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Stress and development: Behavioral and biological consequences

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Abstract
Childhood abuse is an important public health problem; however, little is known about the effects of abuse on the brain and neurobiological development. This article reviews the behavioral and biological consequences of childhood abuse and places them in a developmental context. Animal studies show that both positive and negative events early in life can influence neurobiological development in unique ways. Early stressors such as maternal separation result in lasting effects on stress-responsive neurobiological systems, including the hypothalamic–pituitary–adrenal (HPA) axis and noradrenergic systems. These studies also implicate a brain area involved in learning and memory, the hippocampus, in the long-term consequences of early stress. Clinical studies of patients with a history of abuse also implicate dysfunction in the HPA axis and the noradrenergic and hippocampal systems; however, there are multiple questions related to chronicity of stress, developmental epoch at the time of the stressor, presence of stress-related psychiatric disorders including posttraumatic stress disorder and depression, and psychological factors mediating the response to trauma that need to be addressed in this field of research. Understanding the effects of abuse on the development of the brain and neurobiology will nevertheless have important treatment and policy implications.

Childhood abuse is a major public health concern in this country today (Barnett, Manly, & Cicchetti, 1993). The recent focus on childhood abuse in our society is related to increased publicity generated by media reports as well as the findings of large-scale epidemiological studies which have highlighted the magnitude of the problem (MacMillan, Fleming, Trocme, Boyle, Wong, Racine, Beardslee, & Offord, 1997; McCauley, Kern, Kolodner, Dill, Schroeder, DeChant, Ryden, Derogatis, & Bass, 1997). Women and children are extremely vulnerable to victimization, making young girls at especially high risk for childhood sexual abuse. Boys, however, are also often the victim of both physical and sexual abuse. The sheer magnitude of the problem on a public health scale can be seen by recent nationwide surveys showing that 16% of women have a history childhood sexual abuse (McCauley et al., 1997). This means that at least one out of every seven women in our society has been the victim of childhood sexual abuse at least once before her 18th birthday, abuse being defined as rape, threat of rape, or unwanted genital fondling. Figures of childhood sexual abuse may seem difficult to believe, but multiple studies over the past 15 years have corroborated the findings of high rates of abuse in our country. Sexual abuse is the most common cause of posttraumatic stress disorder (PTSD) in women, affecting 10% of, or about 13 million, women in the country at some time in their lives based on a recent nationwide survey (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995).

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PTSD affects about 8% of the general population and is twice as common in women as in men. For men the cause of PTSD is more likely to be physical abuse or assault. When PTSD rates of 8% are compared with rates of other major psychiatric disorders, such as schizophrenia, which currently affects 1% of the general population, it can be seen that this is a problem that needs to be addressed. Traumatized children are not able to advocate for themselves, and their problems are not as visibly obvious or comprehended by the general community in the same way as other patient groups, such as cancer survivors. This has led to the situation where funding appropriated to cancer research is $9 billion per year and rapidly growing based on recommendations of the U.S. Congress, while only 10 million per year is allocated to studies of childhood abuse-related psychiatric disorders, which are more common than cancer. Our society is spending only $1 per year for every woman in our country with long-term psychiatric disability from childhood sexual abuse, almost none of which is devoted to study effects on physical status, resulting in a situation where essentially nothing is known about this area.

Early studies focused on the prevalence and psychological consequences of abuse, while our understanding of the neurobiological consequences of abuse have lagged behind. In examining the effects of abuse on neurobiological development, animal models can fill in the gaps that have not yet been addressed or cannot be answered by studies in traumatized children. There is ample evidence that stress results in long-term changes in neurobiology, and emerging evidence supports the idea that these effects underlie the symptoms of PTSD and other stress-related disorders (see also Bremner & Narayan, 1998; Bremner, Southwick, & Charney, 1999; Charney & Bremner, 1999; Friedman, Charney, & Deutch, 1995; Lopez, Akil, & Watson, 1999; McEwen, 2000; Newport & Nemeroff, 2000). Most of these studies have focused on the biological consequences of trauma in adulthood. Studies have only recently begun to look at the effects of early stress on neurobiological development (Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000). The development of the organism is driven by a complex interaction between nature and nurture or, put another way, between genetics and environment. One of the most important environmental factors that can affect development is stress early in life. The relationship between genetics and environment is also not as dichotomous as once believed. For instance, environmental events such as stressors can modify the way in which the genome is transcribed. Repeated exposure to stressors early in life has effects on stress-responsive neurobiological systems that persist throughout life. These stress-responsive systems include the hypothalamic–pituitary–adrenal (HPA) axis, locus coeruleus and norepinephrine, benzodiazepine, serotonin, dopaminergic, neuropeptide systems, and central amino acid systems, as well as brain memory systems, including hippocampus, amygdala, and prefrontal cortex (Figure 1). Understanding the effects of early stress on neurobiology provides a basis for understanding the effects of childhood abuse on neurobiological development. This paper reviews preclinical studies (i.e., studies performed in animals) and clinical studies of the effects of early stress on neurobiological development, and integrates these findings in a developmental context with an attempt to understand approaches to assessment and treatment.

Animal Models for the Effects of Early Stress on Neurobiology

Animal models are commonly used in the study of biological bases in psychiatric disorders. These models have been useful in the understanding of stress-related psychiatric disorders, including PTSD and depression (McKinney & Bunney, 1969; Rasmusson & Charney, 1997; Treit, 1985; Weis & Simson, 1985; Yehuda & Antelman, 1993). Typical animal models of stress include exposure to repeated electric shocks over which the animal has no control, forced swim in cold water, exposure to a predator, or defeat by another animal. More recently models have been developed which are specific to early stress, including separation of the animal from its mother (Ladd, Owens, & Nemeroff, 1996;

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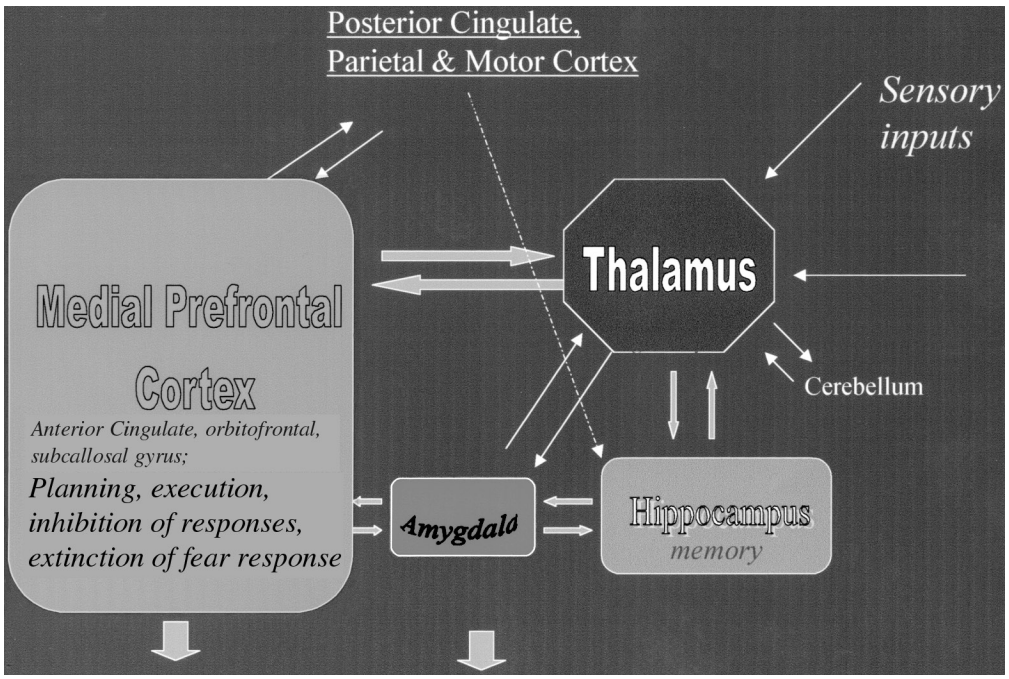


Figure 1. Functional neuroanatomy of childhood abuse. The functional anatomy of childhood abuse-related PTSD involves hippocampus, amygdala, thalamus, and medial prefrontal cortex.

Meaney, Aitken, van Berkel, et al., 1988; Plotsky & Meaney, 1993). Exposure to early stressors results in changes in behavior that are similar to human anxiety and that persist into adulthood, including freezing, fear-potentiated startle, stress-induced analgesia, contextual fear, hyperarousal, restlessness, increased gastrointestinal motility, decreased food intake, increased defecation, sleep disturbances, deficits in memory and attention, or avoidance of novel stimuli like an open field. Stressors are also associated with acute release of stress-related neuropeptides, hormones, and transmitters, including corticotropin releasing factor (CRF) which causes release of adrenocorticotropin hormone (ACTH), cortisol, norepinephrine, benzodiazepines, serotonin, dopamine, and opiates. Early stress can have a negative effect on neurobiology and the developing brain (Anand, Coskun, Thrivikraman, Nemeroff, & Plotsky, 1999). These effects can become apparent even before birth. For example, exposure of pregnant female rats to stressors during the last trimester of pregnancy resulted in alterations in the morphological and behavioral development of the offspring (Hennessy, Davis, McCrea, Harvey, & Williams, 1999). Studies in animals show that early life stressors can have long-term effects on neurobiology that persist into adult life. These findings are reviewed in more detail below.

It is important to fully understand the strengths and limitations of animal models of early stress. Animal models of early stress are helpful for our understanding of effects on neurobiology and for generation of hypotheses; however, the findings from these studies do not necessarily translate into a blueprint for the effects of abuse on children. Animal models involve a more or less one dimensional approach to stressors, whereas childhood abuse is complex, and multiple factors need to be taken into account, including the copresence of neglect, the family environment, psychological mechanisms of coping and defense, and the individual's response to the stressor. It is also important to consider the stage of development at which the stressor takes place (Nelson & Carver, 1988; Toth & Cicchetti, 1988). Stressors very early in life

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appear to have a greater effect on personality and dissociation, while later stressors result in more of a hyperarousal response. We hypothesize that differences in neurobiological function determine these responses. Animals also lack the complexity of cerebral organization seen in humans, and it is this cerebral complexity that makes us unique and that makes the individual's response to stressors so complex.

Effects of Early Stress on the HPA Axis, Memory, and the Hippocampus

The stress responsive system that has been most studied to date in relation to early stress is the HPA axis and the hippocampus (which is involved in learning and memory). Stress results in release of CRF from the hypothalamus, with stimulation of ACTH release from the pituitary, resulting in glucocorticoid release from the adrenal, which in turn have a negative feedback effect on the axis at the level of the pituitary as well as central brain sites including hypothalamus and hippocampus. In addition to its role in triggering the HPA axis, CRF acts centrally to mediate fear-related behaviors (Owens & Nemeroff, 1992) and triggers other neurochemical responses to stress such as the noradrenergic system via the brain stem locus coeruleus (Melia & Duman, 1991).

Studies in animals showed that early stress has lasting effects on the HPA axis (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999). During infancy animals do not demonstrate HPA axis responses to stress. However, infant animals exposed to stressors demonstrate increases in immediate early genes (e.g., c-*fos* and nerve growth factor inducible gene) in the paraventricular nucleus of the hypothalamus (Smith, Kim, Van Oers, & Levine, 1997). These studies demonstrate that a stress-responsive system is present, even though it does not invoke the HPA axis at that stage of development. A variety of early stressors, including maternal deprivation, resulted in increased glucocorticoid response to subsequent stressors (Fride, Dan, Feldon, Halevy, & Weinstock, 1986; Levine, Weiner, & Coe, 1993; Stanton, Gutierrez, & Levine, 1988). Maternally deprived rats had decreased numbers of glucocorticoid receptors, as measured by dexamethasone binding, in the hippocampus, hypothalamus, and frontal cortex (Ladd et al., 1996). Stressed animals demonstrated an inability to terminate the glucocorticoid response to stress (Sapolsky, Krey, & McEwen, 1994a, 1994b), which could be related to decreased glucocorticoid receptor binding in the hippocampus (Makino, Smith, & Gold, 1995). Early postnatal adverse experiences increased hypothalamic CRF mRNA, median eminence CRF content, and stress induced glucocorticoid (Plotsky & Meaney, 1993) and ACTH release (Ladd et al., 1996). These effects could be mediated by an increase in synthesis of corticotropin releasing hormone (CRH) mRNA following stress (Makino, Schulkin, Smith, Pacak, Palkovits, & Gold, 1995). In nonhuman primates, adverse early experiences resulted in long-term effects on behaviors, as well as elevated levels of CRF in the cerebrospinal fluid (Coplan, Andrews, Rosenblum, Owens, Friedman, Gorman, & Nemeroff, 1996). These observations suggest early adverse experience permanently affects the HPA axis.

The hippocampus, a brain area involved in learning and memory, is particularly sensitive to the effects of stress, which are at least partially mediated by release of glucocorticoids (McEwen, 2000; Sapolsky, 1996, 2000; Sapolsky, Uno, Rebert, & Finch, 1990). The hippocampus, a major target organ for glucocorticoids in rat brain (McEwen, de Kloet, & Rostene, 1986), although apparently not to the same degree in primate (Sanchez, Young, Plotsky, & Insel, 2000), has an inhibitory effect on the HPA axis (Herman, Schafer, & Young, 1989; Jacobson & Sapolsky, 1991), so that hippocampal lesions will be predicted to result in hypercortisolemia. Stress has resulted in decreased dendritic branching or neuronal loss in the CA3 region of the hippocampus (Magarinos, McEwen, Flugge, & Fuchs, 1996; Uno, Tarara, Else, Suleman, & Sapolsky, 1989). Studies in a variety of animal species showed that direct glucocorticoid exposure results in decreased dendritic branching (Virgin, Taryn, Packan, Tombaugh, Yang, Horner, & Sapolsky, 1991; Woolley, Gould,

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& McEwen, 1990), alterations in synaptic terminal structure (Magarinos & McEwen, 1995; Magarinos, Verdugo, & McEwen, 1997), a loss of neurons (Uno et al., 1989), and an inhibition of neuronal regeneration (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998) within the CA3 region of the hippocampus. The effects of glucocorticoids are mediated through disruption of cellular metabolism with increased vulnerability to endogenously released excitatory amino acids (Sapolsky, 1996). These findings are consistent with a relationship between high levels of glucocorticoids released during stress and hippocampal damage with associated memory deficits.

High levels of glucocorticoids seen with stress have been associated with deficits in new learning, in addition to damage to the hippocampus (Luine, Villages, Martinex, & McEwen, 1994). Glucocorticoids play a role in hippocampal-based long-term potentiation, which is felt to represent the molecular basis of new learning and memory (Pavlides, Kimura, Magarinos, & McEwen, 1995). Long-term subcutaneous implants of glucocorticoids which mimic the chronic stress situation were shown to result in deficits in new learning and memory for maze escape behaviors. Moreover, the magnitude of deficits in new learning of maze escape behaviors was correlated with the number of damaged cells in the CA3 region of the hippocampus (Arbel, Kadar, Silberman, & Levy, 1994). Physiologic levels of glucocorticoids can impair memory, even without the loss of hippocampal neurons (Bodnoff, Humphreys, Lehman, Diamond, Rose, & Meaney, 1995). The implication of these findings to childhood abuse is that abuse may be associated with the development of problems in learning and academic achievement which are neurologically based (Cicchetti, Toth, & Hennessy, 1993).

Other neurochemical systems interact with glucocorticoids to mediate the effects of stress on memory and the hippocampus. Brain-derived neurotrophic factor (BDNF) is a recently isolated neuropeptide that has important trophic effects on the hippocampus and other brain regions (Smith, Makino, Kvetnansky, & Post, 1995). Stress resulted in a reduction in BDNF mRNA in the hippocampus, an effect that may be partially related to glucocorticoid release (Smith, Makino, Kim, & Kvetnansky, 1995) or 5-HT_{2A} receptor stimulation (Vaidya, Marek, Aghajanian, & Duman, 1997). Given the trophic effects of BDNF these findings suggest that decreased levels of BDNF in stress may result in hippocampal atrophy or cell death, which has been associated with stress at early stages of development (Zhang, Smith, Li, Weiss, & Post, 1998).

Treatments increasingly used in the treatment of traumatized children have important effects on the hippocampus. Antidepressant drugs and electroconvulsive therapy increased BDNF levels in the CA3 and CA1 regions of the hippocampus (Nibuya, Morinobu, & Duman, 1995), reversing the effects seen in stress. Recently, antidepressants (including fluoxetine) were shown to increase expression of cAMP response element binding protein (CREB) mRNA in the CA3 and CA1 regions of the hippocampus (Nibuya, Nestler, & Duman, 1995). CREB is an intracellular protein that regulates gene transcription and among other actions increases translation of BDNF protein. Serotonin reuptake inhibitors also increase dendritic branching within the hippocampus (Duman, Heninger, & Nestler, 1997), an effect that may be mediated through CREB. Phenytoin (dilantin), a medication used to treat epilepsy, inhibits excitatory amino acid transmission and blocks the effects of stress on the hippocampus (Watanabe, Gould, & McEwen, 1992). These findings have implications for treatment of traumatized children. In a recent study of adults with PTSD primarily related to childhood abuse, we found that 1 year of treatment with the serotonin reuptake inhibitor paroxetine resulted in an improvement in hippocampal-based verbal declarative memory function (20% improvement in delayed recall of a paragraph, measured with the Wechsler Memory Scale).

The hippocampus demonstrates an unusual capacity for neuronal regeneration. Elevated glucocorticoids or stressors suppress the capacity for neuronal regeneration in the dentate gyrus of the hippocampus (Gould, Cameron, Daniels, Woolley, & McEwen, 1992; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997;

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Gould et al., 1998). Psychosocial stress in the tree shrew likewise results in an inhibition of neurogenesis in the dentate gyrus of the hippocampus, an effect mediated by the *N*-methyl-D-aspartate (NMDA) receptor (Gould et al., 1997). Furthermore, glucocorticoids have an important effect on neurogenesis during development. The hypocortisolemic period of infancy is normally associated with rapid cell death in the dentate gyrus—this effect is inhibited by administration of glucocorticoids (Gould, Woolley, Cameron, Daniels, & McEwen, 1991). However, glucocorticoids in this period of development also inhibit cell birth (Gould, Woolley, & McEwen, 1991), demonstrating that glucocorticoids play an important role in both cell birth and death in the hippocampus. Changes in the environment (e.g., social enrichment) can also modulate neurogenesis in the dentate gyrus of the hippocampus and slow the normal age-related decline in neurogenesis (Kempermann, Kuhn, & Gage, 1998). These findings may have implications for victims of abuse, especially given recent findings that the human hippocampus also demonstrates the capacity for neurogenesis (Eriksson, Pefilieva, Bjork–Eriksson, Alborn, Nordborg, Peterson, & Gage, 1998; Gage, 1988). Increased maternal care in rat pups has also been associated with increased cholinergic input to the hippocampus and enhanced spatial learning and memory, as well as increased BDNF (Liu, Diorio, Day, Francis, & Meaney, 2000). Together these findings indicate that early environmental events, both positive and negative, have long-term effects on brain structure and function, especially for sensitive areas such as the hippocampus.

An animal model that has been applied to studying beneficial early interventions is postnatal handling. Postnatal handling has important effects on the development of behavioral and endocrine responses to stress. For example, daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) resulted in increased Type II glucocorticoid receptor binding that persisted throughout life. This was associated with increased feedback sensitivity to glucocorticoids, and reduced glucocorticoid-mediated hippocampal damage in later life (Meaney, Aitken, Bhatnager, van Berkel, & Sapolsky, 1988; Meaney, Aitken, Sharma, & Sarrieau, 1989). These effects appear to be due to a type of "stress inoculation" from the mothers repeated licking of the handled pups (Liu, Diorio, Tannenbaum, Caldji, Rancis, Freedman, Sharma, Pearson, Plotsky, & Meaney, 1997). Considered together, these findings suggest that early in the postnatal period there is a naturally occurring brain plasticity in key neural systems that may "program" an organism's biological response to stressful stimuli.

Noradrenergic Systems

Accumulated evidence suggests a relationship between alterations in noradrenergic brain systems and stress (reviewed in Bremner, Krystal, Southwick, & Charney, 1996a, 1996b; Tanaka, Yoshida, Emoto, & Ishii, 2000). The majority of noradrenergic cell bodies are located in the locus coeruleus, a nucleus in the dorsal pons region of the brain stem, with a dense network of axons that extend throughout the cerebral cortex and to multiple cortical and subcortical areas, including hippocampus, amygdala, thalamus and hypothalamus, bed nucleus of stria terminalis, nucleus accumbens, as well as descending projections which synapse at the level of the thoracic spinal cord (Foote, Bloom, & Aston–Jones, 1983). Exposure to stressors results in activation of the locus coeruleus, with release of norepinephrine throughout the brain (Abercrombie & Jacobs, 1987a, 1987b; Foote et al., 1983). Acute stressors (e.g., a cat seeing a dog or another aggressive cat) result in an acute increase in firing of neurons in the locus coeruleus (Levine, Litto, & Jacobs, 1990), the hippocampus, and medial prefrontal cortex (Finlay, Zigmond, & Abercrombie, 1995). Chronic stress is associated with potentiated release of norepinephrine with exposure to subsequent stressors (Nisenbaum, Zigmond, Sved, & Abercrombie, 1991). Repetitive stress is associated with an increased turnover and release of norepinephrine in the cortex, hippocampus, amygdala, hypothalamus, and locus coeruleus (Nisenbaum et al., 1991; Tanaka et al., 2000).

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Early stress is associated with lifelong increases in sensitivity of the noradrenergic system (Francis et al., 1999). Noradrenergic input stimulates release of CRF from the paraventricular nucleus of the hypothalamus. Maternal separation resulted in an increased release of norepinephrine in the paraventricular nucleus of the hypothalamus. Maternal separation also resulted in a decrease in the alpha-2 autoreceptors of the locus coeruleus (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000). Since the alpha-2 receptor is inhibitory, this would be expected to result in an increase in locus coeruleus activity, with increased noradrenergic reactivity. In summary, early stress is associated with lasting increases in noradrenergic responsivity.

Dopaminergic Systems

The three major dopaminergic neuronal systems include nigrostriatal (projecting from substantia nigra to striatum), mesolimbic (projection from midbrain to nucleus accumbens), and mesocortical–mesoprefrontal (projection from midbrain to prefrontal cortex) systems. Dopamine innervation of the medial prefrontal cortex (mPFC) appears to be particularly vulnerable to even mild and brief stress. Preclinical studies are in support of the fact that both acute and chronic stress may have a negative impact on the normal function of the dopaminergic system. Sufficiently low intensity stress (such as that associated with conditioned fear) or brief exposure to stress increases dopamine release and metabolism in the prefrontal cortex in the absence of overt changes in other mesotelencephalic dopamine regions (Deutch & Roth, 1990; Deutch, Tam, & Roth, 1985). Low intensity electric footshock increases in vivo tyrosine hydroxylase and dopamine turnover in the mPFC but not the nucleus accumbens or striatum. Thus, the mPFC dopamine innervation is preferentially activated by stress compared to mesolimbic and nigrostriatal systems, whereas the mesolimbic dopamine innervation appears to be more sensitive to stress than the striatal dopamine innervation (Deutch et al., 1985; Deutch & Roth, 1990). Intracranial self-stimulation of dopaminergic systems has been used as a model for anhedonia, or the inability to experience pleasure when engaging in normally pleasurable activities, suggesting that numbing, decreased interest, or being cut off may be related to alterations in dopaminergic systems.

The prefrontal cortex has been suggested to play a role in "working memory" in conjunction with other brain areas like hippocampus. A critical range of dopamine turnover is necessary for keeping this "working memory system" active and ready for optimal cognitive functioning (Horger & Roth, 1996), a situation that is impaired in situations of extreme or chronic stress (Arnsten, 2000). The mesofrontal dopaminergic system also plays a role in emotional responses, as well as selective information processing, and coping with the external world (Vogt, Finch, & Olson, 1992; reviewed in Pani, Porcella, & Gessa, 2000). The mPFC has inhibitory inputs to the amygdala that have been hypothesized to play a role in the extinction of fear responses. The area of the effects of early stress on mesofrontal dopamine function is not well developed; however, imaging findings from patients with childhood abuse implicate dysfunction of medial prefrontal cortex, as reviewed below.

Serotonin

The majority of serotonin neurons in the brain are located in the dorsal raphe (midbrain), with projections to cortical and subcortical areas. Animals exposed to a variety of stressors, including foot shock, tail shock, tail pinch, and restraint stress, have all been shown to produce an increase in serotonin turnover in the medial prefrontal cortex (Adell, Garcia–Marquez, Armario, & Gelpi, 1988; Inoue, Tsuchiya, & Koyama, 1994; Pei, Zetterstrom, & Fillenz, 1990; Petty & Sherman, 1983), nucleus accumbens, amygdala, and lateral hypothalamus, and locus coeruleus (Kaehler, Singewald, Sinner, Thurnher, & Philippu, 2000) with preferential release during conditioned fear in medial prefrontal cortex (Inoue et al., 1994). Chronic electric shock producing learned helplessness behavioral deficits was associated with reduced in vivo release of serotonin in frontal cortex (Petty,

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Kramer, & Wilson, 1992), probably reflecting a situation where synthesis is not able to keep pace with demand. After inescapable stress, 5-HT_{2A} receptor density was decreased in the hypothalamus in helpless rats as compared to control rats that were stressed but not helpless. While there were no changes in density in 5-HT_{1A} receptors in any brain region, decreases were found for 5-HT_{2A} receptor density in hippocampus and amygdala, related to stress but not related to helplessness. In mPFC, the serotonin transport sites showed decreased density in helpless rats as compared to controls but not to nonhelpless rats (Wu, Kramer, Kram, Steciuk, Crawford, & Petty, 1999). Chronic restraint, however, has been shown to result in a decrease in 5-HT_{1A} binding in the hippocampus (Watanabe, Sakai, McEwen, & Mendelson, 1993). Animals exposed to social stress also had a decrease in binding of 5-HT_{1A} receptors in hippocampus and dentate gyrus and a decrease in 5-HT_2 binding in parietal cortex (McKittrick, Blanchard, Blanchard, McEwen, & Sakai, 1995). Preclinical studies have provided evidence that the capability for increased serotonin metabolism during exposure to inescapable stress prevents learned helplessness (Ronan, Steciuk, Kramer, Kram, & Petty, 2000). Serotonin antagonists produce behavioral deficits resembling those seen following inescapable shock. Drugs that enhance serotonin neurotransmission (selective serotonin reuptake inhibitors) are effective in reversing the learned helplessness. Pre-administration of benzodiazepines or tricyclic antidepressants has been described to prevent stress-induced decreases in serotonin and the acquisition of behavioral deficits (Petty et al., 1992), while injection of serotonin (5-HT) into the frontal cortex after stress exposure reverses behavioral deficits. Administration of 5-HT_{1A} agonists such as buspirone resulted in a reversal of stress-induced behavioral deficits. A natural increase in the level of 5-HIAA in the lateral septum seemed protective from adverse behavioral consequences of inescapable stress (Ronan et al., 2000). In summary, chronic stressors result in long-term alterations in serotonergic function. These findings may have implications for understanding the efficacy of treatment of PTSD with serotonin reuptake inhibitor medications. Work to date has not focused on early stressors and serotonergic function—research is needed in this area.

Endogenous Benzodiazepines

Endogenous benzodiazepines also play an important role in the stress response and anxiety. Benzodiazepine receptors are present throughout the brain, with the highest concentration in cortical gray matter. Benzodiazepines potentiate and prolong the synaptic actions of the inhibitory neurotransmitter GABA. Central benzodiazepine receptors and GABA receptors are part of the same macromolecular complex. These receptors have distinct binding sites, although they are functionally coupled and regulate each other in an allosteric manner. Agents that block the benzodiazepine receptor increase anxiety, while medications like Valium, which bind to the receptor, result in a decrease in anxiety. Several studies have shown that chronic stress results in a decrease in benzodiazepine receptor binding in frontal cortex, with some studies showing a decrease in hippocampus (reviewed in Bremner et al., 1999). Studies of early maternal separation also showed reduced benzodiazepine receptor binding in frontal cortex, as well as amygdala and locus coeruleus (Caldji, Sharma, Plotsky, & Meaney, 2000).

Neuropeptides and Amino Acids

Exposure to stress has marked effects on the activity of a number of other central nervous system (CNS) neuropeptides systems. The neuropeptides that are considered to mediate the response to stress, based upon preclinical studies, are CRF, endogenous opioid peptides, neurotensin, somatostatin, cholecystokinin (CCK), neuropeptide Y, and others, like substance P, vasopressin, oxytocin, vasointestinal polypeptide (VIP) and thyrotrophin releasing hormone (TRH). Neuropeptides account for neurotransmission at a very large percentage of synapses in the brain. Since many neuropeptides are hypothalamic pituitary hormones, directly controlling the

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secretion of anterior pituitary hormones, they can function both as hormones in the hypothalamic–hypophysial portal system and as neurotransmitters in CNS. Stress is associated with an increase in endogenous opiate release with decreased density of μ-opiate receptors, which may mediate the analgesia associated with stress (reviewed in Bremner et al., 1999). Neurotensin (NT) also has a primary role as a neurotransmitter in CNS. NT and its receptor are distributed in hypothalamus, septum, amygdala, and hippocampus, and the receptors are proximal to the cell bodies of origin of the classical neurotransmitters. A role for NT in stress is suggested by the protective effects of centrally administered NT on restraint-stress-induced gastric ulcers in rats (Nemeroff, Hernandez, Orlando, & Prange, 1982). Somatostatin (somatotropin release-inhibiting factor [SRIF]) is the major inhibitor of growth hormone (GH) secretion. Chronic daily immobilization stress has resulted in an increase basal, as well as stress-induced SRIF release and decreased GH release; prolonged increase in SRIF has been reported to counter an increase in GH releasing factor and suppresses GH secretion (Armario & Jolin, 1992). CCK is an anxiogenic neuropeptide synthesized in the gastrointestinal tract and exerting its effects there as well as in the brain, which has recently been suggested as a neural substrate for human anxiety. Preclinical data suggest that agonists of CCK_B produce anxiogenic-like effects, while CCK_B antagonists induce anxiolytic-like responses in several models of anxiety (reviewed in Bremner et al., 1999). Neuropeptide Y (NPY) is one of the most abundant neuropeptides in the brain. It is present in brain stem nuclei, nucleus accumbens, amygdala, hypothalamus, and cerebral cortex. Direct injection of NPY in the amygdala has an anxiolytic effect (Heilig, McLeod, Brot, Heinrichs, Menzaghi, Koob, & Britton, 1993) and is protective against restraint-stress-induced gastric ulceration in rats (Penner, Smith, & Glavin, 1993).

Glutamate has a role as a neurotransmitter acting via several types of receptor, including the NMDA receptor, non-NMDA inotropic receptor subtypes, and glutamate receptors. It is involved in long-term synaptic connectivity by initiating long-term potentiation (LTP) and depression (LTD), produces long-lasting changes in synaptic structure and function, neuronal migration, and neuronal viability. Exposure to stress has been shown to increase release of glutamate in the prefrontal cortex and hippocampus (Moghaddam, Bolinao, Stein–Behrens, & Sapolsky, 1997).

The Neurobiology of Early Stress in Children

The few studies of the effects of early stress on neurobiology conducted in clinical populations of traumatized children have generally been consistent with findings from animal studies. Research in traumatized children have been complicated by issues related to psychiatric diagnosis and assessment of trauma. Some studies have not specifically examined psychiatric diagnosis, while others have focused on children with trauma and depression, and others on children with trauma and PTSD. In our view the issues of diagnosis are important in this area. Not all children will develop psychopathology following exposure to abuse, and we hypothesize that stress-induced changes in neurobiology underlie the development of psychopathology in those who do develop psychiatric symptoms.

Studies in adults with a history of early childhood abuse and the diagnosis of PTSD have been consistent with long-term changes in HPA axis. An increase in cerebrospinal fluid concentrations of CRF was shown in adult patients with combat-related PTSD compared to healthy controls (Bremner, Licinio, et al., 1997). Consistent with increased levels of CRF, combat-related PTSD patients had a blunted ACTH response to CRF challenge (Smith, Davidson, Ritchie, Kudler, Lippen, Chappell, & Nemeroff, 1989). Some studies in adults with chronic PTSD, but not others, found decreased levels of cortisol in 24-hr urines (reviewed in Yehuda et al., 1995). Other findings in combat-related PTSD include increased suppression of cortisol with low dose (0.5 mg) dexamethasone (Yehuda, Southwick, Krystal, Bremner, Charney, & Mason, 1993), and increased number of glucocorticoid receptors on peripheral lym-

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phocytes (reviewed in Yehuda et al., 1995). Sexually abused girls (in which effects of specific psychiatric diagnosis was not examined) had blunted ACTH response to CRF (De Bellis, Chrousos, et al., 1994) and hypercortisolemia (Lemieux & Coe, 1995). Another study of traumatized children in which the diagnosis of PTSD was established showed increased levels of cortisol measured in 24-hr urines (De Bellis et al., 1999a). Adult women with a history of childhood abuse showed increased suppression of cortisol with low dose (0.5 mg) dexamethasone (Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Preliminary data from Bremner and colleagues in women with PTSD related to early childhood sexual abuse showed decreased baseline cortisol and increased baseline ACTH based on 24-hr diurnal assessments of plasma, blunted ACTH response to CRF, and lower cortisol response to ACTH and CRF challenge relative to controls.

Few studies have examined noradrenergic function related to childhood abuse. Studies have found increased noradrenergic function in adults with PTSD (reviewed in Bremner et al., 1996b). Studies in children with abuse in which diagnosis of PTSD was not established found increased catecholamines in 24-hr urine (including norepinephrine, epinephrine, and dopamine; De Bellis, Lefter, Trickett, & Putnam, 1994). Studies in children with the diagnosis of PTSD are also consistent with elevations in catecholamine (De Bellis, Baum, et al., 1999). These findings are consistent with animal studies showing increased noradrenergic activity following early stress.

Another important outcome of childhood abuse is depression. Hypercortisolemia is a well-replicated finding in a subgroup of patients with depression (Schatzberg & Nemeroff, 1988). Depressed patients also showed increased rates of nonsuppression on the dexamethasone suppression test (consistent with excessive levels of cortisol in the periphery; Carroll, 1982), elevated CRF levels in cerebrospinal fluid (Nemeroff, Widerlov, Bissette, Walleus, Karlsson, Eklund, Kilts, Loosen, & Vale, 1984), and blunted ACTH response to CRF challenge (consistent with excessive CRF release; Gold, Loriaux, Roy, Kling, Calabrese, Kellner, Nieman, Post, Pickar, Galluci, Avgerinos, Paul, Oldfield, Cutler, & Chrousos, 1986). Findings in adolescents with depression are less clear, with a smaller number of patients exhibiting hypercortisolemia, which may be specific to nighttime cortisol levels (Dahl, Puig–Antich, Ryan, Nelson, Novacenko, Twomey, Williamson, Goetz, & Ambrosini, 1989, 1991; Kutcher, Malkin, Silverberg, Marton, Williamson, Malkin, Szalai, & Katic, 1991; Birmaher, Ryan, Dahl, Rabinovich, Ambrosini, Al-Shabbout, Novacenko, Nelson, & Puig–Antich, 1992; Dorn, Burgess, Susman, von Eye, DeBellis, Gold, & Chrousos, 1996). These discrepant findings may be related to the fact that hypercortisolemia is more common in patients with trauma histories (De Bellis, Chrousos, et al., 1994; Hart, Gunnar, & Cicchetti, 1996; De Bellis, Baum, et al., 1999). In a study of ACTH response to CRF challenge in children with depression with and without a history of childhood abuse, children with depression and abuse had an increased ACTH response to CRF challenge compared to children with depression without abuse. These children were in a chaotic environment at the time of the study, indicating that the ongoing stressor may have played a role in the potentiation of the ACTH response to CRF (Kaufman, Birmaher, Perel, Dahl, Moreci, Nelson, Wells, & Ryan, 1997). Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, & Nemeroff (2000) found that adult women with depression and a history of early childhood abuse had an increased cortisol response to a stressful cognitive challenge relative to controls.

Studies in clinical populations of adult survivors of early abuse have shown changes in hippocampal structure and function (Bremner, 1999). Studies in patients with epilepsy who underwent surgical resection of the hippocampus showed that deficits on specific neuropsychological tests of long-term memory function (verbal Selective Reminding Test [vSRT]; Hannay & Levin, 1985) and percent retention during paragraph recall on the Wechsler Memory Scale (WMS; Russell, 1978) were correlated with a loss of neurons in the CA3

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region of the hippocampus (Sass, Spencer, Kim, Westerveld, Novelly, & Lencz, 1990). Using the WMS and vSRT as probes of hippocampal-based verbal declarative memory function Bremner et al. (1993) found deficits on these measures in combat veterans with PTSD relative to matched controls. Similar deficits in verbal declarative memory as measured by the WMS and vSRT were found in patients with childhood physical and sexual abuse in comparison to controls (Bremner, Randall, Capelli, et al., 1995). Deficits in verbal memory in the childhood abuse patients were significantly correlated with severity of childhood sexual abuse. A number of studies showed similar deficits in verbal declarative memory tasks, including paragraph delayed recall and word list learning, in patients with depression (Burt, Zembar, & Niederehe, 1995) that are reversible with antidepressant treatment (Bartfai, Asberg, Martensson, & Gustavsson, 1991). High levels of cortisol seen during depressive episodes were correlated with deficits in memory and cognition, and memory deficits associated with depressive episodes improved when cortisol levels were lowered following successful treatment (Wolkowitz, Reus, Roberts, Manfredi, Chan, Raum, Ormiston, Johnson, Canick, Brizendine, & Weingartner, 1997).

Based on the animal studies reviewed above, there was a rationale to measure hippocampal volume in patient with PTSD and depression. An initial study used magnetic resonance imaging (MRI) volumetric techniques to show an 8% reduction in hippocampal volume in patients with combat-related PTSD compared to controls (Bremner, Randall, Scott, et al., 1995). In a second study comparing 17 patients with PTSD related to early childhood abuse to 17 case-matched controls, there was an 12.0% reduction in left hippocampal volume that was statistically significant ($p < 0.05$; Bremner, Randall, Vermetten, et al., 1997; Figure 2). Two other published studies showed hippocampal volume reduction, one in combat-related PTSD (Gurvits, Shenton, Hokama, Ohta, Lasko, Gilberson, Orr, Kikinis, Lolesz, McCarley, & Pitman, 1996) and a second in women with early sexual abuse, most of whom met criteria for PTSD (Stein et al., 1997). In an unpublished study we found a reduction in bilateral hippocampal volume in women with early childhood sexual abuse and PTSD, relative to abused women without PTSD and nonabused non-PTSD women. In a study of children with abuse-related PTSD there was a smaller intracranial and cerebral volume, with no reduction in hippocampal volume (De Bellis, Keshavan, et al., 1999). MRI studies in adult depression showed smaller hippocampal volume in adults with depression (Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Bremner, Narayan, Anderson, Staib, Miller, & Charney, 2000). There are therefore four published replicated studies in adults with PTSD, two of which are in survivors of abuse, showing hippocampal volume reduction, with one study in children showing no reduction and two studies of adult patients with depression showing a hippocampal volume reduction. These studies suggest that chronicity of PTSD illness may be a factor determining hippo-

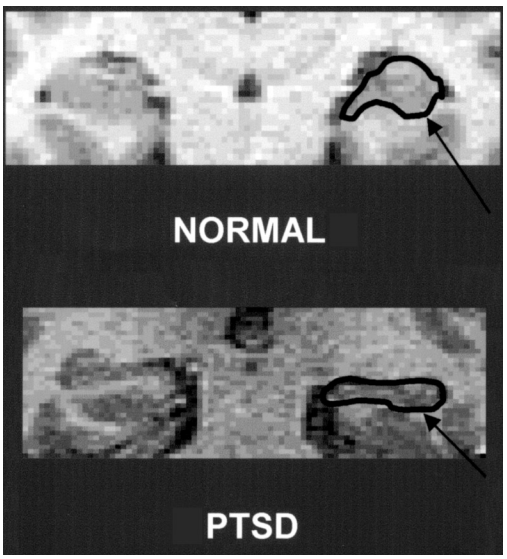


Figure 2. Hippocampal volume in abuse-related PTSD. Hippocampus is shown on a coronal magnetic resonance imaging (MRI) scan in a representative patient with abuse-related PTSD and a normal control. There is a visible reduction in the hippocampus (outlined) in a patient with abuse-related PTSD relative to a normal subject.

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campal volume reduction. Similarly, chronicity of depression has been associated degree of hippocampal atrophy. Studies are needed to examine hippocampal volume in children and adolescents with depression and a history of abuse.

The hippocampus has important connections with the prefrontal cortex that may underlie symptoms related to childhood abuse. As noted above, the medial prefrontal cortex has inhibitory inputs to the amygdala that have been hypothesized to play a role in extinction of fear responses. We have hypothesized that dysfunction of this region may play a role in pathological fear responses and other symptoms of abuse-related PTSD. We conducted a study of adult women with a history of childhood sexual abuse with and without PTSD. Women were exposed to scripts related to their own childhood sexual abuse, in conjunction with positron emission tomography (PET) imaging of brain function. Women with PTSD (but not non-PTSD) had a decrease in brain function in medial prefrontal cortex. PTSD women also had a decrease in right hippocampal blood flow with traumatic reminders (Bremner, Narayan, Staib, Southwick, McGlashan, & Charney, 1999). In a second study, women with abuse-related PTSD had a decrease in medial prefrontal blood flow during remembrance of stressful word pairs (e.g., "rape-mutilate") relative to neutral word pairs (Bremner et al., 3/1/01). These findings are consistent with dysfunction of medial prefrontal cortex and hippocampus in abuse-related PTSD.

Concluding Remarks

Early stress has long-term effects on brain structures and systems that play an important role in the stress response. Animal models of early stress have most commonly involved maternal separation. Early stressors result in long-term dysregulation of stress response systems, including increased activation of CRF and the HPA axis and noradrenergic systems. Early stressors result in changes in morphology of the hippocampus, a brain area that plays an important role in learning and memory. Studies in patients with a history of childhood abuse and with depression and PTSD are consistent with long-term dysregulation of the HPA axis and noradrenergic systems. Studies are also consistent with deficits in hippocampal-based declarative memory function in abuse-related PTSD, and reductions in hippocampal volume measured with MRI. Functional imaging studies have also implicated dysfunction in medial prefrontal cortex in abuse-related PTSD. These studies have started to outline circuits and systems that play a role in the symptoms of abuse-related psychiatric disorders, including depression and PTSD. This knowledge should help us to outline targets of treatment for abuse-related psychopathology.

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