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Neurobiological and Psychiatric Consequences of Child Abuse and Neglect

ABSTRACT: *The effects of early-life trauma and its consequences for the treatment of depression are reviewed. The prevalence and clinical sequelae of early sexual and physical abuse, neglect and parental loss are described. An overview of preclinical studies that help guide clinical research and practice is presented. Human clinical studies on the neurobiological consequences of early trauma are summarized. Moderating factors, such as genetic variation and sex differences, are discussed. The few current treatment outcome studies relevant to this research area are described. Guidance for the management of patients with depression and a history of child abuse and neglect are provided. Most patients who have experienced early traumatic experiences are likely best treated with a combination of psychotherapy and pharmacotherapy. This review is dedicated to the memory of Seymour Levine who pioneered the field of early experience research and to a considerable extent inspired the clinical studies described in this review.* © *2010 Wiley Periodicals, Inc.* Dev Psychobiol 52: 671–690, 2010.

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INTRODUCTION

Our understanding of the importance of early-life trauma and its impact on vulnerability to psychiatric disorders in adults has increased in recent years. Early-life trauma predisposes individuals to develop a number of psychiatric syndromes, particularly mood and anxiety disorders, and is therefore a significant public health problem. It is important to elucidate the specific mechanisms by which early-life trauma increases risk for adult psychopathology and how to develop more effective and specific treatments, both psychotherapeutic and pharmacological, for those who have experienced early trauma.

This review is dedicated to the memory of Seymour Levine, who is the founding father of the concept of Early Experience and its impact on behavior and physiological regulation. In the 1950s and 1960s, Seymour Levine pioneered studies in developmental psychobiology by evaluating the effects of early experimental manipulations, such as postnatal handling of laboratory animals, on later behavior and adaptation. He documented the lasting effects of early experience on endocrine, immune, and central nervous systems. His work provided the evidence that early handling induces improved development outcomes and promotes stress resilience. He also discovered important sex differences in the effects of early experience. While these studies should not be considered early stress studies, they have provided the first proof of principle that early experience does shape behavior and physiology of systems relevant to stress. Our clinical

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studies, described in this review, have been remarkably influenced by Seymour Levine's seminal insights, and he continued to be an invaluable source of advice and inspiration until his death in October of 2007. His legacy lives on in current research projects that attempt to identify further the psychobiological outcomes of early adversity and their reversal.

EARLY-LIFE TRAUMA: SEXUAL AND PHYSICAL ABUSE, NEGLECT, AND PARENTAL LOSS

Epidemiology

The prevalence rate of early traumatic experiences is significant. In the US alone, there are approximately 3 million child maltreatment reports annually, of which nearly 1 million are substantiated; among the substantiated cases, about 60% are classified as neglect, 20% as physical abuse, and 10% as sexual abuse (Children's Bureau, Administration of Children, Youth, and Families, 2006). Child abuse often occurs in the context of other important risk factors. Obviously, many—if not most—instances of child abuse are unreported.

Several epidemiological studies estimate trauma exposure in children to be 25–45% (Costello & Angold, 2000; McCloskey & Walker, 2000). A recent retrospective self-report study of an adult community sample revealed a prevalence of childhood maltreatment of 30% in women and 41% in men (Scher, Forde, McQuaid, & Stein, 2004). Of the sample studied, 35% experienced at least one form of abuse. In this large sample of 967 adults, the prevalence rates ranged from 5% for sexual abuse to almost 19% for physical abuse. Briere and Elliott (2003) examined the prevalence and psychological sequelae of childhood sexual and physical abuse in adults from the general population through a mailed questionnaire. A national sampling service generated a geographically stratified, random sample of 1,442 US subjects. Of all potential subjects, 935 (64.8%) returned substantially completed surveys. Sixty-six men and 152 women (14.2% and 32.3%, respectively) reported childhood sexual abuse experiences, and 22.2% males and 19.5% females met criteria for physical abuse.

Other studies utilizing surveys and interviews have reported that approximately 20–25% of women and 8–9% of men suffer from sexual abuse before the age of 18 (Gorey & Leslie, 1997; Holmes & Slap, 1998; McCauley et al., 1997). Even after statistically correcting for survey nonresponse rates, the adjusted estimate for females is 12–17% and 5–8% for males. In addition, 28% of sexually abused girls between the ages of 6 and 16 years are victims of physical abuse (Horowitz, Putman, Noll, & Trickett, 1997). Although more difficult to define and substantiate, both emotional abuse and neglect appear to be even more prevalent than sexual and physical abuse. Parental loss due to separation or death is another early traumatic experience that has been associated with increased psychopathology in adulthood (Agid et al., 1999). The major limitation of retrospective studies and interviews is the accuracy of memory. Other limitations include the wide range of abuse and neglect. However, clearly the rates of these early traumatic experiences are significant and unfortunately such trauma is frequent.

Clinical Consequences

Child abuse and neglect are nonspecific risk factors for various psychiatric syndromes. A particularly strong link has been identified between childhood trauma and the mood and anxiety disorders, including unipolar depression, bipolar disorder, generalized anxiety disorder, panic disorder, phobias, and posttraumatic stress disorder (PTSD; e.g., Agid et al., 1999; Famularo, Kinscherff, & Fenton, 1992; Heim & Nemeroff, 2001; Hill, 2003; Katerndahl, Burger, & Kellogg, 2005; Kendler et al., 2000; Kendler, Kuhn, & Prescott, 2004; Kendler, Neale, Kessler, Heath, & Eaves, 1992; McCauley et al., 1997; Molnar, Buka, & Kessler, 2001; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Nemeroff & Vale, 2005; Saunders, Villoponteaux, Lipovsky, Kilpatrick, & Veronen, 1992; Stein et al., 1996; Wise, Zierler, Krieger, & Harlow, 2001). In addition, traumatic experiences early in life are associated with increased rates of schizophrenia, reactive attachment disorder, eating disorders, and personality disorders (Ackard & Neumark-Sztainer, 2003; Agid et al., 1999; Famularo et al., 1992; Felitti et al., 1998; Kaplan & Klinetob, 2000; Noll, Horowitz, Bonanno, Trickett, & Putnam, 2003; Romans, Martin, Anderson, Herbison, & Mullen, 1995; Saunders et al., 1992; Zeanah et al., 2004). A link between childhood abuse and later substance abuse has also been reported (Briere & Woo, 1991; Burnam et al., 1988; Gutierres & Todd, 1997; Kendler et al., 2000; Wilsnak & Beckman, 1984).

Childhood trauma also dramatically increases the risk for later suicide attempts. In a landmark Centers for Disease Control (CDC) study, Dube et al. (2001) reported an increased risk of suicide attempts throughout the life span among primary care patients with histories of childhood abuse, as measured by the Adverse Childhood Experiences (ACE) Scale. This patient population consisted of 17,337 male and female adult primary care patients in San Diego studied between 1995 and 1997. In those patients with no ACE's, the prevalence of attempted

suicide was 1.1%. The lifetime prevalence of having at least one suicide attempt in this patient population with reported adverse childhood events was 3.8%. Adverse Childhood Experiences in any category (sexual abuse, physical abuse, etc.) increased the risk of attempted suicide two- to fivefold. The ACE score was positively correlated with attempted suicide during childhood or adolescence and adulthood and exhibited a strong, graded relationship. Compared with those patients with no ACE's, the adjusted odds ratio (OR) of ever attempting suicide among persons with 7 or more experiences was 31.1.

Childhood trauma is not only related to increased risk for psychiatric disorders, but also impacts on clinical course. For example, in a 5-year prospective study, among patients with anxiety disorders and major depression, those with a positive trauma history were less likely to remit from depression than those without a trauma history (Zlotnick, Warshaw, Shea, & Keller, 1997). In a study with 235 outpatients seeking treatment with major depression, childhood sexual abuse was linked to a longer duration of the index depressive episode (Zlotnick, Mattia, & Zimmerman, 2001). The chronicity of depressive episodes has also been associated with childhood adversity, both family violence and sexual abuse (Brown & Moran, 1994). In the latter study, childhood adversity predicted failure to recover from major depression at 12-month follow-up. This finding was also reported by Tanskanen et al. (2004).

Exposure to multiple traumas is an important factor in the relationship between childhood trauma and negative adult mental health outcomes as well as clinical course (Banyard, Williams, & Siegel, 2001). A greater number of traumatic experiences was associated with greater risk for major depressive disorder in primary care patients in a cross-sectional study (McQuaid, Pedrelli, McCahill, & Stein, 2001) and in a population-based study (Tanskanen et al., 2004). Additional data strongly suggest that increasing severity, frequency, and duration of abuse results in an increased likelihood of developing depression (Bifulco, Brown, & Adler, 1991; Briere & Runtz, 1988; Mullen, Martin, Anderson, Romans, & Herbison, 1993; Murphy et al., 1988; Sedney & Brooks, 1984).

The association between early trauma and psychopathology is already present in children. For example, Widom, DuMont, and Czaja (2007) performed a prospective longitudinal study of major depression and comorbidity in 676 children with substantiated abuse and neglect experienced before the age of 11 years and a control group of 520 children. Childhood trauma was associated with an increased risk of current major depression in young adulthood (OR = 1.51). Those children who were physically abused or experienced multiple types of abuse were at increased risk for lifetime major depression with ORs of 1.59 and 1.75, respectively. Childhood neglect also increased the risk for current major depression (OR = 1.59). Traumatized children showed an earlier onset of major depression compared with controls, as well as higher levels of comorbidity.

As noted above, parental loss is another risk factor for developing major depression and other disorders (Weller, Weller, Fristad, & Bowes, 1991). Death of a mother or lengthy separation from mother by the age of 11 years is a risk factor that may interact with later stressors resulting in increased rates of depression (Brown, Harris, & Bifulco, 1986). Poor quality of the home environment and impaired parenting add to the risk factor of parental loss in developing adult major depression (Lara & Klein, 1999; Rutter, 2005). Hill et al. (2000) found that low maternal care and childhood sexual abuse each contributes independently to the risk of developing depressive symptoms in adult women. Agid et al. (1999) compared rates of early parental loss (due to parental death or permanent separation before the age of 17 years) among individuals with major depression, bipolar disorder, and schizophrenia to those of matched, healthy control individuals. Loss of a parent during childhood significantly increased the likelihood of developing major depression during adult life (OR = 3.8, $p = .001$). The effect of loss due to permanent separation ($p = .008$) was more striking than loss due to death; as was loss before the age of 9 years (OR = 11.0, $p = .003$) compared to later childhood and adolescence. In addition, early parental loss was associated with an increased rate of bipolar disorder (OR = 2.6, $p = .048$). In addition to parental loss, bereavement due to the loss of a sibling is also associated with an increased risk for depression (Brent et al., 1993).

Personal and social difficulties that follow abuse have been identified, such as insecure attachment, avoidance in social relationships, and deficits in social-interpersonal processing (Stevenson, 1999). Other types of dysfunction associated with early-life trauma include: preverbal assumptions regarding self and others; conditioned associations between abuse stimuli and emotional distress; implicit or sensory memories which may elicit difficulty for the individual (e.g., flashbacks) when activated by trauma-reminiscent stimuli; narrative or autobiographical memories that may be activated by verbal cues and in turn may elicit strong emotional reactions; and difficulties with affective and emotional regulation (Briere, 2002).

The concatenation of data strongly suggests that increasing severity, frequency, and duration of abuse results in an increased likelihood of developing depression and other psychological disorders.

Protective Factors

Fortunately, emerging preclinical and clinical data suggest that long-term effects of early-life stress can be ameliorated by the availability of positive supports and optimal subsequent caregiving experiences (Barbazanges et al., 1996; Huot, Thrivikraman, Meaney, & Plotsky, 2004; Wiedenmayer, Magarinos, McEwen, & Barr, 2003). Preclinical studies suggest that the negative effects of early childhood trauma can be somewhat attenuated through enrichment in the environment later in life and by treatment with selective serotonin-reuptake inhibitors (Bredy et al., 2004; Charmandari, Tsigos, & Chrousos, 2005; Francis, Diorio, Plotsky, & Meaney, 2002; Huot et al., 2004). Clinical studies suggest that the availability of a caring and stable caregiver is one of the most important factors that distinguishes abused children with good developmental outcomes from those without such positive outcomes (Kaufman & Henrich, 2000). When there is the loss of a parent due to death or divorce, positive support of remaining family members is a highly important variable in creating resilience to the loss (Kendall-Tacket, Williams, & Finkelhor, 1993).

It is estimated that approximately one-third of individuals who have experienced sexual abuse will not exhibit adult psychiatric problems (Fergusson & Mullen, 1999; Stevenson, 1999). McGloin and Widom (2001) found that 48% of children with documented histories of abuse or neglect did not meet criteria for an adult psychiatric disorder. Collishaw et al. (2007) studied resilience for the development of psychopathology after childhood maltreatment. They utilized data from the Isle of Wight Community epidemiological sample, assessed in adolescence, and then again at midlife. Ratings of psychiatric disorder, peer relationships, and family functioning were obtained in adolescence. Adult assessments included a lifetime psychiatric history, personality and social functioning assessments, and retrospective reports of childhood sexual and physical abuse. Ten percent of individuals reported repeated or severe physical or sexual abuse in childhood, and not surprisingly they exhibited increased rates of adolescent psychiatric disorders. A substantial minority of abused individuals, however, reported no mental health problems in adult life. Their resilience was related to perceived parental care, adolescent peer relationships, the quality of adult love relationships, and personality style.

Resilience might be in part related to timing of early-life adversity. There is some evidence of sensitive or critical periods for the effects of early trauma during development. Emerging data suggest that sensitive periods clearly exist. Some studies report that adversity during earlier childhood is associated with a greater propensity for negative outcomes (Agid et al., 1999; Kaufman & Henrich, 2000; McClellan et al., 1996). Maercker, Michael, Fehm, Becker, and Margraf (2004) report that women exposed to trauma before the age of 13 years were at equal risk of major depression or PTSD; whereas, females abused after the age of 13 years were more likely to develop PTSD. Taken together, not all abused children go on to experience mental health problems later in life. The availability of a caring and stable parent or guardian is one of the most important factors that distinguish abused individuals with good developmental outcomes from those with more negative outcomes (Kaufman & Henrich, 2000). Learning more about resilience, including genetic factors and sensitive periods, will help us in guiding prevention and treatment of those traumatized in early childhood.

CONCEPTUAL MODELS: PRECLINICAL NEUROBIOLOGY

Mechanisms that mediate the consequences of early adverse experience have been studied in laboratory animals and humans. Numerous rodent and nonhuman primate studies have revealed a number of persistent neurobiological consequences of early-life trauma (e.g., reviewed in Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Heim & Nemeroff, 2001; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Ladd et al., 2000; Meaney, 2001). Selected results are summarized below.

Hypothalamic–Pituitary–Adrenal Axis and Behavior

As early as the 1950s and 1960s, the pioneering work of Seymour Levine revealed that manipulation of neonatal rats, such as handling or mild shock, permanently alters behavior as well as corticosteroid responsiveness to later stressors (e.g., Levine, 1967; Levine, Chevalier, & Korchin, 1956). While Levine's studies provided evidence that early handling, which involves brief separations (3–15 min) of pups from their mothers, improves developmental outcomes, more potent early stressors, such as maternal separation, which involves longer separations (3 or more hours) of pups from their mothers, have adverse effects on development. Maternal separation of rodents early in life is often used as a model of human parental neglect. Maternal separation in rats in the first 2 weeks of life has been found to result in heightened neuroendocrine and autonomic responses to stress as well as depression-like behavior (e.g., decreased preference for sucrose), anxiety (e.g., increased startle), alcohol

preference, and cognitive impairment in adulthood. These changes that occur as a function of early maternal separation persist throughout life (Huot, Thrivikraman, Meaney, & Plotsky, 2001; Ladd et al., 2000). Similar changes have been observed in rats that were reared by mothers with naturally occurring low expression of maternal care-giving behavior (Meaney, 2001). In contrast, rats that were reared by mothers expressing high levels of care developed into adult rats with less anxiety and more stress resilience (Meaney, 2001). In fact, levels of maternal care are critical in mediating the positive effects of early handling: It has been shown that dams increase licking and grooming of rats that have been briefly handled (Barnett & Burn, 1967; Francis, Diorio, Liu, & Meaney, 1999).

Central Nervous System

The peripheral and behavioral changes that occur as a function of early environment occur due to changes in neural circuits that coordinate stress responses and behavior. Multiple studies have documented that early-life stress produces effects on the developing brain, leading to an adult phenotype with vulnerability to stress, depression, and anxiety. Thus, maternal separation has been found to impact on several neurotransmitter systems, most notably central nervous system (CNS) corticotropin-releasing hormone (CRH) circuits. The 41-amino acid peptide CRH is generally accepted to be the main CNS coordinator of the mammalian stress response, including the behavioral, autonomic, immune, and endocrine components (Heim & Nemeroff, 2001). The hypothalamic paraventricular nucleus (PVN) CRH cell bodies in the medial parvocellular region form the central component of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis constitutes the major neuroendocrine stress response system. CRH is released from the PVN upon stress exposure into the hypothalamo-hypophysial portal circulation and binds to CRH receptors in corticotrophs of the anterior pituitary gland stimulating the production and release of adrenocorticotropin (ACTH), proopiomelanocortin-derivatives and β-endorphin. ACTH then stimulates the production and release of glucocorticoids (cortisol in primates) from the adrenal cortex into the systemic circulation. Glucocorticoids provide negative feedback to the hypothalamus, hippocampus, and anterior pituitary to regulate the HPA stress response; these feedback effects are mediated through two types of receptors, the glucocorticoid receptors and the mineralocorticoid receptors.

In addition to its neuroendocrine function, CRH acts also as a neuropeptide transmitter with neurons and receptors widely distributed throughout the brain, including cortical, limbic and brain-stem areas. There are two well-known CRH receptors, CRH-R1 and CRH-R2, distributed in the CNS. CRH-R1 deficient mice show a reduced hormonal stress response and blunted anxiety-like behaviors (Smith et al., 1998; Timpl et al., 1998). CRH-R2 deficient mice show exaggerated anxiety behaviors and are hypersensitive to stress (Bale et al., 2000; Coste et al., 2000). This would suggest that CRH-R1 is the primary CRH receptor mediating the stress response and CRH-R2 may help in modulating this response (Bale et al., 2002). Several other neurotransmitter systems interact with CRH in enhancing (norepinephrine) or buffering (gamma-aminobutyric acid [GABA], oxytocin, neuropeptide Y) stress responses (see Kaufman et al., 2000).

Maternal separation in rats results in increased CRH concentrations and increased CRH mRNA expression in the hypothalamus, locus coeruleus, and the amygdala (Plotsky et al., 2005). Further, maternal separation is associated with upregulation of CRH-R1 receptors in various brain regions and increased noradrenergic activity, which contribute to increased stress responsiveness (Plotsky et al., 2005). It should be noted that increased central CRH activity along with increased anxiety have been observed in a nonhuman primate model, in which infant macaques are exposed to a variable foraging demand condition that produces chronically stressed mothers which display decreased maternal care (Coplan et al., 1996).

Increased stress responsiveness might be mediated through impaired glucocorticoid feedback due to impaired glucocorticoid receptor function. Accordingly, decreased glucocorticoid receptor density and mRNA expression have been reported in the hippocampus and frontal cortex of rats exposed to maternal separation. Seminal studies by Meaney and coworkers have demonstrated the existence of direct epigenetic effects of variations in maternal care on a neuron-specific promoter region of the glucocorticoid receptor gene (Weaver et al., 2004). Specifically, altered cytosine-methylation of this gene has been documented as a function of early maternal care, leading to silencing of the gene and thus glucocorticoid resistance. Such early programming results in life-long effects on stress reactivity. In addition, reduced neurogenesis has been observed in the hippocampus of maternally deprived rats (Mirescu, Peters, & Gould, 2004).

Other CNS changes reported after early maternal deprivation in rats include a decrease in 5-HT1B receptor expression (Gutman & Nemeroff, 2002), decreased expression of GABAA receptors (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000) and impaired dopamine transporter (DAT) expression (Meaney, Brake, & Gratton, 2002). These maternally deprived rats also exhibit a preference for ethanol and cocaine compared

to nondeprived rats, suggesting risk for substance abuse (Huot et al., 2001; Matthews, Robbins, Everitt, & Barak, 1999).

One important research area pertains to the question of whether these neurobiological effects of early adversity are reversible. Huot et al. (2001) reported that administration of the selective serotonin reuptake inhibitor (SSRI) paroxetine to maternally deprived rats reduced serum adrenocorticotropin (ACTH) and corticosterone concentrations and CRH mRNA expression comparable to those of the control rats. This treatment also restored the rats' preference for sucrose and reversed their preference for alcohol. The neurobiological alterations related to maternal deprivation returned following discontinuation of the SSRI. Particularly exciting are findings that epigenetic effects of early-life stress are reversible in rats by administering a diet that contains methyl supplementation (Weaver et al., 2005). Such research approaches have particular relevance for innovative conceptualizations of novel approaches to prevent and treat the negative outcomes of early developmental adversity.

Protective Factors

Preclinical studies suggest that deleterious effects of early trauma can be attenuated through enrichment in the environment later in life (Bredy et al., 2004; Charmandari et al., 2005; Francis et al., 2002). One preclinical study with rats examining prenatal stress (Barbazanges et al., 1996) found that crossfostering of male offspring to a dam without prenatal stress reversed the HPA axis alterations usually observed in early-life stress paradigms. In addition to the above described positive effects of early handling and high maternal care on stress response systems, studies in monkeys have shown that milder forms of stress during early development can have a ''toughening'' effect, leading to resilience later in life (Lyons, Parker, & Schatzberg, in press).

Preclinical studies showing a number of persistent neurobiological consequences of early-life trauma have led to studies of neurobiological consequences of early-life trauma in humans.

CONCEPTUAL MODELS: HUMAN NEUROBIOLOGY

Neurobiological consequences of early developmental stress in humans have been reviewed in detail elsewhere (Gladstone, Parker, Mitchell, Malhi, & Austin, 2004; Heim, Meinlschmidt, & Nemeroff, 2003; Heim, Plotsky, & Nemeroff, 2004; Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Heim & Nemeroff, 2001; Nemeroff, 1999, 2004; Nemeroff & Vale, 2005). Due to the increased rates of several psychiatric disorders after early-life and based on the results from animal models, early-life stress has been hypothesized to induce a vulnerability to the effects of stress in later life, predisposing victims of child abuse and neglect to numerous psychiatric sequelae. The combination of genetic influences, early-life trauma, and ongoing stress ultimately determines stress responsiveness of the individual and vulnerability to psychiatric disorders. Early-life traumatic events have been posited to induce a persistent sensitization of stress-responsive neural circuits. This hypothesis has been tested in human clinical studies.

Hypothalamic–Pituitary–Adrenal Axis

Persistent changes in CRH-mediated stress responses due to early-life trauma in genetically predisposed individuals have been posited to result in heightened stress sensitivity and increased risk of depression. Major depression is associated with increased CSF concentrations of CRH, increased CRH immunoreactivity, increased CRH mRNA expression in the hypothalamic PVN, and downregulation of CRH-1, but not CRH-2, receptors in the cerebral cortex (Nemeroff, 1998; Nemeroff et al., 2006; Nemeroff & Vale, 2005). Reduced CRH binding sites in the frontal cortex of suicide victims are consistent with the idea that CRH is hypersecreted in patients with depression (Merali et al., 2004; Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988). A growing number of clinical studies have investigated whether early-life trauma contributes to CRH and HPA axis changes observed in depressed patients.

Available evidence indicates that severe life stressors in childhood are associated with a long-term disturbance of the HPA axis in depressed patients (Heim et al., 2000, 2002; Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). Women who had experienced early childhood abuse, with or without depression, had a significantly greater ACTH responses in a stress challenge, compared to controls and to depressed women who had not experienced childhood abuse. These results suggest that the increased HPA axis activity previously thought to be indicative of depression may instead be due to the persistent effects of early-life trauma. Using provocative HPA axis reactivity tests, Heim et al. (2001) reported that depressed women with and without childhood abuse and nondepressed women with childhood abuse exhibited blunted cortisol responses in a standard ACTH stimulation test. Decreased cortisol response under conditions of repeated stress might result in a relative lack of the regulatory effects of cortisol at the CNS level, which might then result in perpetuated and increased activation of the central CRH system and symptoms of depression.

A lack of cortisol effects might be particularly expected if there was additional resistance to the effects of cortisol in the form of glucocorticoid receptor resistance. The combined dexamethasone-CRH test allows for testing feedback inhibition of the HPA axis via glucocorticoid receptors under stimulated conditions. Dexamethasone is a synthetic and more potent form of cortisol. When given orally at 11 p.m., dexamethasone administration results in profound suppression of cortisol release on the next day. This is followed by injection of CRH, which can produce an ''escape'' of cortisol from suppression. Such an escape is a common feature among depressed patients and also identifies depression risk in never-depressed relatives of patients. Our group has shown that childhood abuse indeed is also associated with escape of cortisol from suppression in this combined dexamethasone-CRH test, suggesting relative glucocorticoid resistance under challenge as a consequence of early adversity (Heim, Mletzko, et al., 2008).

Taken together, all of these HPA axis changes are concordant with increased CNS CRH activity as a function of early-life stressors. Accordingly, two studies suggest that childhood stress is more predictive of increased cerebrospinal fluid (CSF) CRH concentrations than is a diagnosis of depression. Thus, Carpenter et al. (2004) reported that a history of early adverse life events before age 6 was a more powerful predictor of elevated CSF CRH concentrations than major depression per se. Heim et al. (2008b) observed that histories of multiple abuse types, but physical abuse in particular, predict increased CSF CRH concentrations. Recently, Heim, Young, et al. (2009) observed decreased CSF oxytocin concentrations as a function of multiple abuse exposure. Reduced oxytocin availability in the CNS might contribute to heightened stress responsiveness and anxiety, in addition to reduced propensity to form close relationships.

Heim et al. (2004, 2008) have suggested that many of the biological changes thought to be characteristic of major depression may, in fact, be secondary to early-life trauma and represent risk to develop depression. It is of note that women with major depression and early-life trauma exhibit an HPA axis profile distinct from those with major depression without early-life trauma. Thus, depression with early-life trauma appears to represent a distinct endophenotype (Heim et al., 2004, 2008b). These data on the HPA axis consequences of early-life trauma may help identify new targets for antidepressant medication development, as well as predictors of treatment response in patients with this early trauma-related endophenotype.

Hippocampus

A number of studies in survivors of childhood trauma have focused on the hippocampus. The hippocampus is critically involved in the regulatory control of the HPA axis. In addition, the hippocampus is important for cognitive functions and contextual aspects of fear conditioning. The hippocampus is one of the most plastic regions of the brain with neurogenesis occurring throughout the lifespan. Stress and glucocorticoids impair the hippocampus and reduce neurogenesis (Lupien, McEwen, Gunnar, & Heim, 2009). Adults with PTSD, including those with abuse-related PTSD, have been reported to have reduced hippocampal volume as assessed by magnetic resonance imaging (MRI) (Bremner et al., 1995, 1997). Bremner et al. (2003) reported a relationship between hippocampal volume and function and PTSD associated with early-life sexual abuse. Functional imaging studies using positron emission tomography (PET) revealed decreased hippocampal activation on memory testing in patients with a history of child abuse. Stein, Koverola, Hanna, Torchia, and McClarty (1997) reported that women with early-life trauma exhibit decreased hippocampal volume. Of note, Vythilingam et al. (2002) measured hippocampal volume in depressed females with and without early-life trauma, as well as in a control group. In this study, decreased hippocampal volume was found only in those women with major depression and early-life trauma, consonant with the above neuroendocrine results. The authors noted that previous reports of decreased hippocampal volume in depression may be related to early-life trauma and not depression per se. Three possible mechanisms of reduced hippocampal volume or atrophy include neuronal atrophy, neurotoxicity, and disruption of neurogenesis (Cameron & Gould, 1996; Sapolsky, 1996; Uno et al., 1994; Watanabe, Gould, & McEwen, 1992).

Epigenetics

Of particular importance is a recent study that provided the first evidence that childhood abuse induces epigenetic changes in hippocampal neurons. Using postmortem brain from suicide victims, altered cytosine-methylation of the neuron-specific promoter region of the glucocorticoid receptor gene in hippocampal tissue was found in those suicide victims with documented histories of childhood abuse, whereas this methylation pattern was not observed in suicide victims without childhood abuse (McGowan et al., 2009). Such methylation causes silencing of the gene which results in decreased glucocorticoid receptor expression and, hence, potentially increased stress response. This remarkable result closely parallels preclinical findings (Weaver et al., 2004). The potential reversal of epigenetic changes might provide an important new opportunity for preventing and treating the long-term effects of childhood trauma in humans.

Sensitive Periods

Another important recent development concerns the notion of sensitive periods for the effects of early-life trauma on brain development. As noted above, Maercker et al. (2004) found that age of traumatization predicted risk for depression versus PTSD in young women. A recent seminal study by Andersen et al. (2008) was the first to provide evidence for differential effects of early trauma on regional brain volumes in 26 young adult women aged 18–22 years as a function of timing of sexual abuse. Hippocampal volume was reduced in association with childhood sexual abuse experienced at ages 3–5 years and ages 11–13 years, and frontal cortex was attenuated in subjects with childhood sexual abuse at ages 14–16 years.

Environmental and Biological Interactions

Craighead and Nemeroff (2005) described a biopsychosocial conceptual framework to inform clinical assessment and intervention, as well as to guide clinical research. This involves the interaction of ''Person'' and ''Environmental'' factors. The ''Person'' variables include behavioral, cognitive, and emotional characteristics of the individual that interact with the environment to determine the impact of external events upon that individual. Biological factors include the individual's genome with its unique combination of polymorphisms, for example, of the serotonin transporter (SERT), CRH receptor, FK506 binding protein 5 (FKBP5), and brain derived neurotrophic factor (BDNF) genes, and other biological factors as well. Some of the ''Environmental'' factors that may impact the individual include family, friends or social, morals or religion, spouse or partner, and work or academics. Obviously, the family environment is of great significance in both abuse and loss of a parent. The support by the family (particularly the mother) is a strong moderator of the long-term sequelae of the abuse. Other external variables are of varying importance in determining the long-term effects of sexual abuse and parental loss, and certainly play a role in defining the significance of the specific traumatic event for each type of clinical sequelae. Family support of a close friend, for example, may temper the impact of sexual abuse, trauma, and family emotional abuse (Brown et al., 1986; Jenkins & Smith, 1990). Syndromes and symptoms are a function of the interaction of the ''Person'' variable vulnerabilities with the ''Environmental'' stressors and buffers experienced by the individual. Exposure to stress, especially during neurobiologically vulnerable periods of development, is clearly one way the environment increases the likelihood of depression in genetically susceptible persons (Gillespie & Nemeroff, 2005). Accordingly, Rutter, Moffitt, and Caspi (2006) discuss several types of gene–environment interactions: These include epigenetic mechanisms by which environmental influences alter the effects of genes, variations in heritability according to environmental circumstances, gene–environment correlations, and the interaction between specific identified genes and specific environmental risks.

Multiple studies provide evidence for genetic and environmental influences on depression risk. For example, an epidemiologic twin study of 1,404 female adult twins indicated that major depression is a function of genetic predisposition, early-life trauma, and recent life stress (Kendler, Kessler, Neale, Heath, & Eaves, 1993; Kendler, Kuhn, & Prescott, 2004). Genetic and childhood environmental factors are major influences that predispose women to major depression as adults. Environmental influences included childhood sexual abuse and other stressful life events. The more severe the childhood sexual abuse, the more sensitive the woman was to the effects of stressful life events in precipitating depression. Another exemplary study investigated the relationship between family history of mood disorders and stressful life events as risk factors for depression in a preschool sample of children aged 3.0–5.6 years old (Luby, Belden, & Spitznagel, 2006). Both family history and stressful life events predicted depression severity measured by parent reports 6 months later. This analysis demonstrates that stressful life events mediate the relationship between family history and depression in preschool age.

Several genetic polymorphisms have been identified that regulate vulnerability to depression related to childhood stress. A polymorphism in the SLC6A4 gene, the serotonin-transporter-linked promoter region (5HTTLPR), has been most intensively scrutinized. The short (s) form of the 5HTTLPR confers greater vulnerability to depression in children, adolescents, and young adults who were exposed to early-life stress, whereas the long (l) allele appears to be protective (Caspi et al., 2003; Cervilla et al., 2007; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Reiley, 2005; Wilhelm et al., 2006). However, these results have not been uniformly replicated (Risch et al., 2009; Vergne & Nemeroff, 2006). It is important to note that a variant within the l allele, the Lg allele, also confers vulnerability to depression, which might explain some of the discordant results. Kaufman et al. (2004) demonstrated the importance of social support in further moderating the risk for depression in maltreated children with the s/s genotype. Wilhelm et al. (2006) further report that the 5HTTLPR genotype is a significant predictor of age of onset of major depression following multiple adverse events.

Particularly germane to our discussion of the preeminent role for CRH systems in mediating the depressogenic effects of child abuse and neglect are observations

that polymorphisms of the CRH-R1 are major determinants as to whether early-life trauma is associated with depression, an effect as large as the SERT polymorphism (Bradley et al., 2008). This result was recently replicated for a UK birth cohort (Polanczyk et al., 2009). The same genotype also moderates the effects of childhood trauma on HPA axis reactivity, as measured in the dexamethasone-CRH test: Persons who had childhood trauma but carried the protective gene variant exhibited a reduced cortisol response to this test (Tyrka et al., 2009). Our group found that a protective CRH-R1 polymorphism was associated with the reduction of cortisol response in the dexamethasone-CRH test specifically in males (Heim, Bradley, et al., 2009). In addition, a polymorphism of the glucocorticoid receptor cochaperone, FKBP5, moderates risk to develop PTSD in association with childhood trauma (Binder et al., 2008). Of note, the risk genotype is also associated with dexamethasone hypersuppression, a well-validated endophenotype of PTSD.

Several recent studies have focused on gene–gene interactions in moderating depression after childhood trauma. Kaufman et al. (2006) hypothesized that a polymorphism (Val66Met polymorphism) in the BDNF gene might interact with the 5HTTLPR genotype to increase further the risk of depression in those with early-life trauma. They studied maltreated children and matched control subjects and found a significant 3-way interaction between the BDNF Val66Met polymorphism, the 5HTTLPR genotype, and maltreatment history in predicting depression in these children. Children with the BDNF gene Val66Met polymorphism and the s/s 5HTTLPR genotype had the highest depression scores, with the vulnerability associated with these two genotypes only elevated in the maltreated children. The s/s 5HTTLPR genotype was associated with an increase in maltreated children's depression scores, which was greatest for the children without positive supports and the additional presence of the Val66Met allele of the BDNF polymorphism. Recently, an interaction between CRH-R1 and 5HTTLPR polymorphisms in moderating depression risk after childhood trauma was also reported (Ressler et al., 2010).

SEX DIFFERENCES

Major depression is twice as common in women as in men (Weiss, Longhurst, & Mazure, 1999; Young, 1998). It may be hypothesized that this sex difference may, in part, reflect higher rates of early adversities in girls relative to boys. However, according to the National Child Abuse and Neglect Data System, 2007), rates of reported cases of victimization are almost equally distributed among girls and boys, though abuse types are not specified. In studies of adults, women report more sexual abuse than men (see the Epidemiology Section). In addition to potential sex differences in exposure to different types of early trauma, there might be sex differences in the *response* to a childhood trauma. In fact, work by Seymour Levine's group suggested that the early handling procedure resulted in increased exploratory behavior in female rates, whereas male rats showed opposite changes (Weinberg, Krahn, & Levine, 1978). Rodent studies suggest that females generally exhibit greater magnitude and duration of HPA axis responses to stress than males (Rhodes & Rubin, 1999), though findings in humans are not entirely consistent (Kudielka & Kirschbaum, 2005). Sex differences in neuroendocrine stress responses may be attributed to direct effects of circulating estrogen on CRH neurons (Vamvakopoulos & Chrousos, 1993). Other factors that might determine sex differences in the stress response include genomic differences, organizational differences in brain structures or developmentally programmed effects of gonadal steroids (McEwen, 2001; Roca et al., 2005). Of note, sex steroids play a role in lifelong structural plasticity of several brain regions, including areas involved in stress responsiveness, that is, hippocampus and amygdala (McEwen, 2001). These processes, taken together, may eventually converge into the basis of sex differences in the long-term neurobiological consequences of childhood trauma that in turn translate into differential risk for psychopathology. Gene–environment interactions might occur in a sex-specific manner, adding to sex differences in the risk for depression as a function of early-life trauma. Thus, Heim, Bradley, et al. (2009) reported that the CRH-R1 polymorphism specifically protects males from depression after a history of childhood trauma.

COGNITION

Cognitive characteristics of the victim also predict outcome after childhood trauma experiences (Gold, 1986). Using a clinical sample, McGinn, Cukor, and Sanderson (2005) examined the relationship between early experiences with symptoms of depression, and the mediating effects of cognitive style. Cognitive style was evaluated using the Young's Schema Questionnaire (YSQ; Young & Brown, 1990) designed to measure five schema domains. Individuals who rated their parents as being more abusive and neglectful reported a greater degree of depression. This relationship was mediated by dysfunctional cognitive style on all five YSQ schema domains, including Disconnection-Rejection, Over-Vigilance, Other-Directedness, Impaired Autonomy or Performance, and Impaired Limits. These findings provide support for the role of cognitive factors in mediating the

link between negative parenting and psychopathology. Similarly, women with a positive abuse history were found to have more maladaptive cognitive schema and were significantly more depressed than those women who did not report a history of childhood abuse (Cukor & McGinn, 2006) Cognitive styles which were found to be most pathogenic were interpersonal disconnection and rejection. In a study by Shah and Waller (2000), the relationship between perceived parenting and adult depression as mediated by cognitive styles was examined. Three cognitive schema (defectives-shame, self-sacrifice, and insufficient self-control) differentiated between depressed patients and controls. Within the depressed group, only low paternal care and high maternal overprotection were associated with maladaptive core beliefs. Five particular core beliefs (dependence, emotional inhibition, failure to achieve, unrelenting standards, and vulnerability to harm) mediated the relationship between poor parenting and adult depression. These results suggest that poor care and a parenting style of high control create a vulnerability to depression by creating maladaptive cognitive schema.

TREATMENT APPROACHES

Given that childhood trauma appears to be associated with distinct biological and cognitive styles in depression, it is conceivable that a history of such trauma may serve as a predictor of treatment response in depression. However, few treatment studies have been performed to specifically address the impact of early-life trauma on treatment response in depression. Initial studies suggested that childhood adversity is associated with higher likelihood of relapse and treatment-resistant depression (Hayden & Klein, 2001; Kaplan & Klinetob, 2000; Lara, Klein, & Kasch, 2000; Walker et al., 2000). For example, Hayden and Klein (2001) studied 86 outpatients with dysthymic disorder that started before age 21 in a prospective 5-year study, with follow-up assessments at 30 and 60 months. Chronic stress was associated with a lower rate of recovery. Poor childhood maternal and paternal relationships and childhood sexual abuse predicted higher levels of depression at follow-up. Patients with a history of childhood emotional abuse who suffer from complex forms of PTSD may present clinically as having depression with resistance to treatment with antidepressant medication (Kaplan & Klinetob, 2000). Walker et al. (2000) studied patients with mild, moderate, and severe depression in an HMO setting. They used a multifaceted intervention targeting patient, physician, and process of care, using collaborative management with a psychiatrist and primary care physician. Patients were randomized to either stepped collaborative care (subsequent visits with a psychiatrist depend on initial treatment response) or usual care. Patients randomized to the usual care arm received treatment for depression from their primary care physicians. Baseline information about early family environment, current stressors, family history of psychiatric illness, the personality trait of neuroticism, and social support was collected. Patients with more severe depression were found to have a higher prevalence rate of childhood emotional abuse. The group of patients with severe depression who received stepped intervention showed improvements from the usual care control group at 3 months, but no differences were present at 6 months, indicating relapse at 6 months in this group when the psychiatrist visits were stopped. The severe depression subgroup was also more likely to have comorbid panic disorder.

Taken together, these studies suggested that patients who present with depression as their primary complaint should be screened for childhood maltreatment and comorbid anxiety disorders and that the patients with severe depression in the context of childhood trauma may require more intensive clinician follow-up or psychotherapy to achieve sustained improvement from depressive symptoms.

Psychotherapy

A number of studies suggest that various forms of psychotherapy are efficacious in the treatment of adults who have experienced early childhood trauma. For example, group psychotherapy for survivors of childhood sexual abuse can be effective in reducing symptoms and enhancing functioning. Kessler, White, and Nelson (2003) provide a critique of the outcome research of 13 group psychotherapy studies (6 uncontrolled and 7 controlled) of adults who suffered childhood sexual abuse. Although many of the studies contained methodological limitations, the results generally indicated that group therapy treatment helps reduce symptomatology in the short-term and at follow-up. Group treatments appear to be efficacious with two caveats: (1) group therapy is indicated for women who have experienced less severe abuse and symptoms; and (2) disorder-specific treatments are more likely to benefit women with more severe psychiatric symptomatology. Thus, women who meet criteria for more severe clinical disorders likely need more intensive individual and disorder specific therapies (Stalker & Fry, 1999).

Briere (1996, 2002) has developed a therapeutic model to guide the treatment of adults who were sexually abused as children. Compared to traditional CBT, a greater emphasis is placed on maladaptive suppressed cognitive processes and learning of emotional regulation, similar to Linehan's Dialectical Behavior Therapy (DBT) (1993).

Briere and Jordan (2004) suggested the need for interventions that are individualized to the specific problems and sociocultural issues experienced by the individual, address a larger proportion of the victim's symptomatic experience, and are multimodal in approach; that is, an approach involving not only cognitive-behavioral and relational methodologies but also interventions and advocacy in the victim's social environment. They support the need for individualized, flexible intervention strategies.

Emotion Focused Therapy (EFT) seems effective in the treatment of adults who have experienced early childhood abuse. EFT is a 20-week individual psychotherapy based on current emotion theory and experiential therapy theory and research. It involves a safe, collaborative relationship in which emotions are the primary focus of therapy. Resolution of interpersonal difficulties, past and present, are essential to its success. Paivio and Nieuwenhuis (2001) examined the effectiveness of EFT in 32 adult survivors of childhood emotional, physical, or sexual abuse. Participants were assigned to EFT or a variably delayed therapy condition. Patients receiving EFT achieved significant improvements in multiple domains of disturbance. Individuals in the delayed treatment condition showed minimal improvements over the wait period, but after EFT, they showed significant improvements comparable to the immediate therapy group. These effects were maintained at the 9-month follow-up.

There appear to be no randomized controlled clinical trials evaluating therapies for adults who were separated from their mother for a sustained period of time or whose mother died during childhood. There are some data which indicate that grief or bereavement counseling/therapy may sometimes be effective as an intervention for bereavement. Bereavement counseling's greatest effectiveness appears to occur when the counseling is focused on emotional development and coping skills of older children and adolescents who have suffered such losses (Jordan & Neimeyer, 2003; Schut, Stroebe, Van Den Bout, & Terheggen, 2001). One effective program for adolescents who experienced loss and their families is the Family Bereavement Program (FBP) developed by Sandler et al. (2003). The FBP is a 2-component group intervention for parentally bereaved children ages 8–16. The program involves separate groups for caregivers, adolescents, and children. The groups are designed to change potentially modifiable risk and protective factors for bereaved children. Three of the family-level variables are: increasing the positive quality of the relationship between caregiver and child, decreasing mental health problems of the caregiver, and decreasing children's exposure to negative events. The latter involves decreasing the occurrence of negative events in the family, such as serious conflicts between caregivers and children, and encouraging caregivers not to involve children in stressors that are the adult's responsibility. A fourth family-level factor, effective discipline, was also selected. Several individual-level factors are targeted: attempts to improve self-esteem, increase adaptive beliefs about why negative events occur, improving positive coping, and decreasing negative thoughts about stressors. The program focuses on increasing children's beliefs that their feelings are understood by their caregivers and reducing their need to inhibit the negative expression of grief-related feelings.

Sandler et al. (2003) have evaluated FBP by random assignment of 156 families to the FBP or a self-study condition. Results at 11-month follow-up indicate that the FBP led to improved parenting, coping, and caregiver mental health and to reductions in stressful events. Also the FBP led to reduced internalizing and externalizing problems specifically for girls and those who had higher problem scores at baseline.

Generalization from this small literature to interventions for adults who experienced trauma as children is limited. However, Craighead and Nemeroff (2005) noted that the same psychotherapeutic conceptualizations of treating trauma survivors seem to be consistent across the reviewed literature. They suggested that treatment is more effective when the treatment is individualized, when it is specific to the presenting disorder, and when the person seeks treatment for distress caused by the trauma. The greatest confidence can be placed in treatments that systematically and concurrently address behavioral, emotional, cognitive, and neurobiological dysfunctions (Stevenson, 1999).

Pharmacotherapy

There is evidence from laboratory animal studies that SSRI treatment can reverse some of the persistent neurobiological effects of early-life trauma (Gutman & Nemeroff, 2002). Thus, persistent increases in CRH concentrations and CRH mRNA expression associated with early-life trauma may be at least partially reversed with paroxetine treatment. Decreasing the CRH response to stress may be a component of the therapeutic response in mood and anxiety disorders (Nemeroff & Vale, 2005). The CRH receptors are logical targets for drug development. CRH receptor antagonist clinical trials are currently ongoing (Nemeroff & Vale, 2005). One open, uncontrolled clinical trial in depression has been published (Zobel et al., 2000) and was positive. A second study of another CRH receptor antagonist showed no evidence of efficacy in major depression (Binneman et al., 2008). New treatments strategies might be derived from recent seminal insights into epigenetic regulation by early-life trauma which, in animal models, are reversible (see above). It remains to be tested whether methyl

supplementation (Weaver et al., 2005) or other interventions targeting the epigenome may be suitable in humans to prevent and treat the negative outcomes of early developmental adversity.

Combination of Psychotherapy and Pharmacotherapy

In addition to monotherapies, there is a large database of effective psychotherapies and pharmacotherapies that can be successfully combined (Craighead & Nemeroff, 2005; Nathan & Gorman, 2002; Schatzberg & Nemeroff, 2004). Recent neurobiological data indicate that these treatments seem to act upon distinct biological substrates to obtain more broadly effective clinical outcomes (Goldapple et al., 2004). Goldapple and coworkers found that CBT resulted in significant clinical improvement in the 14 patients who completed the study. Treatment response was associated with significant metabolic changes: increased metabolic change in the hippocampus and dorsal cingulate (Brodmann's area [BA] 24) and decreased metabolic change in the dorsal (BA 9/46), ventral (BA 47/11), and medial (BA 9/10/11) frontal cortex. Thus, CBT seems to affect clinical recovery by modulating the functioning of specific sites in limbic and cortical regions. The investigators noted that this pattern is distinct from that seen with paroxetine-treated clinical recovery, in which prefrontal metabolic increases and hippocampal and subgenual cingulate decreases were observed. Mayberg et al. (2000) studied fluoxetine treatment of major depression by changes in brain glucose metabolism as assessed by PET. They also found clinical improvement to be specifically associated with limbic and striatal decreases in glucose metabolism in the subgenual cingulate, hippocampus, insula, pallidum, and brain stem. Clinical improvement was also specifically associated with dorsal cortical metabolism increases in the prefrontal, parietal, anterior, and posterior cingulate. Although childhood trauma was not assessed in these studies, these findings raise the important question as to whether there are subtypes of patients with depression who might benefit from psychotherapy versus those who might require pharmacotherapy. Childhood trauma may be one of several potential factors that might characterize such treatment response subtypes.

Differential Treatment Selection

As noted above, a pertinent question concerns differential treatment selection for a given patient. More specifically, clinicians face a choice among different treatment approaches and there is limited guidance or predictors to decide which treatment strategy might be most effective for a given patient. As described in this review, depressed patients with childhood trauma experiences have a very specific neurobiological phenotype that distinguishes these patients from depressed patients without early traumatic experiences (Heim et al., 2004, 2008b). Our group has thus suggested that these subtypes of depression might also be responsive to different treatment strategies that target different pathways involved in the development of these forms of depression (Heim et al., 2004, 2008b). Therefore, the presence or absence of childhood trauma may serve as an indicator to guide differential treatment decisions in depression. Nemeroff et al. (2003) addressed this important question by reanalyzing data from a large, multicenter, double-blind randomized controlled trial. The original study had evaluated the relative effectiveness of the antidepressant nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), and their combination in the treatment of patients with chronic depression, with the index episode of depression lasting for 2 years or longer (Keller et al., 2000). The primary finding of the original study was that the combination of the antidepressant and this form of cognitive-behavior therapy (CBASP) was more effective than either treatment alone in alleviating chronic and recurrent depression. Nemeroff et al. (2003) reanalyzed the data for the 681 patients in this chronic depression treatment study. Of note, two-thirds of the chronic depression population had sustained early-life trauma. One-third of the patients had experienced loss of a parent before 15 years of age. Forty-five percent reported experiences of physical abuse, 16% reported experiences of sexual abuse and 10% reported experiences of neglect during childhood. One-third of the patients had experienced multiple types of childhood trauma. Importantly, the distribution of childhood trauma was comparable across the three randomized treatment groups. When stratifying the treatment groups by presence or absence of childhood trauma, the results differed from the original report by Keller et al. (2000): for chronically depressed patients with childhood trauma experience, the efficacy of psychotherapy (CBASP) alone was significantly superior to nefazodone monotherapy alone. The combination of the antidepressant with CBASP had no further advantage in the patient group that was chronically depressed and had a history of early-life trauma. Chronically depressed patients without childhood trauma benefited more from nefazodone than psychotherapy. Although in need of replication with studies in which patients with and without childhood trauma history are randomly assigned to treatment groups, this study suggests that, until such studies are done, an individual, disorder-specific psychotherapy should be the first line of treatment for depressed patients who have suffered from early-life trauma.

These findings can be discussed in the context of the above study by Mayberg and coworkers (Goldapple et al.,

2004) that suggested that depressed patients who respond to CBT have different functional activation patterns compared to depressed patients who respond to drug therapy. Results by Nemeroff et al. (2003) suggest that early-life trauma might be one factor that contributes to treatment response-specific brain types. This assumption should be tested in future studies. Replication of the results by Nemeroff et al. (2003) is needed as well as studies that test the general assumption with various forms of psychotherapy and different medications.

Treatment Recommendations

Craighead and Nemeroff (2005) summarized five findings from the available literature. First, in those with early-life trauma, the basic cognitive schema regarding trust and safety are absent or disrupted. Thus, the fundamental therapeutic task in working with these patients is to build a therapeutic alliance around trust and safety. One effective therapy for developing and maintaining this initial alliance is Schema Focused Therapy (Young, Klosko, & Weishaar, 2003). Schema Focused Therapy allows the patient to develop fundamental beliefs that people can be trusted, that the world can be safe, and that social and interpersonal relationships can be lasting.

The second finding is that it is essential to recognize that resensitization to the trauma events and stimuli can easily occur (Craighead & Nemeroff, 2005). For example, in a study on the effectiveness of grief counseling for bereavement, Jordan and Neimeyer (2003) reported that many of the participants (up to 38% in one study) would have had a better outcome by having been assigned to the no-treatment control group as compared to the grief counseling group. Thus, it is possible for therapy to have no effect, or even a negative impact, on individuals (Craighead & Craighead, 2003). Inappropriate exposure to the original traumatic event can reactivate the emotional states, cognition, and behavioral patterns originally associated with the traumatic event (Briere, 2002). The therapist needs to understand what happened to the patient during the trauma as well as afterward. It is important that the therapist not expose the patient too soon, though the use of some form of exposure therapy may be necessary to treat trauma survivors. The timing of exposure requires knowledge of the scientific literature, good clinical judgment, and sensitivity. Recalling early-life trauma nearly always results in a substantial exacerbation of clinical symptoms before the patient is able to process and use this material therapeutically (Carver, Stalker, Steward, & Abraham, 1989; Craighead & Nemeroff, 2005). The most successful treatments use a therapeutic process that is neither too fast nor too slow in exposing the patient to early-life traumas in therapy; and, are adapted to the individual experiences and clinical states of the patient.

Third, Craighead and Nemeroff (2005) suggested that individuals who suffer severe sequelae from early-life trauma need longer-term therapy rather than acute treatment. Pertinent research literature is consistent with this observation. For example, Linehan's DBT was lengthened so that it now typically takes more than a year for completion (Linehan, 1993). Similarly, Schema Focused Therapy (Young et al., 2003), which is designed to help the patient change underlying schema (such as trust, safety, control, dependence, abandonment, alienation, autonomy, and avoidance), usually takes several months. Current studies are underway evaluating long-term CBT for those who fail to remit during the typical 16–20 sessions.

A fourth characteristic of therapy for early-life trauma is that the individual must learn better emotional regulation (Craighead & Nemeroff, 2005). Therapies such as Greenberg's Emotion Focused Therapy (Greenberg & Paivio, 1997) have been developed to focus on teaching emotional regulation. Therapies that use mindfulness have been incorporated into cognitive and behavioral therapies such as Linehan's DBT (1993) and Segal, Williams, and Teasdale's Mindfulness CBT (2002) to allow the patient to learn better emotional regulation. It requires considerable time for the internalization of emotional control to develop. Briere (2002) has also used teaching skills that aid emotion regulation.

CONCLUSIONS

The seminal work of Seymour Levine has to a large extent served as the impetus for translational research into the effects of early experience on brain development and behavior. Since his early pioneering work, over the course of decades, there have been tremendous advances in our understanding of the importance of early environmental factors in determining developmental outcomes and the mechanisms involved. Research from animal models has shown that early adverse experience produces an adult phenotype with neurobiological sensitivity to stress. Positive early environments or milder stressors exert protective effects and result in stress resilience. More recently, research has focused on the clinical relevance of the psychobiological consequences specifically of early adverse experiences. Research from human clinical studies has provided evidence that childhood trauma induces neurobiological changes that are similar to those described in animal models. These established neurobiological consequences of early-life adversity in humans contribute to significant psychiatric morbidity, including depression, anxiety and other disorders as well. Important

areas of current investigation include gene–environment interactions that moderate the effects of early trauma, the identification of sensitive periods for the effects of early trauma, epigenetic processes, and the prevention or reversal of the pathogenic effects of early trauma. While a number of treatment approaches are available for victims of early trauma, more clinical research is needed to identify specific neurobiological targets for intervention and to identify specific predictors of treatment selection based on early developmental, genetic, and clinical features. Treatment effects are likely larger when the treatment is individualized, specific to the presenting disorder and the nature of the early-life trauma as well as gene–environment interactions.

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