. (1999). *Behavioral and neuroendocrine consequences of early deprivation in institutionalized Romanian infants.* Manuscript in preparation.
Carlson, M., Dragomir, C., Earls, F., Farrell, M., Mocovei, O., Nystrom, P., & Sparling, J. (1995). Effects of social deprivation on cortisol regulation in institutionalized Romanian infants. *Society of Neuroscience Abstracts, 21,* 524.
Challis, J., & Brooks, A. (1989). Maturation and activation of hypothalamic-pituitary adrenal function in fetal sheep. *Endocrine News, 10,* 182–204.
Chalmers, D. T., Lovenberg, T. N., Grigoriadis, D. E., Behan, D. P., & DeSouza, E. (1995). Corticotropin-releasing factor receptors: From molecular biology to drug design [Review]. *Trends in Pharmacological Science, 17,* 166–172.
Chappell, P., Smith, M., Kilts, C., Bissette, G., Ritchie, J., Anderson, C., & Nemeroff, C. (1986). Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. *Journal of Neuroscience, 6,* 2908–2914.
Chen, R., Lewis, K., Perrin, M., & Vale, W. (1993). Expression cloning of a human corticotropin-releasing factor receptor. *Proceedings of the National Academy of Sciences of the USA, 90,* 8967–8971.
Chugani, H., & Phelps, M. (1986). Maturational changes in cerebral function in infants determined by 18FDG positron emission tomography. *Science, 231,* 840–843.
Cicchetti, D. (1993). Developmental psychopathology: Reactions, reflections, and projections. *Developmental Review, 13,* 571–602.
Cohn, J., Matias, R., Tronick, E., Lyons–Ruth, K., Connell, D., & Lyons–Ruth, K. (1986). Face-to-face interactions of depressed mothers and their infants. In T. Field & E. Tronick (Eds.), *Maternal depression and infant disturbance* (pp. 31–46). San Francisco: Jossey–Bass.
Coplan, J., Andrews, M., Rosenbaum, L., Owens, M., Friedman, S., Gorman, J., & Nemeroff, C. (1996). Persistent elevations of CSF concentrations of CRF in adult non-human primates exposed to early life stressors: Implications for the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences of the USA, 93,* 1619–1623.
Coplan, J., Trost, R., Owens, M., Cooper, T., Gorman, J., Nemeroff, C., & Rosenbaum, L. (1998). Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. *Archives of General Psychiatry, 55,* 473–477.
Cordia, M., & Biggio, G. (1986). Stress and GABA-ergic transmission: Biochemical and behavioral studies. In G. Biggio & E. Costa (Eds.), *GABA-ergic transmission and anxiety* (pp. 121–135). New York: Raven Press.
Davidson, R., & Fox, N. (1989). Frontal brain asymmetry predicts infants' response to maternal separation. *Journal of Abnormal Psychology, 98,* 127–131.
Dawson, G., Klinger, L., Panagiotides, H., Speiker, S., & Frey, K. (1992). Infants of mothers with depressive symptoms: Electroencephalographic and behavioral findings related to attachment status. *Development and Psychopathology, 4,* 67–80.
Dawson, G., Klinger, L., Panagiotides, H., Hill, D., & Speiker, S. (1992). Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. *Child Development, 6,* 725–737.
DeBellis, M., Chrousos, G., Dorn, L., Burke, L., Helmers, K., Kling M., Trickett, P., & Putnam, F. (1994). Hypothalamic pituitary adrenal dysregulation in sexually abused girls. *Journal of Clinical Endocrinology and Metababolism, 78,* 249–255.
Dunn, A., & Berridge, C. (1990). Physiological and behavioral responses to corticotropin-releasing factor administration: Is CFR a mediator of anxiety or stress responses? *Brain Research Reviews, 15,* 71–100.
Dunner, D., Patrick, R., & Fieve, R. (1979). Life events at the onset of bipolar affective disorder. *American Journal of Psychiatry, 136,* 508–511.
Economou, G., Andronikou, S., Cholevas, V., & Lapatsanis, P. (1993). Cortisol secretion in stressed babies during the neonatal period. *Hormone Research, 40,* 217–221.
Egeland, B., Sroufe, L., & Erikson, M. (1983). Developmental consequence of different patterns of maltreatment. *Child Abuse and Neglect, 7,* 459–469.
Erikson, M., Egeland, B., & Pianta, R. (1989). The ef-

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press

fects of maltreatment on the development of young children. In D. Cicchetti & V. Carlson (Eds.), *Child maltreatment: Theory and research on the causes and consequences of child abuse and neglect* (pp. 647–684). New York: Cambridge University Press.

Ernst, C., Angst, J., & Foldenyi, M. (1993). Sexual abuse in childhood. Frequency and relevance for adult morbidity data of a longitudinal epidemiological study. *European Archives of Psychiatry and Clinical Neurology, 242,* 293–300.

Fergusson, D., Horwood, L., & Lynsky, M. (1996). Childhood sexual abuse and psychiatric disorder in young adulthood: II. Psychiatric outcomes of sexual abuse. *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 1365–1374.

Field, T. (1998). Maternal depression effects on infants and early interventions. *Preventive Medicine, 27,* 200–203.

Field, T., Fox, N., Pickens, J., & Nawrocki, T. (1995). Relative right frontal EEG activation in 3–6 month old infants of depressed mothers. *Developmental Psychology, 31,* 358–363.

Fox, N. (1991). If it's not left, it's right. *American Psychologist, 46,* 863–872.

Fox, N., Rubin, K., Calkins, S., Marshall, T., Coplan, R., Porges, S., Long, J., & Stewart, S. (1995). Frontal activation asymmetry and social competence at 4 months of age. *Child Development, 66,* 1770–1784.

Fride, E., Dan, Y., Feldon, J., Halevy, G., & Weinstock, M. (1986). Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. *Physiology and Behavior, 37,* 681–687.

Friedman, M., & Southwick, S. (1995). Towards pharmacotherapy for post-traumatic stress disorder. In M. Friedman, D. Charney, & A. Deutch (Eds.), *Neurobiological and clinical consequences of stress* (pp. 465–483). Philadelphia: Lippincott–Raven.

Gaensbauer, T., & Hiatt, S. (1984). Facial communication of emotion in early infancy. In N. Fox & R. Davidson (Eds.), *The psychobiology of affective development* (pp. 207–230). Hillsdale, NJ: Erlbaum.

Garrison, N., & Earls, F. (1986). Epidemiological perspectives on maternal depression and the young child. In E. Tronick & T. Fields (Eds.), *Maternal depression and infant disturbance* (pp. 13–30). San Francisco: Jossey–Bass.

Gold, P., Goodwin, F., & Chrousos, G. (1988). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress. *New England Journal of Medicine, 319,* 413-420.

Green, B. (1994). Psychosocial research in traumatic stress: An update. *Journal of Trauma and Stress, 7,* 341–362.

Grigoriadis, D., Pearsall, D., & DeSouza, E. (1989). Effects of chronic antidepressant and benzodiazepine treatment on corticotropin-releasing factor receptors in rat brain and pituitary. *Neuropsychopharmacology, 2,* 53–60.

Grino, M., Burgunder, J., & Eskay, R. (1989a). Onset of glucocorticoid responsiveness of anterior pituitary corticotrophs during development is scheduled by corticotropin-releasing factor. *Journal of Endocrinology, 124,* 2686–2692.

Grino, M., Burgunder, J., & Eskay, R. (1989b). Ontogeny of expression of the corticotropin-releasing factor gene in the hypothalamic paraventricular nucleus and the propriomelenocortin gene in rat pituitary. *Journal of Endocrinology, 124,* 60–68.

Gunnar, M. (in press). The effects of adversity on neurobehavioral development. In C. A. Nelson (Ed.), *Early adversity and the development of stress reactivity and regulation.* Hillsdale, NJ: Erlbaum.

Gurvits, T., Shenton, M., Hokama, H., Ohta, H., Lasko, N., Gilberson, M., Orr, S., Kikinis, R., Lolesz, F., McCarley, R., & Pitman, R. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry, 40,* 193–199.

Hammen, C., Davila, J., Brown, G., Ellicot, A., & Gitlin, M. (1992). Psychiatric history and stress: Predictors of severity of unipolar depression. *Journal of Abnormal Psychology, 101,* 45–52.

Hart, J., Gunnar, M., & Cicchetti, D. (1996). Altered neuroendocrine activity in maltreated children related to symptoms of depression. *Development and Psychopathology, 8,* 201–214.

Hart, J., Gunnar, M., & Cicchetti, D. (1995). Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. *Development and Psychopathology, 7,* 11–26.

Heim, C., Owens, M., Plotsky, P., & Nemeroff, C. (1997). Persistent changes in corticotropin-releasing factor systems due to early life stress: Relationship to pathophysiology of major depression and PTSD. *Psychopharmacology Bulletin, 33,* 185–192.

Heim, C., Owens, M., Plotsky, P., & Nemeroff, C. (1996). The role of early adverse life events in the etiology of depression and post-traumatic stress disorder. *Annals of the New York Academy of Sciences, 813,* 1–14.

Henriques, J., & Davidson, R. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *Journal of Abnormal Psychology, 99,* 22–31.

Hertsgaard, L., Gunnar, M., Erikson, M., & Nachmias, M. (1995). Adrenocortical responses to the Strange Situation in infants with disorganized/disoriented attachment relationships. *Child Development, 66,* 1100–1106.

Hirshfeld, D., Rosenbaum, J., Biederman, J., Bolduc, E., Faraone, S., Snidman, N., & Reznick, J. (1992). Stable behavioral inhibition and its association with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 31,* 103–111.

Hitchcock, J., & Davis, M. (1996). Lesions of the amygdala, but not of the cerebellum, block conditioned fear measured with the potentiated startle paradigm. *Behavioral Neuroscience, 100,* 11–22.

Insel, T., Battaglia, G., Fairbanks, D., & DeSouza, E. (1988). The ontogeny of brain receptors for corticotropin-releasing factor and the development of their functional association with adenelate cyclase. *Neuroscience, 8,* 4151–4158.

Jones, N., Field, T., Davalos, M., & Pickens, J. (1997). EEG stability in infants/children of depressed mothers. *Child Psychiatry and Human Development, 28,* 59–70.

Kagan, J. (1982). Heart rate and heart rate variability as signs of a temporal dimension in infants. In C. Izard (Ed.), *Measuring emotions in infants and children* (pp. 38–66). Cambridge: Cambridge University Press.

Kagan, J., Reznick, J., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240,* 167–171.

Kalin, N., & Takahashi, L. (1988). Altered hypothalamic–pituitary–adrenal regulation in animal models of depression. In P. Gild & G. Chrousos (Eds.), *The hy-*

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press

pothalamic–pituitary–adrenal axis (pp. 67–70). New York: Raven Press.

Kaplan, S., Grumbach, M., & Aubert, M. (1976). The ontogenesis of pituitary hormones and hypothalamic factors in the human fetus: Maturation of central nervous system regulation of anterior pituitary function. *Recent Progress in Hormone Research, 32,* 161–243.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R., Moreci, P., Nelson, B., Welss, W., & Ryan, N. (1997). The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biological Psychiatry, 42,* 669–679.

Keller, S., Ackerman, S., & Schleifer, S. (1983). Effect of premature weaning on lymphocyte stimulation in the rat. *Psychosomatic Medicine, 45,* 75.

Kraiem, Z. (1985). Serum cortisol levels: The first ten days in full-term and pre-term infants. *Israel Journal of Medical Science, 21,* 170–172.

Krisch, B. (1981). Somatostatin-immunoreactive fiber projections into the brainstem and spinal cord of the rat. *Cell Tissue Research, 217,* 531–552.

Krishnan, K., Doraiswamy, P., Lurie, S., Figiel, G., Hsain, M., Boyko, O., Ellinwood, E., & Nemeroff, C. (1991). Pituitary size in depression. *Journal of Clinical Endocrinology and Metabolism, 72,* 256–259.

Ladd, C., Owens, M., & Nemeroff, C. (1996). Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology, 137,* 1212–1218.

Laudenslager, M., Capitanio, J., & Reite, M. (1985). Possible effects of early separation experiences on subsequent immune function in adult macque monkeys. *American Journal of Psychiatry, 142,* 862–864.

Levine, S. (1962). Plasma-free corticosteriod response to electric shock in rats stimulated in infancy. *Science, 135,* 795–796.

Levine, S., Haltmeyer, G., & Karas, G. (1967). Physiological and behavioral effects of infantile stimulation. *Physiology and Behavior, 2,* 55–63.

Liang, K., & Lee, E. (1988). Intra-amygdala injections of corticotropin-releasing factor facillitate inhibitory avoidance learning and reduce exploratory behavior in rats. *Psychopharmacology, 96,* 232–236.

Liaw, C., Lovenberg, T., Barry, G., Oltersdorf, T., Grigoriadis, D., & DeSouza, E. (1996). Cloning and characterization of the human corticotropin-releasing factor-2 receptor complementary deoxyribonucleic acid. *Endocrinology, 137,* 72–77.

Lovenberg, T., Chalmers, D., Liu, C., & DeSouza, E. (1995). CRF2a and CRF2b receptor mRNA's are differently distributed between the rat central nervous system and peripheral tissues. *Endocrinology, 136,* 4139–4142.

Lovenberg, T., Liaw, C., Grigoriadis, D., Clevenger, W., Chalmers, D., DeSouza, E., & Oltersdorf, T. (1995). Cloning and characterization of the human corticotropin-releasing factor facilitate inhibitory avoidance learning and reduce exploratory behavior in rats. *Psychopharmacology, 96,* 232–236.

Lynch, M., & Cicchetti, D. (1998). An ecological–transactional analysis of children and contexts: The longitudinal interplay among child maltreatment, community violence, and children's symptomatology. *Development and Psychopathology, 10,* 235–257.

Main, M., & Solomon, J. (1990). Procedures for identifying infants as disorganized/disoriented during the Ainsworth Strange Situation. In M. Greenberg, D. Cicchetti, & M. Cummings (Eds.), *Attachment during the pre-school years* (pp. 121–160). Chicago: University of Chicago Press.

McCauley, J., Kern, D., Kolodner, K., Dill, L., Schroeder, A., DeChant, H., Ryden, J., Derogatis, L., & Bass, L. (1997). Clinical characteristics of women with a history of childhood abuse. *Journal of the American Medical Association, 277,* 1362–1368.

McEwen, B. (1994). The plasticity of the hippocampus is the reason for its vulnerability. *Seminars in Neurology, 6,* 239–246

McEwen, B. (1998). Protective and damaging effects of stress mediators. *Seminars in Medicine of the Beth Israel Deaconess Medical Center, 338,* 171–179.

McEwen, B., & Stellar, E. (1993). Stress and the individual: Mechanisms leading to disease. *Archives of Internal Medicine, 153,* 2093–2101.

McKinney, W., & Bunney, W. (1969). Animal model of depression. I. Review of evidence: Implications for research. *Archives of General Psychiatry, 21,* 240–248.

Meaney, M., Aitken, D., & Bhatnagor, S. (1991). Postnatal handling attenuates neuroendocrine, anatomical, and cognitive impairments related to the aged hippocampus. *Science, 239,* 766–768.

Meaney, M., Aitken, D., & Sapolsky, M. (1988). Environmental regulation of the adrenocortical stress response in female rats and its implications for individual differences in aging. *Neurobiology of Aging, 12,* 31–38.

Melia, K., & Duman, R. (1991). Involvement of corticotropin-releasing factor in chronic stress regulation of the brain noradrenergic system. *Proceedings of the National Academy of Sciences of the USA, 88,* 8382–8386.

Mullen, P., Martin, J., Anderson, J., Romans, S., & Herbison, G. (1994). Childhood sexual abuse and mental health in adult life. *British Journal of Psychiatry, 163,* 721–732.

Mullen, P., Martin, J., Anderson, J., Romans, S., & Herbison, G. (1996). The long-term impact of the physical, emotional, and sexual abuse of children: A community study. *Child Abuse and Neglect, 20,* 7–21.

Musselman, D., Schatzberg, A., & Nemeroff, C. (1998). Biology of mood disorders. In A. Schatzberg & C. Nemeroff (Eds.), *Textbook of psychopharmacology* (pp. 439–478). Washington, DC: American Psychiatric Press.

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development, 67,* 508–522.

Nemeroff, C. (1996). The corticotropin-releasing factor hypothesis of depression: New findings and new directions. *Molecular Psychiatry, 1,* 336–342.

Nemeroff, C., Krishnan, K., Reed, D., Leder, R., Beam, C., & Dunnick, N. (1993). Adrenal gland enlargement in major depression. *Archives of General Psychiatry, 49,* 384–387.

Nemeroff, C., Owens, M., Andorn, A., & Stanley, M. (1988). Reduced corticotropin-releasing factor binding sites in the frontal cortex of suicide victims. *Archives of General Psychiatry, 45,* 577–579.

Nemeroff, C., Wilderlov, E., Bisette, G., Walleus, H., Karlsson, L., Ecklund, K., Kilts, C., Loosen, P., & Vale, W. (1984). Elevated concentrations of CSF corticotropin releasing factor-like immunoreactivity in depressed patients. *Science, 226,* 1342–1344.

O'Hara, M., Zekoski, E., Phillips, L., & Wright, E. (1990). Controlled prospective study of postpartum

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press

mood disorders: Comparison of childbearing and nonchildbearing women. *Journal of Abnormal Psychology, 99,* 3–15.

Owens, M., & Nemeroff, C. (1991). Physiology and pharmacology of corticotropin-releasing factor. *Pharmacological Review, 43,* 425–473.

Owens, M., & Nemeroff, C. (1994). Role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. *Clinical Chemistry, 40,* 288–295.

Owens, M., Plotsky, P., & Nemeroff, C. (1996). Biology of schizophrenia and affective disorders. In S. Watson (Ed.), *Symposium on Corticotropin-Releasing Factor* (pp. 59–84). London: John Wiley & Sons.

Pauk, J., Kuhn, C., Field, T., & Schanberg, S. (1986). Positive effects of tactile vs. kinesthetic or vestibular stimulation of neuroendocrine and ODC activity in maternally deprived rat pups. *Life Sciences, 39,* 2081–2087.

Pavlova, E., Pronina, T., & Skebel'skaya, Y. (1968). Histostructure of adenohypophysis of human fetuses and contents of somatotropic and adrenocorticotropic hormones. *General and Comparative Endocrinology, 10,* 269–276.

Pikoher, C., Owens, M., Kuhn, C., Schanberg, S., & Nemeroff, C. (1993). Maternal separation in neonatal rats elicits activation of the hypothalamic–pituitary axis: A putative role for corticotropin-releasing factor. *Psychoneuroendocrinology, 18,* 485–493.

Plotsky, P., & Meaney, M. (1993). Early, post-natal experience alters hypothalamic corticotropin-releasing factor (CRF) release in adult rats. *Molecular Brain Research, 18,* 195–200.

Plotsky, P., Thrivikraman, K., & Meaney, M. (1993). Central and feedback regulation of hypothalamic corticotropin-releasing factor secretion. In D. Chadwick, J. Marsh, & K. Ackrill (Eds.), *Symposium on Corticotropin-Releasing Factor* (pp. 59–84). London: John Wiley & Sons.

Potter, E., Sutton, S., Donaldson, C., Chen, R., Perrin, M., Lewis, K., Sawchenko, P., & Vale, W. (1994). Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. *Proceedings of the National Academy of Sciences of the USA, 91,* 8777–8781.

Primus, R., Yevich, E., Baltazar, C., & Gallager, D. (1997). Autoradiographic localization of CRF1 and CRF2 binding sites in the adult rat brain. *Neuropsychopharmacology, 17,* 308–316.

Raadsheer, F., Hoogendijk, W., Stam, F., Tilders, F., & Swaab, D. (1994). Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology, 60,* 436–444.

Raadsheer, F., VanHeerikhuize, J., Lucassen, P., Tilders, F., & Swaab, D. (1995). Corticotropin-releasing hormaone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *American Journal of Psychiatry, 152,* 1372–1376.

Radke–Yarrow, M., Cummings, E., Kuczynski, L., & Chapman, M. (1985). Patterns of attachment in two and three year olds in normal families and families with parental depression. *Child Development, 56,* 884–893.

Reite, M. (1987). Infant abuse and neglect: Lessons from the primate laboratory. *Child Abuse and Neglect, 11,* 347–355.

Rezek, M., Havlicek, V., Hughes, K., & Friesen, H. 1976). Cortical administration of somatostatin (SRIF): Effects on sleep and motor behavior. *Pharmacology, Biochemistry, and Behavior, 3,* 73–77.

Rivier, C., & Vale, W. (1985). Involvement of corticotropin-releasing factor and somatostatin in stress-induced inhibition of growth hormone secretion in the rat. *Endocrinology, 117,* 2478–2482.

Robicki, W., Forest, M., Loras, B., Bonnet, H., & Bertrand, J. (1990). Free cortisol in the first three months of life. *Biology of the Neonate, 57,* 21–29.

Rosenbaum, J., Biederman, J., Bolduc–Murphy, E., Faraone, S., Chaloff, J., Hirshfeld, D., & Kagan, J. (1993). Behavioral inhibition in childhood: A risk factor for anxiety disorders. *Harvard Review of Psychiatry, 1,* 2–16.

Sapolsky, R. (1992). Glucocorticoid's endanger hippocampal neurons. In R. Sapolsky (Ed.), *Stress, the aging brain and the mechanisms of neuron death* (pp. 119–145). Cambridge, MA: MIT Press.

Sapolsky, M., & Meaney, M. (1986). Maturation of the adrenocortical stress response: Neuroendocrine control mechanisms and the stress hyporesponsive period. *Brain and Research Reviews, 11,* 65–76.

Schanberg, S., Evoniuk, G., & Kuhn, C. (1984). Tactile and nutritional aspects of maternal care: Specific regulators of neuroendocrine function and cellular development. *Proceedings of the Society for Experimental Biology and Medicine, 175,* 135–146.

Sheline, Y., Wang, P., Gado, M., Csernansky, J., & Vannierr, M. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the USA, 93,* 3908–3913.

Sigman, M., & Parmalee, A. (1989). *Longitudinal predictors of cognitive development*. Paper presented at the AAAS Meeting, San Francisco.

Smith, M., Yehuda, R., Koverola, C., & Hanna, C. (1997). Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biological Psychiatry, 42,* 680–686.

Spangler, G., & Grossman, K. (1993). Biobehavioral organization in securely and insecurely attached infants. *Child Development, 64,* 1439–1450.

Stout, S., Kilts, C., & Nemeroff, C. (1995). Neuropeptides and stress. In M. Friedman, A. Deutch, & D. Charney (Eds.), *Neurobiological and clinical consequences of stress* (pp. 103–123). Philadelphia: Lippincott–Raven.

Styron, T., & Janoff–Bulman, R. (1997). Childhood attachment and abuse: Long-term effects on adult attachment, depression, and conflict resolution. *Child Abuse and Neglect, 21,* 1015–1023.

Takahashi, L., & Kalin, N. (1991). Early developmental and temporal characteristics of stress-induced secretion of pituitary–adrenal hormones in prenatally stressed rat pups. *Brain Research, 558,* 75–78.

Thierry, A., Tassin, J., Blanc, G., & Glowinski, J. (1976). Selective activation of mesocortical DA system by stress. *Nature, 263,* 242–244.

Uno, H., Tarara, R., Else, J., Suleman, M., & Sapolsky, R. (1989). Hippocampal damage associated with prolonged and fetal stress in primates. *Journal of Neuroscience, 9,* 1705–1711.

Valentino, R., Foote, S., & Aston–Jones, G. (1983). Corticotropin-releasing factor activates noradrenergic neurons of the locus ceruleus. *Brain Research Reviews, 270,* 363–367.

Van derKolk, B., Dreyfuss, D., Michaels, M., Shera, D.,

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press

Berkowitz, R., Fisler, R., & Saxe, G. (1994). Fluoxetine in posttraumatic stress disorder. *Journal of Clinical Psychiatry, 55*, 517–522.

Veith, R., Lewis, N., & Langohr, J. (1992). Effect of desipramine on cerebral spinal fluid concentrations in human subjects. *Psychiatry Research, 436*, 1–8.

Walker, C., Perrin, M., Vale, W., & Rivier, C. (1986). Ontogeny of the stress response in the rat: Role of the pituitary and the hypothalamus. *Endocrinology, 118*, 1445–1451.

Walker, C., Sapolsky, M., & Meaney, M. (1986). Increased pituitary sensitivity to glucocorticoid feedback during the stress hyporesponsive period in the neonatal rat. *Endocrinology, 119*, 1816–1821.

Weiss, J., & Kilts, C. (1995). Animal models of depression and schizophrenia. In A. Schatzberg & C. Nemeroff (Eds.), *Textbook of psychopharmacology* (pp. 81–113). Washington, DC: American Psychiatric Press.

Weiss, J., Stout, J., Aaron, M., Owens, M., & Nemeroff, C. (1994). Experimental studies of anxiety and depression: Locus coeruleus and corticotropin-releasing factor. *Brain Research Bulletin, 35*, 561–572.

Whiffen, V., & Gotlib, I. (1989). Infants of postpartum depressed mothers: Temperament and cognitive status. *Journal of Abnormal Psychology, 98*, 274–279.

Winslow, J., & Insel, T. (1991). The infant rat separation paradigm: A novel test for anxiolytics. *Trends in Pharmacological Sciences, 12*, 402–404.

Yehuda, R., Giller, E., Southwick, S., Lowy, M., & Mason, J. (1991). Hypothalamic–pituitary–adrenal dysfunction in post-traumatic stress disorder. *Biological Psychiatry, 30*, 1031–1048.

https://doi.org/10.1017/S0954579499002205 Published online by Cambridge University Press