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The neurobiological Correlates of Childhood Adversity and Implications for Treatment

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Abstract

Objective—This paper provides an overview of research on the neurobiological correlates of childhood adversity and a selective review of treatment implications.

Method—Findings from a broad array of human and animal studies of early adversity were reviewed.

Results—Topics reviewed include neuroendocrine, neurotrophic, neuroimaging, and cognitive effects of adversity, as well as genetic and epigenetic influences. Effects of early life stress on treatment outcome are considered, and development of treatments designed to address the neurobiological abnormalities is discussed.

Conclusion—Early adversity is associated with abnormalities of several neurobiological systems that are implicated in the development of psychopathology and other medical conditions. Early life stress negatively impacts treatment outcome and individuals may require treatments that are specific to this condition.

Keywords

Early life stress; childhood abuse; neurobiology; treatment

Introduction

Childhood maltreatment, a well-known risk factor for psychopathology, including major depressive disorder (MDD) and anxiety disorders, is increasingly understood to be an environmental exposure that acts much like a toxin, with the potential to influence several neurobiological systems implicated in the pathophysiology of these disorders. Childhood adversity, such as abuse, neglect, parental loss, and other stressful experiences, has been

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estimated to account for 45% of the variance in childhood-onset psychopathology and 26-32% of the risk for later-onset psychiatric disorders (1). The consequences of stress exposures occurring in early development are especially profound because 1) young children are entirely dependent on caregivers for their basic physical, social and emotional needs, and 2) this period involves rapid and large-scale developmental changes in neural pathways that regulate emotion and behavior (2, 3). Work with rodents and non-human primates demonstrates that early caregiving behaviors play a critical role in the normal development of brain circuits involved in the regulation of stress reactivity, learning and memory, neuroplasticity, and behavior (4). Early adversity in humans also results in long-lasting alterations in these neurobiological, behavioral, and social systems (5).

Investigations of early stress in humans are complicated by the fact that several important factors can modify the effects of stress exposure, including the type, frequency, and nature of the stress, the co-occurrence of multiple stressors, and the developmental period when the stress occurs; these are difficult to measure in humans. Adverse experiences can have heritable influences, such as abuse due to parental psychopathology, so that genetic and environmental contributions to the correlates of early life stress can be difficult to disentangle. Finally, the assessment of neurobiological influences involves indirect measures of peripheral markers or neuroimaging techniques which may not adequately reflect neuronal signaling in relevant brain circuits thought to underlie risk for psychopathology. In contrast, animal models do allow causal inferences because they involve selected stressors, control of potentially confounding variables, and direct examination of behavior and brain tissue. However, the utility of these models depends upon the degree to which they parallel human processes.

Aims of the study

Here we provide a selective review of the burgeoning literature on the neurobiological correlates of early-life stress in humans, with inclusion of important relevant findings from animal models. Where available, we identify studies that may hold particular promise for influencing treatment development and clinical decision-making, particularly in relation to risk for depressive and anxiety disorders.

Material and methods

Findings from a broad array of human and animal studies of early adversity are reviewed. Topics include neuroendocrine, neurotrophic, neuroimaging, and cognitive effects of adversity, as well as genetic and epigenetic influences. Studies examining effects of early life stress on treatment outcome are reviewed, and investigations of treatments designed to address the neurobiological abnormalities associated with stress exposure are discussed. The Figure provides a model depicting the mediators and moderators of the neurobiological correlates of childhood adversity reviewed in this paper.

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Results

Neuroendocrine Response to Stress

Stress exposure activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, which play a major role in coordinating the neural and behavioral response to stressors. Following stress exposure, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are released from the hypothalamus. CRH serves as a neurotransmitter and modulates sympathetic arousal; it also acts in concert with AVP to stimulate secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the adrenal cortex to synthesize and release glucocorticoids; cortisol is the most abundant and potent glucocorticoid in humans. In addition, the sympathetic nervous system secretes catecholamines. In the context of normative acute stress experiences, this activation results in the alteration of several physiological systems to allow adaptive responses to stressors. Appetite, gastrointestinal activity, sexual function, and fuel storage are inhibited in order to prioritize metabolism for rapid cognitive and muscular action. Cardiovascular activation increases blood pressure, heart rate, and cardiac output, and blood is diverted to muscles and brain (6). This system is regulated homeostatically, with negative feedback from cortisol acting at hypothalamic and pituitary glucocorticoid receptors to terminate the acute stress response. However, when stressors are excessive or prolonged, attempts at maintaining homeostasis can lead to alterations of basal and provoked HPA axis activity and associated functioning of autonomic, metabolic, and immune systems (7, 8).

Childhood Stress, Neuroendocrine Function, and Psychopathology

Early-life stress is linked to altered neuroendocrine function in adults with psychiatric disorders such as MDD, post-traumatic stress disorder (PTSD), and borderline personality disorder (9, 10). While several studies in adults and children with MDD documented increases in basal and provoked HPA axis activity, attenuated HPA axis function has also been associated with MDD and depressive symptoms (11). PTSD has been associated with decreased basal or stress-induced cortisol concentrations in several studies, but increased ACTH and/or cortisol concentrations in others (12). HPA axis dysfunction may be more proximally linked to the experience of childhood adversity, which often precedes the onset of depression and PTSD. It is now well established that early adversity alters HPA axis function, with evidence of both exaggerated and attenuated cortisol and ACTH levels (3, 13-15). The precise mechanism underlying diminished cortisol responses is not known, but a trajectory of initial hyperactivation of the HPA system in response to excessive and prolonged stress exposure, progressing to a state of chronic adrenal stress hyporeactivity, has been proposed (16, 17).

Severe and Chronic Stress: Neurotoxicity and Anxiogenesis

Glucocorticoid receptors are widely distributed throughout the limbic system, including the hypothalamus, hippocampus, amygdala and prefrontal cortex (PFC). In rodents, chronic stress and glucocorticoid administration result in remodeling and inhibition of cell proliferation in the PFC and hippocampus (17). In the amygdala, a brain region that regulates fear and anxiety, glucocorticoid exposure results in neuronal proliferation and dendritic growth (17). CRH mediates anxiety and fear responding in the amygdala, and in

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contrast to the negative feedback effect of cortisol on CRH secretion from the hypothalamus, in the amygdala cortisol enhances CRH activity. Administration of CRH to the brain in rodents and monkeys produces anxiety-like behavior, including neophobia, suppression of exploratory, social, reproductive, and appetitive behavior, and increased physiological reactivity to novel or stressful stimuli. Glucocorticoids, CRH, AVP, ACTH, cortisol, and epinephrine enhance unconditioned fear responses and learning in aversive conditioning paradigms (18). This may provide important clues to the development and treatment of fear and anxiety following trauma exposure, as occurs in PTSD, as discussed further below.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a key role in the growth, differentiation, maintenance, and survival of neurons (19). BDNF is decreased in rodent stress models and in patients with MDD, and may play a critical role in glucocorticoid-induced neurotoxicity. Rodent models involving early stress or the administration of glucocorticoids decrease BDNF expression and lead to hippocampal and cortical atrophy, as well as behavioral changes associated with depression. Importantly, chronic treatment with exercise, antidepressants, and electroconvulsive shock have all been shown to increase BDNF levels and hippocampal neurogenesis in rodents (19). Peripheral BDNF administration produced behavioral antidepressant-like effects and increased hippocampal neuronal survival in rodents (20).

In humans, evidence is mounting that BDNF may be involved in the pathogenesis of stress-related disorders such as MDD. Postmortem brains of suicide victims show reduced BDNF expression in hippocampal and cortical brain regions (21), and this corresponds to neuroimaging findings of decreased volumes of hippocampus and PFC in adults with a history of childhood maltreatment, MDD, or PTSD (4). BDNF is also reduced in the blood of medication-naïve patients with MDD and is increased in patients with MDD who are on antidepressants (22). A few recent studies have shown that early stress exposure is linked to peripheral BDNF levels in subjects with a lifetime history of MDD (e.g. (23-25)). These findings, combined with data from animal studies showing reduced BDNF and behavioral changes associated with depression, suggest that neurotoxic effects of stress may be causally involved in major depression.

Childhood Adversity: Neuroimaging and Cognitive Correlates

As mentioned above, several neuroimaging studies of children and adults have examined effects of early adversity. Structural imaging studies examine the volume of brain regions and functional studies evaluate activity of brain regions during tasks or resting states. Much of this work has focused on frontal and limbic systems involved in emotional processing, motivation, working memory, and behavioral regulation. In particular, the PFC, amygdala and hippocampus represent key nodes in the brain stress circuitry, and are strongly implicated in the pathophysiology of mood and anxiety disorders. These regions have a high density of glucocorticoid receptors and therefore may be more susceptible to the neurotoxic effects of excessive glucocorticoid exposure during key developmental periods. The body of literature on this topic is growing and many of the findings are mixed, but overall, structural and functional neuroimaging results indicate that childhood maltreatment is associated with

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abnormalities in the PFC, corpus callosum, amygdala, and hippocampus (for reviews see (26, 27)).

In addition to their role in affective and cognitive processing, some of these same regions function together in the "default mode network," which is active during resting states and may be involved in self-reflection and readiness for future events. Decreased connectivity within this network has been linked to early life stress and PTSD, suggesting a link between stress exposure and disrupted processing of internal experiences, which may contribute to the pathophysiology of stress-related illnesses (28, 29).

Taken together, these neuroimaging findings suggest that childhood maltreatment may impair frontal brain regions that are necessary for inhibitory control of limbic responses. For example, loss of "top-down" control by the PFC may lead to anxiety symptoms, as the ascending signals from the amygdala are not sufficiently modulated (30). As discussed above, animal models demonstrate that stress, glucocorticoids, and alteration of neurotrophic factors lead to structural changes in cortical and limbic brain regions. While studies of this effect in healthy adults have yielded mixed findings, cortisol has been linked to smaller volumes of PFC (31), hippocampus (32) and anterior cingulate (33) in adults and children with early adversity. Increased cortisol concentrations have also been associated with diminished functional connectivity between the PFC and amygdala (34).

Consistent with neuroimaging findings, children with early adversity may have impaired cognitive function. For example, children institutionalized before adoption had poorer cognitive performance that was associated with longer durations of institutionalization. Deficits include overall decrements in intelligence quotient (IQ) as well as specific problems with working memory, language, attention, and executive function (27, 35) that are present even after controlling for IQ (36). In terms of other cognitive and affective faculties, younger maltreated children, particularly neglected children, have difficulty discriminating facial expressions of emotion, and physically abused children may have enhanced sensitivity to angry and threatening emotional expressions (27). Academic performance may be impaired in adults with a history of childhood maltreatment, but IQ deficits have not been documented in this group. Methodological differences between studies of adults and children may account divergent findings regarding IQ (discussed below), or some deficits may resolve over time, perhaps in response to environmental enrichment (27, 37). Consistent with findings with children, however, adults with a history of childhood maltreatment show increased sensitivity to negative emotional expressions (38).

Genetic Influences on the Effects of Early Stress

Although early stress increases risk for the development of psychopathology, some individuals are resilient and do not suffer many of the detrimental effects of adverse childhood exposures. Interactions of risk or protective genes and environmental exposures (G × E interactions) have long been proposed to account for these divergent outcomes, and recent studies have identified genes involved in monoaminergic, neuroendocrine, and neurotrophin systems as likely candidates. Much of this work has focused on genes that regulate the serotonin system, in particular *5-HTTLPR*, a functional polymorphism in the promoter region of the serotonin transporter gene. In 2003, Caspi and colleagues (39)

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published a groundbreaking prospective study of a representative birth cohort in Dunedin, New Zealand in which they reported a G × E interaction of *5-HTTLPR* with both early adversity and adult stressful life events. Stress exposure significantly increased the risk of developing depression, and individuals with the short (s) variant of the gene who were exposed to stress had the greatest risk. The finding of a stress × *5-HTTLPR* interaction has been replicated in numerous studies. Substantial controversy was generated by negative findings from two meta-analyses of a subset of these studies (40, 41). However, a broader view of this literature (42) and a more inclusive meta-analysis (43) support an interaction effect of this gene with psychosocial stress in the development of depression, and indicate that the most robust findings are from studies of childhood maltreatment as the stressor.

Additional work has demonstrated interactions of early adversity with other serotonin genes as well as genes that regulate other systems, such as the HPA axis and neurotrophin systems, as reviewed in Nugent et al (44). For example, the gene for the type I CRH receptor (*CRHR1*) interacts with childhood maltreatment to increase risk for depressive symptoms or diagnoses (44-46), as well as abnormal diurnal or provoked cortisol concentrations in children and adults (47, 48). *FKBP5*, a gene that regulates sensitivity of the glucocorticoid receptor, has been shown to interact with childhood maltreatment to predict PTSD and depression (49). As discussed above, BDNF is a nerve growth factor that is reduced in response to stress in animal studies and in patients with MDD. The Met allele of a functional variant of the BDNF gene (*Val66Met*) results in abnormal intracellular packaging and secretion of BDNF. Several studies have now shown that this allele interacts with early-life stress to increase risk for depression in children and adults (44, 50).

It is important to acknowledge that the efforts to identify risk genes for major depression and other psychiatric conditions have rarely yielded robust findings. Among other reasons for this, it is likely that many genes are involved, and, given the heterogeneous nature of our diagnostic categories, different genes may be critical for different individuals. Similarly, genes that are sensitive to the influences of stress exposure may only be relevant for those with a significant history of adversity. As with other studies of childhood adversity, methodological considerations are paramount in interpreting the findings of investigations of gene-environment interactions (see below for a discussion).

Epigenetic Effects of Early-Life Stress

Gene variants such as those discussed above arise from differences in the sequence of DNA, whereas epigenetic alterations to DNA do not influence DNA sequence, but alter the likelihood that genes will be expressed. Animal work and a few human studies implicate epigenetic changes to the glucocorticoid receptor gene as a mechanism underlying the neurobiological effects of early adversity. Animal models of early stress have also found epigenetic changes to other genes that regulate neuroendocrine function (e.g., 51). Methylation is a stable form of epigenetic modification that can block binding of transcription factors and reduce gene expression. In rodents, low levels of maternal care (licking, grooming, and arched-back nursing) result in greater methylation of the promoter region of the glucocorticoid receptor gene.. In rodents, low levels of maternal care (licking, grooming, and arched-back nursing) result in greater methylation of the promoter region of

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the glucocorticoid receptor gene. As discussed above, the glucocorticoid receptor serves an important regulatory function in modulating stress responses, and this animal model leads to reduced numbers of glucocorticoid receptors and abnormal hormonal and behavioral responses to stress (52).

Very few human studies of epigenetic changes in relation to early-life stress have been conducted thus far, but early results are consistent with the animal findings. Suicide victims with childhood maltreatment had greater methylation of the glucocorticoid receptor gene promoter in the hippocampus (53). Maternal depressed/anxious mood in the third trimester was associated with greater methylation of this gene in a study of infant cord blood, and methylation was positively associated with salivary cortisol responses to stimulation of the infants at age three months (54). A small study found that maternal exposure to intimate partner violence was associated with greater methylation of this gene in adolescent offspring (55). Our group recently found greater methylation of the promoter region of this gene in peripheral blood of adults with a history of early adversity, and methylation was linked to altered cortisol response to a standardized endocrine challenge test (56). Other genes that regulate stress-responses in humans, such as genes in the BDNF, serotonin, and dopamine systems, have also been examined for stress-related epigenetic changes with encouraging preliminary results. One study showed that lifetime stress predicted epigenetic changes to the gene for catechol-O-methyltransferase (COMT), an enzyme that degrades catecholamines. Stress and COMT methylation were linked to alterations in working memory and prefrontal activity (57). Overall, these initial epigenetic findings are consistent with what is known about the neurobiology of these systems and early-life stress exposure, and suggest that epigenetic modulation of neuroendocrine, neurotrophic, and monoaminergic systems could be a key mechanism underlying the neurobiological effects of childhood adversity.

Allostatic Load: Metabolic Syndrome, Immune, and Cellular Aging Effects

Stress and Disease—A recent study found that adults with six or more adverse childhood experiences died on average nearly 20 years earlier than those without such experiences (58). Excessive glucocorticoid activity due to chronic stress can lead to failure of multiple physiologic regulatory systems, termed allostatic load (17). Consistent with this, a history of early-life stress increases risk for several medical conditions, including obesity, cardiovascular disease, diabetes, fibromyalgia, and chronic fatigue (59). Activation of the HPA axis and sympathetic nervous system alters physiologic systems involved in the metabolic syndrome, which consists of central obesity, hypercholesterolemia, and increases in blood pressure and insulin resistance (60, 61). The metabolic syndrome has been associated with HPA axis dysregulation, and our group recently found that indices of the metabolic syndrome were linked to blunted cortisol responses to the dexamethasone (Dex)/CRH test, consistent with the allostatic load hypothesis (62).

Stress and the Immune System—Glucocorticoids have both permissive and suppressive effects on immunity and inflammation. The immunosuppressive actions of exogenous glucocorticoids are well known, and glucocorticoid deficiency results in excessive activation of inflammatory and immune responses (6). Acute stress initiates the

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inflammatory response, involving increases in pro-inflammatory cytokines, as well as chemokines, adhesion molecules, and acute phase reactants (63). Pro-inflammatory cytokines and deficient cellular immunity are involved in a variety of stress-related disorders, including MDD (64), and findings from several studies indicate that early stress may partially account for this association. In a sample of healthy adults without psychopathology, our group found that a history of childhood maltreatment was associated with exaggerated interleukin (IL)-6 responses to psychosocial challenge (65). Childhood adversity has emerged as an independent risk factor for systemic inflammation later in life in large epidemiological samples (66).

Stress and Telomere Shortening—Excessive glucocorticoid and immune activation resulting from chronic or early stress exposure may lead to telomere shortening, a cellular marker of aging that has been linked to morbidity and mortality in cardiovascular disease, diabetes, and cancer, in addition to MDD and bipolar disorder (67). Telomeres are “caps” at the ends of linear chromosomes comprised of DNA repeats that serve to promote chromosomal stability. In replicating somatic cells, chromosome ends shorten with each cell division, and telomeres serve as buffers against loss of genetic information and chromosomal fusion or recombination. Telomeres shorten with each cell division and when they become critically short, the cell undergoes replicative senescence or programmed cell death. Exposure to radiation or toxins has long been known to influence telomere length; more recent work identifies psychosocial stress as an important factor as well. In a study of female caregivers, Epel and colleagues (68) found that psychological stress was linked to leukocyte telomere shortening. Several studies have confirmed this effect in a variety of contexts. Because rates of telomere shortening are fastest during infancy and early childhood and regulation of telomere length may be programmed in early development, childhood maltreatment may have a particularly profound effect on telomere attrition. In a study of healthy adults with no current or past psychiatric disorder, our group found that those with a history of childhood maltreatment had shorter telomeres than adults with no such history (48). The association of shorter telomere length with childhood adversity has been replicated in several studies involving a variety of measures of early adversity in samples of adults and children (67).

In summary, early-life stress has been associated with several medical conditions including obesity, cardiovascular disease, diabetes, fibromyalgia, and chronic fatigue, in addition to major depression and related psychiatric disorders. Psychosocial stress may induce telomere shortening through effects on glucocorticoid and inflammatory activation. These processes may therefore represent a mechanism of the effect of early-life stress on risk for psychiatric and other medical conditions.

Methodological Influences on the Study of Early-Life Stress

The literature reviewed above identifies neurobiological effects of early adversity seen in both animal models and human studies that are associated with psychiatric and medical conditions, and these effects may represent mechanisms of risk for these disorders. However, this broad overview does not allow for a detailed examination of individual findings, where considerable variability can be found. Animal models allow for rigorous

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experimental control, and therefore provide some of the strongest evidence for neurobiological effects of early stress; however, findings are specific to the species and strain of animal as well as the stress paradigm used. In humans there are wide variations in the nature of stress exposure, such as type of adversity, intensity, and duration, as well as mitigating and ameliorating influences. Adverse experiences commonly co-occur, and are often associated with other risk factors, such as parental psychopathology and poverty. Individual differences, including risk and protective genes, as well as buffering environmental experiences, are also critical, yet difficult to study adequately. Timing of exposure to adversity is important, because different brain regions and circuits differ in the timing of development, and attachment and other buffering influences differ across development as well. Effects may resolve or worsen over time, depending on exposure to subsequent risk and protective influences.

It is difficult to comprehensively assess early-life stress in research. Structured interviews may be ideal but are very labor intensive, and in fact, it is possible that the anonymity afforded by questionnaires may yield some benefit. Questionnaires are used most commonly, but it is difficult in this format to accurately measure all important characteristics. These include the precise nature, developmental timing, duration and frequency of occurrences over time, and the subjective level of stress. Studies of general stressors have commonly used stressor checklists which vary between studies and often do not have objective stressor characteristics or subjective stress ratings. Studies of children often use child protective service records to identify maltreatment, which does not capture all experiences of abuse or neglect in maltreatment or control groups. A number of studies have also examined neurobiological systems in children raised in orphanages who experienced neglect. Only a few studies have begun to investigate these complexities in the nature of stress exposure and other individual differences, and no conclusions can yet be drawn regarding specific effects of these influences.

Importantly, most investigations include participants with trauma-related psychiatric illnesses, such as PTSD, MDD, or borderline personality disorder, and many include those on psychotropic medication. Insofar as abnormalities may be specific to particular disorders or to medication treatment, findings of studies that do not account for effects of these disorders will be more difficult to interpret. On the other hand, samples that exclude individuals with trauma-related disorders may be heterogeneous and include both at-risk and resilient individuals. Studies of children with recent trauma exposure can focus on risk, but typically involve more severe maltreatment because such children are identified through social services. In addition, non-maltreated control groups may include children with stress or trauma that has not been measured or detected. Adults, by contrast, self-report their experiences, and these may cover the full range of maltreatment. Such reports may be subject to reporting and memory biases, although false negatives are more common than false positives (69). Adults and children also differ with respect to types of protocols and procedures that they can tolerate. For example, drawing blood from young children, perhaps especially those who have been maltreated, can be traumatic, so studies of neurobiological correlates of stress exposure are often limited to substances that can be measured in saliva. In neuroimaging studies, young children may not be able to remain still in the scanner or participate in complex protocols.

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Treatment Approaches

Treatment of Maltreated Children—A history of childhood maltreatment portends a more unfavorable course of depressive illness and response to conventional pharmacotherapy and psychotherapy in adolescents and adults (70); for example, standard cognitive behavioral therapy (CBT) may not be effective in this population (e.g., (71, 72). On the other hand, trauma-focused CBT (TF-CBT) teaches coping skills combined with gradual exposure to trauma narratives to allow the child to become more tolerant of trauma-reminders, which is associated with reductions in psychological and physical stress-reactivity. In comparison with supportive therapy, TF-CBT is more effective for symptoms of PTSD and depression (73). Another approach, Trauma Systems Therapy (TST), assesses emotional and behavioral dysregulation in the environmental context to develop a team-based treatment plan involving home-and office-based work, and advocacy for social and educational services. A recent uncontrolled study found improvements over 15 months of treatment (74), but controlled studies have yet to be conducted.

Treatment of Adults with a History of Childhood Adversity—Only a few studies have examined whether some treatments are more efficacious than others for adults with a history of childhood maltreatment. A study of treatment of chronic depression found that patients with a history of childhood trauma had better responses to psychotherapy, with or without the antidepressant nefazodone, compared to nefazodone alone (75). A study of inpatients with major depression found that for those with a history of childhood maltreatment, the combination of interpersonal therapy and antidepressants was significantly more effective than antidepressants without psychotherapy (76). Thus, psychotherapy appears to be an important component of treatment for patients with a history of childhood trauma.

Psychotherapeutic approaches that specifically target emotional and behavioral sequelae of childhood maltreatment have been developed for adults. Dialectical behavioral therapy (DBT) utilizes CBT and mindfulness approaches to address problems with emotion regulation, distress tolerance, and interpersonal effectiveness. DBT has demonstrated efficacy for borderline personality disorder and associated problems (77), and for PTSD related to childhood abuse (78). Behavioral approaches that aim to normalize responses to fear-provoking stimuli have also proven successful in treating anxiety disorders, including PTSD. Exposure therapy extinguishes inappropriate fear responding by coupling exposure to the feared situation with a safe environment. Exposure therapy is an effective treatment for PTSD (79). However, exposure therapy does not address difficulties with affect regulation and interpersonal relationships that often result from childhood maltreatment. A treatment that combines skills training in affect and interpersonal regulation (adapted from DBT) followed by exposure therapy has demonstrated efficacy in a randomized controlled trial of child-abuse-related PTSD (80).

Development of Treatment Approaches that Target Stress Neurobiology—A number of treatment approaches that are based on an understanding of stress neurobiology are currently in development. Memories undergo consolidation and re-consolidation over time, and memory retrieval can render a fixed memory unstable and vulnerable to change,

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requiring reconsolidation to be re-established (81). This process has been examined in rodents and humans using fear conditioning and extinction training paradigms, which involve behavioral and learning/memory processes that are similar to those of exposure therapy. For example, a recent fear conditioning experiment in mice found that the combination of fluoxetine plus extinction training, but neither treatment alone, produced an enduring loss of conditioned fear memory (82). Further experiments revealed that fluoxetine, through the actions of BDNF, converted the fear memory circuitry to a more immature state, increasing synaptic plasticity and allowing extinction-guided remodeling of this circuitry.

In humans, pharmacologic treatments have recently been added to exposure therapy in an effort to maximize the therapeutic benefits of behavior therapy. D-cycloserine, a partial agonist at n-methyl-d-aspartate (NMDA) receptors which are involved in synaptic remodeling and memory function, is known to enhance cognition and has been found to facilitate both fear extinction in animals and exposure therapy in humans with some anxiety disorders (83). However, two recent studies did not find an overall augmentation effect of D-cycloserine on exposure therapy for PTSD (84, 85). Drawing on evidence from animal studies that beta-adrenergic blockers abolish stress-induced fear learning and attenuate reconsolidation of fear memories, the beta-blocker propranolol has been tested for prevention and treatment of PTSD. Post-exposure propranolol administration has received only limited support as a preventative treatment for the development of PTSD (86). However, recent evidence suggests that propranolol can reduce the strength of trauma memories and PTSD symptoms when administered following memory reactivation via traumatic script-driven imagery exposure (87). Further treatment development in this area is ongoing in an effort to “erase” fear memories by modulating or re-programming the brain's fear circuitry.

A number of novel pharmacologic treatments that target the neurobiological sequelae of excessive stress exposure are also in development. Several companies have developed CRH receptor antagonists as a potential therapy for MDD, anxiety, and substance use disorders. Clinical trials for depression have not been successful or have found problems with safety or efficacy (88), but studies of other disorders, including PTSD, are ongoing. Antagonists of AVP, which interacts with CRH to activate the HPA axis, have shown potential in animal models of stress exposure (e.g., 51). However, results of four recent double-blind, placebo-controlled trials of a vasopressin V_{1B} receptor antagonist in MDD and generalized anxiety disorder have been disappointing in terms of efficacy, although reassuringly no adverse effects related to the role of AVP as a regulator of fluid and electrolyte balance were observed (89). There are no other such drugs in advanced clinical development (90). Mifepristone, a glucocorticoid receptor antagonist with anti-progesterone activity (also known as the abortifacient RU-486), has been found in preclinical trials to prevent stress-induced depressive-like behaviors (91) and reconsolidation of cue-conditioned fear, which is thought to be a mechanism of PTSD symptoms (92). Clinical trials have suggested that short-term treatment with mifepristone might be effective and is well-tolerated in psychotic depression, but findings are mixed (93-95). Thus, results from studies of drugs that modulate HPA axis function have been disappointing; it remains unknown whether these treatments

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might be more effective in the subset of such patients with a history of significant stress exposure.

As discussed above, a variety of antidepressant treatments increase BDNF and subsequent hippocampal neurogenesis in rodents. Depressed patients taking antidepressant medications also show enhanced peripheral BNDF levels, and some evidence documents increases in peripheral BDNF in response to exercise in humans (96). While the relevance of changes in peripheral BDNF to effects in the brain is unknown, a recent study in rodents showed antidepressant-like effects of peripherally administered BDNF (20). This is not likely to be a viable treatment for humans due to the pharmacokinetics and adverse side effects, but collectively this research suggests that BDNF may be a good indicator of antidepressant efficacy and that drugs targeting BDNF could have therapeutic potential.

Treatment implications of genetic research—Investigations of risk and protective genes aim to identify individuals at greatest risk for stress-induced disorders. This work is complicated by the fact that such pathways are governed by multiple sets of genes, and a particular gene may only account for a small percent of the risk for these disorders. Genetic research on early-life stress also aims to further elucidate the neurobiological pathways involved in the pathogenesis of these disorders, and such research may inform the development of novel treatments.

Another avenue of genetic research aims to determine whether genes that regulate the pathways involved in depression and anxiety confer a differential response to pharmacologic treatment. Although initial reports suggested that several gene variants may predict response to antidepressants, thus far findings have not been consistently replicated (49). However, such studies have only recently examined whether environmental influences might account for variability in these outcomes. There is some early promising evidence that gene variants identified in G × E studies of risk for depression and anxiety may also confer differential response to treatment among individuals who have been exposed to stressful life events. These include *5-HTTLPR* and variants in the *CRHR1* and *FKBP5* genes. Here, too, some of the findings have been inconsistent, and studies have usually focused on adult stress exposure and have not examined the effects of childhood adversity (49). Other evidence suggests that some “risk” genotypes may be better conceptualized as “environmental sensitivity” genotypes. Results of a recent meta-analysis indicate that the s “risk” allele of *5-HTTLPR* actually confers sensitivity to social support and protection from risk in enriched environments (97). Building on this work, Eley and colleagues (98) recently conducted the first study to examine genetic predictors of response to CBT, and found that individuals with two copies of the *5-HTTLPR* s allele have a better response to treatment.

Epigenetic marks have long been thought to be fixed in post-mitotic cells, but rodent studies indicate that DNA methylation can be reversed in adult brain. Thus, it is possible that drugs or even psychotherapeutic approaches could reverse epigenetic effects of early-life stress. Drugs that have shown this effect in animal models are available (e.g., valproic acid and S-adenosyl-methionine, a putative antidepressant) or are in development (e.g., histone deacetylase (HDAC) inhibitors) for the treatment of cancer and other disorders (99, 100). In a rodent model, exercise induced epigenetic changes to a promoter of the BDNF gene in the

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hippocampus (101). Such studies raise the possibility for future research to determine whether modifying the social and environmental experiences of maltreated children might reverse epigenetic effects of early-life stress.

Treatment implications of metabolic, immune, and cellular aging findings— The association of early and chronic stress with inflammation and other health problems in adulthood underscores the importance of preventing early trauma, reducing additional risk factors, and enhancing protective mechanisms. Research on interventions to prevent or alter the biological trajectory from stress to disease pathology is currently lacking. Human biomarker studies have not yet identified a particular diagnostic test or even a consistently "high" or "low" pattern of candidate peripheral cytokine concentrations predictive of specific mental illness. However, a growing body of preclinical evidence, as well as findings from cross-sectional clinical studies, suggests there may eventually be an identifiable subpopulation of depressed patients for whom the role of cytokines is closely linked to psychiatric symptomatology. Agents that target inflammatory processes are being considered for the treatment of depression, including nonsteroidal anti-inflammatory drugs (NSAIDS), TNF-alpha antagonists, and antibiotics (102-104). Other drugs, such as thiazolidinediones with anti-inflammatory effects, are being re-examined for their potential role in the treatment of mood disorders (105). Several nonpharmacological strategies also appear promising. Reduction of adiposity and dietary modifications, such as lowering processed food intake or supplementation with 3-omega fatty acid supplements (106), may be useful to reduce depressive symptoms. Exercise, yoga, meditation, and therapeutic massage have all shown neuroimmune modulatory effects, and as such may offer some therapeutic potential for preventing or reducing mood symptoms, as well as promoting healthy function of other somatic tissues and organ systems.

Of note, there is evidence that enrichment of the environment later in life may reverse some, but not all, of the biological consequences associated with exposure to early life adversity. Additionally, it should be pointed out that not all exposure to stress is deleterious, and that exposure to psychological stress challenge under controlled conditions may eventually be useful as a novel therapeutic or prophylactic treatment approach in psychiatry. For example, "behavioral immunization" has been proposed as a potential mechanism for promoting resilience to psychological stressors (107). This paradigm involves exposure to acute, psychologically stressful experiences of mild intensity, which serves to "innoculate" an individual and enhances emotional resilience by inducing immunological memory, much as pathogen exposure activates the innate immune response to antigen and leads to formation of immunological memory and t-cell function for clearance of an infection. Further research will be needed to determine the efficacy and critical features of strategies employing combinations of novel behavioral and pharmacological tools to build resilience early in development, maintain adaptive capacity across the lifespan, and diminish the proinflammatory effects of stress on physical and emotional well being.

Discussion

It is clear that early-life stress and, most dramatically, childhood maltreatment confer risk for depressive and anxiety disorders. The findings reviewed in this paper broadly indicate

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that 1) the neuroendocrine, neurotrophic, and other physiological systems that are activated in response to extreme or prolonged stress may be the mechanisms by which risk for these disorders is elevated in relation to early-life stress, 2) risk and protective genes influence sensitivity to stress and risk for mood and anxiety disorders, 3) Early-life stress influences treatment outcome, consistent with clinical insights that psychotherapy may be particularly valuable for these patients, and new treatments that target stress-related neurobiological abnormalities are in development.

Much of the research in humans and animals that identifies abnormal function in stress-sensitive brain systems is focused on early-life stress, due to the fact that this period is characterized by dependence on caregivers and other environmental influences, as well as major developmental changes in the neural systems that coordinate stress responding, mood, fear/anxiety, and behavior. Future treatment research will likely benefit from continued refinement in the type and treatment protocols of pharmacological and behavioral strategies used, as well as attention to patient characteristics that may influence outcome. Treatment trials that target the neural and behavioral systems identified in human and animal models of stress exposure have usually focused on depression or PTSD, rather than specifically on those with a history of early stress. Future work should test novel treatments with this population, which may receive the greatest benefit from approaches that target the neurobiologic effects of early stress exposure.

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Clinical Recommendations

- Early adversity negatively impacts treatment outcome; psychotherapeutic approaches that target cognitive, emotional, and interpersonal difficulties associated with childhood stress and trauma have demonstrated efficacy.
- Several key neurobiological systems that are altered in response to early trauma may be involved in the pathogenesis of psychiatric and other medical conditions. Pharmacologic approaches that target the identified neurobiological abnormalities are currently in development.

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Additional Comments

- Risks including poverty, parental mental illness, substance abuse, maltreatment, and other traumatic or stressful life events often co-occur, complicating both research and treatment efforts.
- Studies of neurobiological correlates of childhood adversity are also limited by co-occurring disorders and treatments that may influence the systems of interest.
- More research on effective treatments for the effects of childhood maltreatment and other forms of early adversity is needed.

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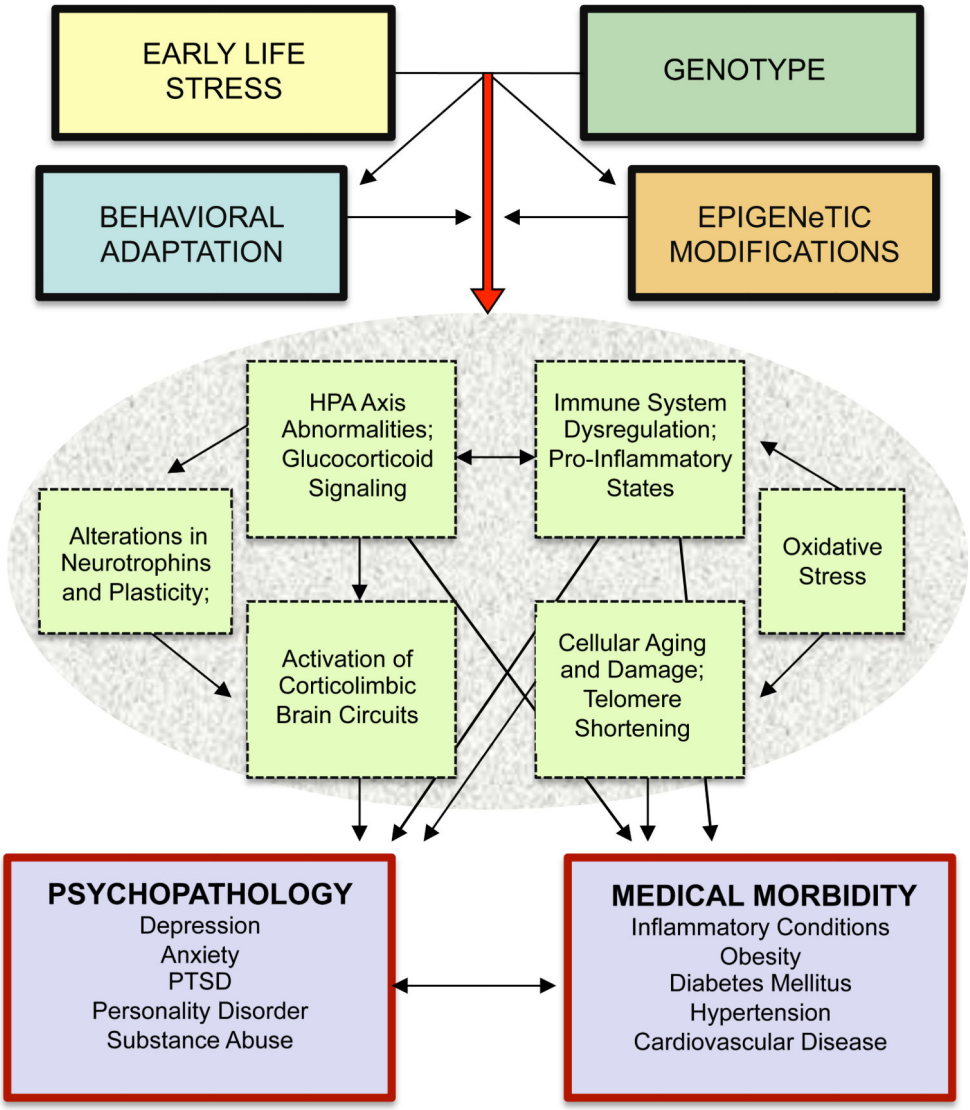

Figure 1.

Model: Neurobiological effects of childhood adversity. Childhood adversity engenders risk for psychopathology and medical morbidity through a number of inter-related pathways. Genetic sensitivity to environmental factors is an important determinant of risk, and epigenetic effects of early adversity influence the biological impact of stress exposure. Behavioral adaptation may exaccerbate or ameliorate these effects. Ensuing alterations of neuroendocrine, neuroimmune, and neurotrophin pathways are thought to be mechanisms of the development of psychiatric disorders and related medical conditions.