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THE PSYCHOBIOLOGY OF DEPRESSION AND RESILIENCE TO STRESS: Implications for Prevention and Treatment*

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■ **Abstract** This review discusses neurobiological and psychosocial factors associated with stress-induced depression and compares these factors with those believed to characterize stress resilience. Neurobiological factors that are discussed and contrasted include serotonin, the 5-HT1A receptor, polymorphisms of the 5-HT transporter gene, norepinephrine, alpha-2 adrenergic receptors, neuropeptide Y, polymorphisms of the alpha-2 adrenergic gene, dopamine, corticotropin-releasing hormone (CRH), dehydroepiandrosterone (DHEA), cortisol, and CRH receptors. These factors are described in the context of brain regions believed to be involved in stress, depression, and resilience to stress. Psychosocial factors associated with depression and/or stress resilience include positive emotions and optimism, humor, cognitive flexibility, cognitive explanatory style and reappraisal, acceptance, religion/spirituality, altruism, social support, role models, coping style, exercise, capacity to recover from negative events, and stress inoculation. The review concludes with potential psychological, social, spiritual, and neurobiological approaches to enhancing stress resilience, decreasing the likelihood of developing stress-induced depression/anxiety, and treating stress-induced psychopathology.

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CONTENTS

INTRODUCTION

It commonly is believed that the combination of genetics, early life stressors, and ongoing stress largely determine vulnerability to psychiatric disorders such as depression. Family, twin, and adoption studies all have repeatedly demonstrated that mood disorders are familial. Studies examining the linkage between biological phenotypes or genetic markers and mood disorders have been less informative because the mode of transmission of most mood disorders is likely to be complex (Dubovsky et al. 2003). Stressful life events, such as being the victim of a crime, financial problems, and divorce also appear to have a strong causal association with depression (Kendler et al. 1999). The link between genetic predisposition and life stressors in the etiology of depression has been most clearly demonstrated in a recent study by Caspi et al. (2003), who found that one or two copies of the short allele of a 5-HT transporter promoter polymorphism, in association with a life stress, significantly increased the risk for developing depression.

In this review, we discuss neurobiological factors associated with stress-induced depression and compare these factors with those believed to characterize stress-resilient individuals. We review psychosocial factors associated with resilience to stress and stress-induced declines in mood, health, and general well-being, and compare these psychosocial factors with those typically seen in individuals suffering with depression. Because these topics are enormously complex and the space allocated for our chapter is limited, our review cannot be comprehensive in nature. Rather, we highlight factors that appear to differentiate individuals who tolerate or even benefit from highly stressful situations from those who become symptomatic, often with mood disorders, as a result of the same stressful situations.

SELECTED NEUROBIOLOGICAL FACTORS IN STRESS-INDUCED DEPRESSION AND STRESS RESILIENCE

Serotonin in Stress-Induced Depression and Stress Resilience

Biochemical, genetic, challenge, neuroimaging, postmortem, and treatment studies have all reported a strong association between abnormal serotonergic function and major depression (see Table 1) (reviewed in Hasler et al. 2004). Particularly strong evidence comes from tryptophan depletion studies, in which subjects ingest a dietary mixture of all essential amino acids (except for the 5-HT precursor tryptophan), which results in a rapid transient reduction of plasma tryptophan, cerebral serotonin synthesis, and central 5-HT concentrations. Acute extreme reduction of serotonin also leads to additional biological changes that have been associated with major depressive disorder (MDD), including altered brain-derived neurotrophic factor (BDNF) gene expression in the dentate gyrus, reduced serotonin transporter mRNA levels, and enhanced norepinephrine transporter mRNA levels (Hasler et al. 2004).

Tryptophan depletion has no clinical effect in never-depressed healthy subjects without family risk for depression. However, it provokes mild transient depressive symptoms in never-depressed healthy subjects with a positive family history for depression (Benkelfat et al. 1994), and marked transient depressive symptoms in remitted depressed patients who are either medicated (Delgado et al. 1994) or unmedicated (Delgado et al. 1999). For vulnerable subjects, tryptophan depletion can provoke a biasing of mood toward negative emotion, alter reward-related behaviors (anhedonia), impair learning and memory consolidation (through diminished ability to attend and concentrate and impaired short- and long-term memory), slow response to positive stimuli, and disrupt inhibitory affective processing (Hasler et al. 2004). Further evidence for the central role of serotonin in depression comes from treatment studies in which pharmacological agents with pronounced effects on serotonin, such as the selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors, consistently have been effective for the treatment of major depression.

Numerous neurobiological studies have implicated the 5-HT1A receptors in the pathophysiology of depression. 5-HT1A receptors are found in cerebral cortex, the hippocampus, the amygdala, and the raphe nucleus. Decreased 5-HT1A receptor binding has been reported in multiple brain regions of patients with MDD (Drevets 2000, Drevets et al. 1999), and a polymorphism associated with 5-HT1A receptor transcription is more common in subjects with MDD than in controls (Lemonde et al. 2003). 5-HT1A receptors also appear to play a role in anxiety-related symptoms and behaviors (Charney 2004). Furthermore, preclinical studies of 5-HT knockout mice have shown that embryonic or early postnatal shutdown of 5-HT1A receptor expression produces an anxiety phenotype that cannot be reversed by restoration of 5-HT1A receptors. The result is lifelong abnormalities in

TABLE 1 The neurochemical response patterns to acute stress

Neurochemical	Acute effects	Brain regions	Key functional interactions	Association with resilience	Association with stress-related psychopathology
Cortisol	Mobilized energy, increased arousal, focused attention, fear memory formation, fear learning	Prefrontal cortex, hippocampus, amygdala, hypothalamus	Increases amygdala corticotrophin-releasing hormone (CRH), increases hypothalamic CRH	Stress-induced increase constrained by negative feedback by means of glucocorticoid receptor and mineral corticoid receptors	Unconstrained release leads to hypercortisolemia-depression, hypertension, osteoporosis, insulin resistance, coronary vascular disease; overconstrained release leads to hypocortisolemia, seen in some posttraumtic stress disorder (PTSD) patients
Dehydroepiandro-sterone (DHEA)	Counteracts deleterious effects of high cortisol neuroprotection; has positive mood effects	Largely unknown; hypothalamus	Antiglucocorticoid actions	High DHEA-cortisol ratios may have preventive effects regarding PTSD and depression	Low DHEA response to stress may predispose to depression and PTSD and the effects of hypercortisolemia
CRH	Activated fear behaviors, increased arousal, increased motor activity, inhibited neurovegetative function, reduced reward expectations	Prefrontal cortex, cingulated cortex, amygdala, nucleus accumbens, hippocampus, hypothalamus, bed nucleus of the stria terminalis, periaqueductal gray matter, locus coeruleus, dorsal raphe	CRH-1 receptor anxiogenic, CRH-2 receptor anxiolytic, increases cortisol and DHEA, activates locus coeruleus-norepinephrine system	Reduced CRH release, adaptive changes in CRH-1 and CRH-2 receptors	Persistently increased CRH concentration may predispose to depression and PTSD; may relate to chronic symptoms of anxiety, depression, fear, and anhedonia

Locus coeruleus-norepinephrine system	General alarm function activated by extrinisic and intrinsic threat; increased arousal, increased attention, fear memory formation, facilitated motor response	Prefrontal cortex, amygdala, hippocampus, hypothalamus	Activates sympathetic axis, inhibits parasympathetic outflow, stimulates hypothalamic CRH	Reduces responsiveness of locus coeruleus-norepinephrine system	Some patients with major depression, PTSD, and panic disorders show evidence of heightened locus coeruleus-norepinephrine activity; unrestrained functioning of locus coeruleus-norepinephrine leads to chronic anxiety, hypervigilance
Neuropeptide Y	Anxiolytic; counteracts the stress-related effects of CRH and the locus coeruleus-norepinephrine system; impairs fear memory	Amygdala, hippocampus, hypothalamus, septum, periaqueductal gray matter, locus coeruleus	Reduces CRH-related actions at amygdala, reduces rate of firing of locus coeruleus	Adaptive increase in amygdala neuropeptide Y is associated with reduced stress-induced anxiety and depression	Low neuropeptide Y response to stress is associated with increased vulnerability to depression and PTSD
Dopamine	High prefrontal cortex and low nucleus accumbens dopamine levels are associated with anhedonic and helpless behaviors	Prefrontal cortex, nucleus accumbens, amygdala	Reciprocal interactions between cortical and subcortical dopamine systems	Cortical and subcortical dopamine systems remain in optimal window of activity to preserve functions involving reward and extinction of fear	Persistently high levels of prefrontal cortical and low levels of subcortical dopamine activity are associated with cognitive dysfunction and depression; persistently low levels of prefrontal cortical dopamine are associated with chronic anxiety and fear
Serotonin (5-HT)	Mixed effects: 5-HT stimulation of 5-HT_2 receptors is anxiogenic; 5-HT stimulation of 5-HT_{1A} receptors is anxiolytic	Prefrontal cortex, amygdala, hippocampus, dorsal raphe	High levels of cortisol decrease in 5-HT_{1A} receptors	High activity of postsynaptic 5-HT_{1A} receptors may facilitate recovery	Low activity of postsynaptic 5-HT_{1A} receptors may predispose to depression and anxiety

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the regulation of anxiety behaviors. However, when 5-HT1A receptor expression is reduced in adulthood and then reinstated, the anxiety phenotype is no longer observed (Gross et al. 2002).

Chronic psychosocial stress has been shown to decrease 5-HT1A receptor density in limbic brain structures. However, stress-induced reductions can be prevented by adrenalectomy, suggesting that postsynaptic 5-HT1A gene expression is under tonic inhibition by adrenal steroids. These results point to a sequence in which stress-induced increases in corticotropin-releasing hormone (CRH) and cortisol downregulate 5-HT1A receptors with an accompanying lowered threshold for anxiogenic stressful life events (Lopez et al. 1998). Alternatively, it is possible that the low 5-HT1A receptor density seen in panic disorder and depression has a genetic basis or is the combined result of inheritance and psychosocial stress (Charney 2004). Of note, 5-HT1A receptor density and function is affected by multiple other neurobiological factors, such as estrogen (Liu et al. 2000).

Abnormalities of the 5-HT transporter have also been reported in subjects with depression. Reduced density of the 5-HT transporter has been found in subjects with depression and in the postmortem brain tissue of suicide victims (Arango et al. 2002, Drevets et al. 1992). The risk of developing depression in response to life stressors is increased by having one or two copies of the short allele of a 5-HT transporter gene promoter polymorphism (Caspi et al. 2003), and the long allele of the serotonin transporter gene promoter polymorphism (as well as the s-allele in healthy women) predicts a depressive response to tryptophan depletion (Moreno et al. 2002, Neumeister et al. 2002). Increased amygdala neuronal activity in response to fear-inducing stimuli has been recently reported in healthy subjects with the serotonin transporter polymorphism that is associated with reduced 5-HT expression and increased fear and anxiety (Hariri et al. 2002).

Taken together, the studies cited above suggest that stress-induced reductions in 5-HT1A receptor binding and alterations in serotonin activity may contribute to the etiology of both anxiety and depression. It may be that under situations of extreme or chronic stress, individuals who are at risk for depression and anxiety experience greater reductions in 5-HT1A binding and greater alterations in serotonin activity than do individuals who are comparatively stress resilient. Numerous genetic, developmental, and neurobiological factors (e.g., reactivity of the HPA axis) are likely to contribute to stress-related reactivity of serotonin and serotonin receptor systems.

The literature on serotonin and learned helplessness, a well-known animal model for depression, may have implications for bolstering resilience. When animals and humans are subjected to inescapable stress, many tend to develop a set of behaviors resembling those seen in depression, including passive withdrawal and resistance to reversing a negative experience (Abramson et al. 1978). In animals, inescapable stress has been associated with a significant reduction in hippocampal cell proliferation. Importantly, the development of learned helplessness can be prevented by facilitation of serotonergic neurotransmission in the dorsal hippocampus (Malberg & Duman 2003). Consistent with these findings,

pretreatment with an SSRI or a tricyclic antidepressant can prevent the behavioral syndrome of learned helplessness; administration of these antidepressants after the development of learned helplessness reverses most symptoms (Bonne et al. 2004). Pre- or post-stress administration of an SSRI or other antidepressant that affects serotonin may enhance resilience in individuals who are particularly vulnerable to stress and are more likely to develop symptoms of learned helplessness and depression.

Norepinephrine and Neuropeptide Y in Stress-Induced Depression and Stress Resilience

A large body of evidence points to depletion of brain norepinephrine as a key feature in the pathophysiology of major depression. Findings in support of the catecholamine hypothesis of mood disorders include decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase (the rate-limiting enzyme of catecholamine biosynthesis), and decreased density of the norepinephrine (NE) transporter in the locus coeruleus (LC) (reviewed in Charney & Manji 2004). An increase in the number of alpha-2 adrenergic receptors in the LC, the major brain NE-containing nucleus, has also been reported in depressed patients who committed suicide.

Further support for the catecholamine hypothesis comes from research assessing the effects of rapid catecholamine depletion on mood in healthy subjects and in subjects with mood disorders. Depletion of catecholamines by administering the tyrosine hydroxylase inhibitor alpha-methylparatyrosine (AMPT) has resulted in minimal mood responses among healthy subjects, but reversal of the antidepressant effects of light therapy and pharmacotherapy (particularly treatment with catecholamine uptake inhibitors) among depressed subjects (reviewed in Hasler et al. 2004).

The relationship between life stress, noradrenergic systems, and depression appears to be mediated, in part, by alpha-2 adrenergic receptor subtypes. Studies employing knockout mice suggest that the alpha-2a adrenergic receptor is stress protective, whereas the alpha-2c adrenergic receptor contributes to stress susceptibility. Additionally, prolonged stress has been shown to decrease alpha-2 adrenergic receptor density in limbic brain structures (Fuchs & Flugge 2003).

During situations of danger, the sympathetic nervous system releases epinephrine and norepinephrine to protect the organism. The magnitude of sympathetic nervous system (SNS) responses to stress and danger varies from one person to the next. Some people have an unusually robust SNS response to stress and in essence overreact. Unchecked persistent SNS hyper-responsiveness may contribute to depression, chronic anxiety, hypervigilance, fear, intrusive memories, and increased risk for hypertension and cardiovascular disease (Southwick et al. 2003). Such responses have been found in individuals diagnosed with major depression and/or posttraumatic stress disorder (PTSD) (Schnurr & Green 2004).

In contrast, it is likely that psychologically resilient individuals maintain SNS activation within a window of adaptive elevation, high enough to respond to danger but not so high as to produce incapacity, depression, anxiety, and fear (Charney 2004, Morgan et al. 2000). A series of studies reviewed by Dienstbier (1989, 1991) suggest that performance is enhanced when this optimal level of SNS activation is characterized by relatively low base rates of epinephrine and norepinephrine (catecholamines) as well as robust increases in catecholamines during stress or challenge, followed by relatively rapid returns to baseline.

One neurochemical that helps to maintain SNS activity within an optimal window or range is neuropeptide Y (NPY), which is an amino acid that is released with norepinephrine when the SNS is strongly activated (reviewed in Southwick 1999). One of NPY's actions is to inhibit the continued release of norepinephrine so that the SNS does not "overshoot." Preliminary studies in highly resilient special-operations soldiers (special forces) have shown that high levels of NPY during extreme training stress are associated with better performance (Morgan et al. 2000, 2002). In these soldiers, robust increases in norepinephrine are held in check by similarly robust increases in NPY.

In contrast, among traumatized combat veterans with chronic PTSD, resting and stress-induced levels of NPY have been reported as low compared with controls (Rasmusson et al. 2000). Veterans with PTSD also experience an increase in norepinephrine when the SNS is stressed or provoked, but the accompanying release of NPY appears insufficient to hold rising levels of norepinephrine in check. Rapid increases in norepinephrine likely contribute to exaggerated increases in heart rate, blood pressure, respiratory rate, anxiety, panic, vigilance, and even intrusive combat-related memories (Southwick 1999). Thus, NPY appears to be a neurobiological resilience factor that helps to maintain SNS reactivity at an optimal level.

NPY has also been implicated in depression. Preclinical studies have found lower hippocampal NPY in maternally deprived rats compared with normally reared rats, and significantly lower hippocampal NPY immunoreactivity in animals bred as "genetic" models for depression. Additionally, increased measures of NPY activity have been reported in animals after repeated electroconvulsive shock treatment and chronic antidepressant treatment. NPY also has been shown to have anxiolytic effects in animals (reviewed in Heilig & Widerlov 1995). Findings in humans have not been as consistent as findings in preclinical studies. Nevertheless, in patients with major depression, decreased NPY has been reported in cerebrospinal fluid, in platelet-poor plasma, and in the frontal cortex and caudate nucleus (in suicide victims) (reviewed in Redrobe et al. 2002). Treatment of depression with electroshock therapy (Mathe et al. 1997) or antidepressant drugs (Caberlotto et al. 1998) has been shown to increase NPY in depressed patients who have low levels of NPY.

Based on the animal and human studies cited above, it is likely that noradrenergic activity is regulated within an optimal window in individuals who are resilient to stress and to the development of stress-related disorders such as PTSD and

depression. Additionally, one might predict that therapies and pharmacological agents that help to contain stress-related noradrenergic responsivity would enhance stress resilience and help to prevent stress-induced depression. Thus, relaxation techniques and cognitive behavioral therapies that bolster cortical control over limbic reactivity as well as pharmacological agents that reduce locus coeruleus firing rate, such as alpha-2 adrenergic agonists (e.g., clonidine and guanfacine), alpha-1 agonists (e.g., prazosin), beta antagonists (e.g., propranolol), and NPY, might serve to foster stress resilience in at-risk individuals, and possibly help prevent the development of stress-induced depression (even if they are ineffective for the treatment of depression once it has developed).

Recent evidence suggests that alpha-2 adrenoreceptor gene polymorphisms may play a role in baseline catecholamine levels, intensity of stress-induced SNS activation, and rate of catecholamine return to baseline after stress. In a study of healthy subjects, homozygous carriers for the alpha-2cDel322-325-AR polymorphism had exaggerated total body noradrenergic spillover at baseline, exaggerated yohimbine (an alpha-2 adrenergic receptor antagonist that increases the release of norepinephrine)-induced increased anxiety and total body noradrenergic spillover, and a slower-than-normal return of total body noradrenergic spillover to baseline after yohimbine infusion (Neumeister et al. 2002). Such individuals may be more vulnerable to stress-related psychiatric disorders such as PTSD and depression.

Dopamine and Reward Systems in Stress-Induced Depression and Stress Resilience

Individuals suffering with depression typically experience low levels of positive affect, anhedonia, and lack of responsiveness to pleasurable stimuli. A number of researchers have proposed that these symptoms may reflect deficits in the reinforcing effects of reward, possibly secondary to underactivation of the brain reward system (also referred to as the reward-based behavioral facilitation system) (Depue & Iacono 1989, Tremblay et al. 2002). For example, Henriques, Davidson, and colleagues (Henriques et al. 1994), using a signal-detection task to examine responsiveness of subjects to different payoff conditions, found that nondysphoric college subjects changed their pattern of responding in both reward and punishment conditions (compared with neutral conditions) in order to maximize their earnings, whereas dysphoric college students changed response patterns in response to punishment but not in response to reward. Similar findings have also been reported in adults meeting criteria for major depression (Henriques 2000).

The neurocircuitry of brain reward systems is highly complex and involves numerous brain regions, including mesolimbic dopamine pathways, the prefrontal cortex, and the amygdala. Mesolimbic dopamine pathways are critically involved in reward, motivation, and hedonic tone (Charney 2004). Dopaminergic neurons in the ventral tegmental area innervate the nucleus accumbens, where increased dopaminergic transmission has been linked to the rewarding effects of drugs of

abuse (Koob et al. 1998). Additionally, firing patterns of dopaminergic neurons in the ventral tegmental area are strongly associated with reward expectations (Schultz et al. 2000).

Dopaminergic neurons in the ventral tegmental area also innervate the prefrontal cortex and the amygdala. In addition, the medial prefrontal cortex receives glutamatergic input from the amygdala and sends glutamatergic projections to the ventral tegmental area and the nucleus accumbens. The rewarding effects of prefrontal cortex electrical stimulation are likely mediated by glutamate release in the ventral tegmental area and dopamine release in the nucleus accumbens. Thus, functional interactions among glutamate, NMDA receptors, dopamine, and dopamine receptors (Charney 2004, Schultz 2002, Wise 2002) appear necessary for optimal functioning of brain reward circuits.

The prefrontal cortex plays an important role in setting goals, guiding behavior, discriminating between potential rewards and punishments, and representing affect in the absence of immediate rewards and punishments. What some investigators have termed "affective working memory" allows the organism to anticipate future affective outcomes and thus engage in behaviors directed toward avoiding punishment and/or acquiring rewards. Deficits in affective working memory, where the individual is unable to imagine a positive future, might lead to hopelessness and pessimism, symptoms commonly seen in depression.

The amygdala, in conjunction with the bed nucleus of the stria terminalis, subiculum, nucleus accumbens, and medial prefrontal cortex, establishes the emotional value of a reward memory as well as its strength and persistence. These rewarding associations appear to depend on cAMP and cAMP-response element-binding protein in the amygdala. Positron emission tomography and functional magnetic resonance imaging studies have shown that greater tonic and phasic activation (in response to aversive stimuli) in the right amygdala is associated with greater dispositional negative affect (Abercrombie et al. 1998, Davidson et al. 2000, Irwin et al. 1998).

Depue & Iacono (1989) have proposed that depression results from decreased dopamine activity and hypoactivation of the brain reward system with subsequent disengagement from the environment, decreased effectiveness of reinforcers, and diminished reward-seeking behaviors. Consistent with this hypothesis is the recent finding that dextroamphetamine, which probes the release of dopamine within the mesolimbocortical system, had greater rewarding effects in patients with severe MDD compared with controls and patients with moderate depression. The exaggerated rewarding effects of dextroamphetamine in severely depressed patients may reflect an adaptive upregulation of dopamine receptors secondary to chronic low levels of dopamine output. Furthermore, Ebert et al. (1996) found increased striatal D2 receptor binding (possibly reflecting upregulation) in depressed patients with psychomotor retardation and anhedonia compared with healthy controls, and Martinot et al. 2001 reported decreased presynaptic dopamine function in depressed patients with affective flattening and psychomotor retardation. Similarly, decreased left-side frontal activation in patients with depression has been viewed

as a potential reflection of deficits in the approach system and in reward-related responding (Henriques 2000).

It has been proposed that people who remain optimistic and hopeful in the context of extreme or chronic stress have a neurobiological reward system that is either hypersensitive or resistant to change (Charney 2004). Such a system would maintain appropriate hedonic tone even during highly stressful and challenging circumstances. A "resilient" reward system might be one that for genetic and possibly developmental reasons has highly sensitive dopamine receptors and/or is resistant to stress-induced cerebral dopamine depletion. Resilient individuals might also possess highly functional affective working memory, allowing them to remain positive and hopeful about the future even when faced with long periods of extreme stress and deprivation.

The findings discussed above may have implications for the enhancement of resilience and for the treatment of individuals at risk for stress-induced depression. Sensitivity to reward may be enhanced by increasing dopamine function in the nucleus accumbens, the orbitofrontal cortex and the ventral tegmental area, and NMDA receptor blockade in the nucleus accumbens and the medial prefrontal cortex. Thus, dopamine receptor agonists (pramipexole), monoamine oxidase inhibitors (selegiline), dopamine reuptake inhibitors, psychostimulants, and NMDA antagonists (memantine) might be useful for preventing anhedonia and hopelessness in individuals at risk for trauma-induced depression or to treat those who have already developed depression secondary to stress.

Additionally, Davidson has questioned whether repeated practice in techniques of emotion regulation, such as meditation and various cognitive behavioral techniques, could lead to enduring changes in patterns of brain activation. At least one study has shown that obsessive-compulsive patients treated with cognitive behavioral therapy experience changes in regional brain activity comparable to those produced by medication (Baxter et al. 1992). Future research might assess regional brain activity and indices of dopaminergic function before and after treatment with cognitive behavioral therapies based on learned optimism (Seligman 1991, 2002), which are designed to enhance positive emotions as well as pleasurable and rewarding experiences.

The HPA Axis in Stress-Induced Depression and Stress Resilience

Alterations in HPA axis physiology and functioning consistently have been reported in patients diagnosed with major depression. In response to acute and chronic stress, the paraventricular nucleus of the hypothalamus secretes corticotropin releasing factor (CRF), which in turn stimulates the anterior pituitary gland to synthesize and release adrenocorticotropin (ACTH). ACTH then stimulates the synthesis and release of adrenal cortical glucocorticoids. Cortisol mobilizes and replenishes energy stores, inhibits growth and reproductive systems, contains the immune response, and affects behavior through actions on multiple

neurotransmitter systems and brain regions (reviewed in Hasler et al. 2004, Yehuda 2002).

In a subset of depressed patients (approximately 50%), the HPA axis appears to be hyperactive. Evidence of hyperactivity includes increased concentrations of CRH in cerebral spinal fluid, increased urinary free cortisol, blunted ACTH response to CRH administration, and decreased tendency for the synthetic glucocorticoid dexamethasone (measured through the dexamethasone suppression test) to suppress plasma cortisol. Antidepressants have been shown to normalize this excessive activation of the HPA axis in patients with major depression (reviewed in Nestler et al. 2002).

Dehydroepiandrosterone (DHEA) is another adrenal steroid that is released under stress. In response to fluctuating levels of ACTH, DHEA is released synchronously and episodically with cortisol. In the brain, DHEA's antiglucocorticoid and antiglutamatergic activity may confer neuroprotection (reviewed in Charney 2004). Data supporting DHEA as a possible neurobiological resilience and stress-protective factor include a negative correlation between DHEA reactivity (in response to ACTH administration) and severity of PTSD symptoms (Rasmusson et al. 2004), a negative correlation between plasma DHEA levels and depression (Goodyer et al. 1998), and a negative relationship between DHEA/cortisol ratio and dissociation, as well as a positive correlation between DHEA/cortisol ratio and performance among elite special forces soldiers undergoing intensive survival training (Morgan et al. 2004). Furthermore, DHEA administration has been shown to have antidepressant effects in patients with major depression (Wolkowitz et al. 1999).

Clinical research also has consistently reported reduced hippocampal volume in subjects with major depression (Bremner et al. 2000, Sheline 1999). In some studies, these reductions in hippocampal volume have been associated with depression and with the deficits in cognitive capacities (e.g., short-term declarative memory) that are commonly observed in depression and are mediated by the hippocampus (Sheline 1999). Preclinical research has clearly demonstrated that prolonged stress-related elevations in glucocorticoids may cause damage to CA3 pyramidal neurons of the hippocampus, with reductions in dendritic branching, a loss of dendritic spines, and a reduction in the growth of new granule cell neurons in the dentate gyrus (Sapolsky 2003). Because the hippocampus exerts inhibitory control over the HPA axis, damage to the hippocampus may result in even greater increases in glucocorticoids, with additional ensuing damage to the hippocampus.

CRF is one of the most important mediators of the stress response. CRH-containing neurons are located in the hypothalamus and throughout the brain. CRH is known to initiate the neuroendocrine response to stress by enhancing pituitary release of ACTH, and LC release of norepinephrine in the PVN, hippocampus, and PFC (Grammatopoulos & Chrousos 2002). Centrally administered CRF produces a number of symptoms and behaviors commonly seen in depression and anxiety, such as increased heart rate, increased blood pressure, decreased appetite, decreased sexual activity, increased arousal, and a reduction in reward expectations

(Owens & Nemeroff 1991). Both CRH-1 and CRH-2 receptors appear to play an important role in the stress response. Evidence suggests that activation of CRH-1 receptors may be responsible for anxiety-like responses, whereas stimulation of CRH-2 receptors may produce anxiolytic-like responses (Bale et al. 2000, 2002). Psychological and physiological responses to stress may be determined, in part, by regulation of these two CRH receptor types in critical brain regions. Furthermore, psychobiological resilience to stress-induced disorders such as PTSD and depression may be related to the organism's ability to restrain or adjust the initial CRH response to acute stress as well as the prolonged CRH response to chronic stress.

Studies investigating the effects of postnatal maternal separation have consistently demonstrated that early stress can promote long-term changes in many of the brain regions and neurotransmitter systems that have been implicated in the pathophysiology of depression and PTSD. For example, maternal separation has been associated with chronic hyper-responsivity of the HPA axis and the LC/NE system, with resultant exaggerated "emotional" reactivity and exaggerated anxiety and/or fear-related responses to stress (Ladd et al. 2000, Liu et al. 2000). It is believed that neurobiological alterations associated with early adverse experiences, such as maternal separation, confer a vulnerability to later development of stress-related disorders, such as depression.

When compared with maternally separated rats or nonhandled rats, the rats that receive 15 minutes of handling per day during the first three weeks of life have demonstrated reduced stress reactivity to stressors in adulthood, reduced fearfulness in novel environments, reduced ACTH and corticosterone responses to stressors, and a more rapid return of corticosterone levels to baseline after exposure to stressors. Thus, early caregiving environments (both depriving and nurturing) appear to "program" the development of stress-related neurobiological systems. Early deprivation promotes future exaggerated neurobiological stress reactivity and vulnerability to depression, whereas early nurturing appears to have the opposite effect (reviewed in Kaufman et al. 2000).

Importantly, evidence also exists that even after early stress-induced (through maternal separation) neurobiological and behavioral alterations have developed, these alterations can be modified by subsequent supportive maternal caregiving and/or pharmacological interventions (Caldji et al. 1998, Kuhn & Schanberg 1998). In animal "adoption" studies, the neurobiological alterations observed in maternally separated rats are reversed if those rats are subsequently raised with "optimal parenting" (i.e., raised by high-licking and -grooming adult females). A variety of pharmacological agents (e.g., SSRIs, benzodiazepines, phenytoin, and adrenal steroid inhibitors) can also prevent or reverse many of the neurobiological alterations (including alterations in the HPA axis) that develop as a result of early life stress (reviewed in Kaufman et al. 2000).

The findings discussed above have implications with regard to stress resilience and the prevention/reversal of stress-induced alterations in neurobiological systems, behaviors, and disorders. For example, it may be possible to enhance stress

resilience in at-risk or already symptomatic individuals by providing nurturing caregiving environments and/or by administering pharmacological agents that stabilize HPA axis functioning. It is possible that blockade of CRF overdrive with CRF antagonists would serve as an anxiolytic, antidepressant, and/or preventive agent for the development of stress-induced mood and anxiety-related disorders. It is also possible that placing traumatized or neglected children (and perhaps even adults) into nurturing and caregiving environments would reverse some of the neurobiological alterations (e.g., sensitization of HPA axis and noradrenergic system) and psychological symptoms (e.g., symptoms of depression and PTSD) that have already developed because of stress.

SELECTED PSYCHOSOCIAL FACTORS ASSOCIATED WITH RESILIENCE TO STRESS AND STRESS-INDUCED DEPRESSION

An enormous body of research has been published on psychosocial factors associated with resilience to stress and stress-induced mood and anxiety disorders (Luther & Cicchetti 2000, Garmezy et al. 1984, Masten et al. 1998, Werner & Smith 1992). In this section, we touch on a number of these factors and relate them to some of the above-mentioned neurobiological factors that have been associated with stress resilience as well as with stress-induced depression. We discuss five basic psychosocial resilience factors. These are: (*a*) positive emotions (including optimism and humor), (*b*) cognitive flexibility (including positive explanatory style, positive reappraisal, and acceptance), (*c*) meaning (including religion, spirituality, and altruism), (*d*) social support (including role models), and (*e*) active coping style (including exercise and training).

Positive Emotions (Including Optimism and Humor)

POSITIVE EMOTIONS AND OPTIMISM Resilient individuals are generally optimistic and are characterized by high positive emotionality (Block & Kremen 1996, Klohnen 1996). Optimism has been associated with greater life satisfaction (Chang et al. 1997) as well as with increased psychological well-being and health (Affleck & Tennen 1996, Goldman et al. 1996). Optimism and positive emotionality appear to play an important role in the capacity to tolerate stressful events, and have been associated with reduced stress-related illness and accompanying use of medical services, as well as with reduced mood disturbances in individuals exposed to Scud missile attacks (Zeidner & Hammer 1992), breast cancer (Carver et al. 1993), and open-heart surgery (Scheier et al. 1989).

Positive and negative emotions frequently co-occur in the same individual during chronic periods of high stress (Folkman & Moskowitz 2000). This is true for individuals with severe or chronic illnesses (Viney 1986), for patients with spinal cord injuries (Wortman & Silver 1987), and for caregiving partners of men with

AIDS (Folkman 1997). It has been proposed that positive affect, in the context of chronic stress, has adaptive value (Folkman & Moskowitz 2000, Lazarus et al. 1980). Positive emotions replenish depleted resources, provide a respite, and support coping efforts (Folkman & Moskowitz 2000).

Fredrickson (2001) has developed a broaden-and-build theory to describe the function of positive emotions. According to this theory, negative emotions heighten autonomic activity and narrow attention in order to support specific actions such as attack or escape. Positive emotions (e.g., joy, interest, contentment, pride, and love), on the other hand, tend to decrease autonomic arousal and to broaden one's focus of attention with reliance on creativity, exploration, and flexibility in thinking (Folkman & Moskowitz 2000, Isen et al. 1987). The result is an expansion and improvement of stress-related coping mechanisms such as positive reappraisal, goal-directed problem-focused coping, and infusion of ordinary events with positive meaning. Over time, the broadening that accompanies positive emotions helps to build enduring physical, psychological, intellectual, and social resources (Fredrickson 2001).

Unlike optimists, individuals who suffer with depression commonly experience anhedonia, low levels of positive emotion, diminished responsiveness to pleasurable stimuli, and an attentional bias toward depression-congruent information such as sad, unpleasant, and negative words, facial expressions, and memories (reviewed in Hasler 2004). As noted earlier, these symptoms may in part reflect decreased dopamine activity, deficits in the reinforcing effects of reward, and possible underactivation of the brain reward system. It is likely that neurobiological contributions to low levels of positive emotion are highly influenced by genetic and developmental/learning factors.

HUMOR The appreciation and use of humor also characterizes many people who exhibit stress resilience. In studies of resilient Vietnam combat veterans (Hendin & Haas 1984), surgical patients (Carver et al. 1993), cancer patients (Culver et al. 2002), and at-risk children (Werner & Smith 1992, Wolin & Wolin 1993), humor has been identified as an important coping mechanism that reduces the threatening nature of stressful situations through cognitive reappraisal (Martin 2003).

Humor has also been identified as one of the most mature defense mechanisms (Vaillant 1977) and as a coping strategy that may lessen the likelihood of developing stress-induced depression. For example, in a study of the mothers of children undergoing bone marrow transplantation, Manne et al. (2003) found that humor was associated with reductions in maternal depressive symptoms. Similarly, Thorson & Powell (1994) and Deaner & McConatha (1993) have reported a negative relationship between sense of humor and depression. It has been suggested that humor may lessen depressive symptoms by reframing a situation as less threatening and thereby fostering a positive perspective on challenging circumstances (Folkman et al. 1991), by reducing tension and discomfort (Vaillant 1992), and by attracting social support (Silver et al. 1990).

Humor has been shown to activate a network of subcortical regions that constitute core elements of the dopaminergic reward system (Mobbs et al. 2003, Moran et al. 2004). In an event-related functional magnetic resonance imaging study of healthy volunteers, Mobbs et al. (2003) found that funny cartoons, in comparison with nonfunny cartoons, elicited activation of the amygdala, ventral striatum/nucleus accumbens, ventral tegmental area, anterior thalamus, and subadjacent hypothalamus. A time-series analysis showed that activity in the nucleus accumbens increased with degree of humor intensity. The nucleus accumbens has been repeatedly linked to psychologically and pharmacologically mediated rewards, and the amygdala has been associated with processing of positive emotions, laughter, and reward magnitude, in addition to its well-known role in fear and fear-related behaviors (Mobbs et al. 2003, Moran et al. 2004).

Cognitive Flexibility (Including Positive Explanatory Style, Positive Reappraisal, and Acceptance)

EXPLANATORY STYLE Resilient and optimistic individuals tend to possess a specific explanatory style that allows them to persevere, embrace challenges, and grow from failure. Seligman and colleagues (Seligman et al. 1988) have proposed that explanatory style has two critical dimensions: permanence and pervasiveness. When faced with difficult problems, resilient individuals do not automatically blame themselves or others for the problem, imagine that the problem is unsolvable, or worry that the problem will affect all areas of their life. Instead, they tend to place blame where it realistically belongs, they assess the difficulty as temporary and usually solvable, and they view the problem as affecting only limited areas of their life.

Explanatory style has been associated with depression. For example, adults diagnosed with clinical depression tend to use permanent and universal explanatory styles to explain bad events. As depressive symptoms subside, explanatory style for bad events becomes increasingly temporary and specific (Peterson & Seligman 1984). Similarly, explanatory style appears to be a strong predictor of depression in children (Seligman 1988, 2002).

COGNITIVE REAPPRAISAL The ability to cognitively reappraise, reframe, or find positive meaning in an adverse event is characteristic of many hardy and resilient individuals. Hardiness/resilience has been associated with a tendency to perceive potentially stressful events in less-threatening terms (Kobasa 1979, Tugade 2004) and to remain optimistic about the ability to cope with stressors. For example, Florian and colleagues (Florian et al. 1995) found that commitment to training and sense of control over stressors among 276 Israeli soldiers predicted mental health at the end of an intensive four-month combat training period. Commitment improved mental health largely by reducing appraisal of threat, whereas control improved mental health by enhancing the appraisal that one could effectively deal with the problem through active problem solving.

In summarizing a large body of literature on resilience, Schaefer & Moos (1992, 1998) concluded that redefining a crisis as a challenge and/or attributing meaning to it tends to result in a more positive outcome. Consistent with this assessment, Tugade & Fredrickson (2002) reported that resilient individuals tended to find greater positive meaning within daily life stressors than did nonresilient individuals.

Janoff-Bulman (1992) has proposed that trauma-related changes in psychology and personality result from questioning, shattering, and rebuilding one's basic assumptions about the world. In her model, lessons learned from trauma might involve greater appreciation for one's already existing strengths (e.g., courage), the development of admirable characteristics (e.g., wisdom), a realization that life is precious, and a shifting of one's priorities. Positive reinterpretation of stressful events has also been associated with stress-related growth in which individuals "learn something from the experience" and/or "grow as a person as a result of the adverse experience" (Park et al. 1996).

A surprisingly high percentage of people describe the impact of their own life crises as both positive and beneficial. Posttraumatic growth has been described in survivors of war, disasters, divorce, and medical conditions such as cancer, cardiac disease, stroke, bone marrow transplantation, and HIV/AIDS. Reported benefits have included a greater sense of kinship with humanity and an enhanced sense of community, greater compassion and acceptance of others, closer ties with family and friends, renewed religious faith, greater appreciation of nature, improved self-esteem and self-respect, increased emotional strength, the development of effective coping skills, commitment to a healthier lifestyle, enhanced wisdom and maturity, greater appreciation of life, and newfound meaning and purpose, often with a shift in values, priorities, perspective, and/or philosophy (reviewed in Anderson & Anderson 2003, Tedeschi et al. 1998).

A recent brain-imaging study has shown that cognitive reappraisal can influence brain regions involved in emotion processing. In a study of healthy volunteers (Ochsner et al. 2002), subjects were asked to view aversive photographs and were given instructions to increase, maintain, or decrease their emotional response to the photographs. Cognitive reappraisal of aversive photographs resulted in decreased negative affect, increased activation of the lateral and medial prefrontal cortex, and decreased activation of the amygdala and medial orbitofrontal cortex. These results suggest that regulation and reappraisal of feelings and thoughts, capacities that are important for stress resilience, depend on effective prefrontal cortical modulation of emotion-processing systems (e.g., amygdala and medial orbitofrontal cortex).

ACCEPTANCE Many hardy individuals cite acceptance as a key ingredient in their ability to tolerate highly stressful circumstances. Acceptance has been described as a common trait among survivors of extreme environmental hardship and threats to life (Siebert 1996) and among highly successful learning-disabled adults (Gerber et al. 1990). Acceptance has also been associated with better psychological and physical health in Mexican American and African American adolescents, fewer

depressive symptoms among mothers coping with children who are undergoing bone marrow transplantation (Manne et al. 2003), and reduced levels of post-traumatic stress symptoms in a nationwide survey of individuals shortly after the terrorism attacks of September 11, 2001 (Silver et al. 2002). In fact, acceptance has been recommended as a coping mechanism to be used in families dealing with pediatric cancer (Health 1996, Kazak et al. 1999).

It is important to note that acceptance is not the same as resignation (Reed et al. 1994). For example, Alcoholics Anonymous members use the Serenity Prayer to express acceptance: "God, grant me the serenity to accept the things I cannot change, courage to change the things I can, and the wisdom to know the difference." In a study of cancer patients recovering from surgery, Carver et al. (1993) found that acceptance was the most commonly reported response at multiple evaluation points during the first year post-surgery, and that acceptance predicted less distress. In addition, optimists were more likely to engage in acceptance than were pessimists. The authors suggested that optimists tended to have overall positive expectancies for the future. This is generally not true for individuals suffering with depression. Although their diagnosis of cancer was a setback, optimists believed that they would experience a good outcome, which likely made it easier for them to accept their diagnosis and to deal with problems that were possible to change (Carver et al. 1993).

Spirituality (Including Religion, Spirituality, and Altruism)

RELIGION AND SPIRITUALITY One important path to meaning comes from religious and spiritual beliefs and practices. Religion and spirituality provide a framework for understanding adversity and making sense of tragedy. Recent meta-analyses have concluded that religion and spirituality may have protective effects on physical and emotional well-being among healthy individuals and may enhance coping in people who are suffering with medical illnesses. In an analysis of 42 independent samples involving 126,000 people, McCullough et al. (2000) found that religious involvement was associated with lower odds of death (higher odds of survival). Although the effect size was small, the religious involvement–mortality association was nontrivial and considered to have practical significance given that the criterion variable was mortality (McCullough et al. 2000).

Higher levels of religiousness also have been associated with lower levels of depression in community-dwelling elderly people living in the United States and Europe (Braam et al. 2001), medically ill older patients (Koenig et al. 1998), elderly patients recovering from hip surgery (Pressman et al. 1990), bereaved adults (Borestein et al. 1973), and Protestant college students possessing a strong intrinsic orientation toward religion (Donahue 1985). Similarly, lower levels of suicidality have been reported in religious compared with nonreligious adolescents (Donahue & Benson 1995). In a study of 838 consecutively admitted medical patients age 50 or older, Koenig et al. (2004) found consistent relationships between religiousness and spirituality and fewer depressive symptoms. In

longitudinal studies, religiousness has also predicted faster remission from depression in community-dwelling and medically hospitalized older individuals (Braam et al. 1997, Koenig et al. 1998). Overall, it appears that many people use religious activities, personal religiousness, and spiritual experiences to cope with illness and that these religious practices buffer against the likelihood of developing depressive symptoms.

Some evidence suggests that variability in 5-HT1A receptor density in the dorsal raphe nuclei, the hippocampal formation, and the neocortex is related to spiritual experiences (Borg 2003). Serotonin's potential role in spiritual experiences is further supported by observations that drugs known to affect the serotonin system, such as lysergic acid diethylamide (LSD), N,N-dimethyltryptamine, 3,4-methylenedioxymethamphetamine, psilocybin, and mescaline, often elicit a sense of insight, spiritual awareness, mystical experiences, and religious ecstasy, as well as distorted perceptions and illusions (Borg 2003). As noted above, serotonin and the 5-HT1A receptor have been strongly implicated in the pathophysiology of depression.

ALTRUISM Religion is not the only framework through which to construct meaning in the face of adversity. Some people find meaning by contributing to society, providing for their families, or striving for worthy work-related goals. For children who have been raised in a variety of stressful environments, altruism consistently has been associated with successful adaptation (Bleuler 1984). During WWII, the phenomenon known as "required helpfulness" was first described. Citizens who cared for the immediate needs of others after aerial bombardments developed fewer trauma-related mood and anxiety symptoms than expected, and individuals with pre–air raid psychological syndromes actually experienced a decrease in their symptoms after bombardments if they performed personally satisfying tasks that were viewed by others as socially necessary (Rachman 1979). Particularly inspiring are individuals who find meaning by embracing a survivor mission. The survivor mission is a direct outgrowth of personal trauma, in which the survivor turns tragedy into activism. Examples include the women who founded Mothers Against Drunk Driving after their children had been injured by drunk drivers, and the young amputee who founded the Marathon of Hope (an annual run across Canada), which has since raised nearly $300 million for cancer research. It is important to note that finding meaning in tragedy does not typically counteract all of the negative consequences of trauma. Rather, the discovery of benefits or meaning may coexist with aversive outcomes as survivors attempt to reframe and reconstruct their world (Anderson & Anderson 2003).

Social Support (Including Role Models)

SOCIAL SUPPORT Social support has been one of the most widely studied psychosocial factors in relation to health and disease. Theoretical models of social support have typically described the social network as having a structural dimension, including social network size and frequency of social interactions, and a functional

dimension, with emotional and instrumental components (Wills & Fegan 2001). Social isolation and low levels of social support consistently have been associated with higher levels of stress, depression, posttraumatic stress disorder, and increased morbidity and mortality in a host of medical illnesses, whereas high levels of social support have been associated with positive outcomes following a wide variety of stressors (Resick 2001). The relationship between good social support and positive mental and physical health outcomes has been observed in inner-city children, college students, blue-collar workers, unemployed workers, business executives, new mothers, widows, and parents of children with serious medical illnesses (Resick 2001).

Decreased social support has also been associated with major depression (Brugha 1995, Paykel 1994), dysthymia (Oxman & Hull 2001), seasonal affective disorder (Michalak et al. 2003, 2004), and depression in comorbid medical illnesses including multiple sclerosis (Mohr et al. 2004), cancer (Manne et al. 1999), cardiac illness (Revenson et al. 1991), and rheumatoid arthritis (Revenson et al. 1991). On the other hand, increased social support has been associated with decreased risk of developing depression, decreased functional impairment in depression (Travis 2004), and greater likelihood of remission of depression (Oxman & Hull 2001, Sayal et al. 2002). To be helpful in depression, social support must be positive, rather than negative, and the best source of support may vary depending on developmental stage. For example, in early adolescence, parental support is usually more important than peer support (Stice et al. 2004). This may not be the case for older adolescents.

Increased social support appears to have protective and buffering effects on mental and physical illness. Rich social networks and emotional support may enhance mental and physical health by reducing the rate at which individuals engage in high-risk behaviors (e.g., smoking, excess alcohol and fatty food intake) (Rozanski et al. 1999), fostering effective coping strategies (Holahan et al. 1995), encouraging less-debilitating appraisals of threat (Fontana et al. 1989), counteracting feelings of loneliness (Bisschop et al. 2004), increasing feelings of self-efficacy, reducing functional disability (Hays et al. 2001, Travis et al. 2004), and increasing treatment compliance. As described below, social support also appears to have neurobiological effects that foster resilience and buffer against illness and the development of depression.

Neural mechanisms underlying the processing of social information and regulation of social behavior (including social recognition, nurturing behavior, and the development of specific social preferences) are undoubtedly complex, involving multiple brain regions, numerous biological pathways, neurotransmitter systems, and neuropeptides. Of particular importance for social behaviors are the neuropeptides oxytocin and vasopressin. Oxytocin is known to play a role in parturition, lactation, regulation of social attachment, and promotion of positive social interactions (Heinrichs et al. 2003, Henrich & Boyd 2001, Insel & Young 2001). In rat pups, oxytocin is critical for learning social cues, such as recognizing the mother rat, but not for learning nonsocial cues. Oxytocin knockout mice exhibit a specific

deficit in social recognition that is fully restored by oxytocin infusion (Ferguson et al. 2000).

Oxytocin, along with prolactin, also serves as a central neuroendocrine mediator of maternal care (Insel & Young 2001). Oxytocin has been shown to promote approach behaviors in rat mothers toward their young, and prolactin has been shown to enhance maternal retrieval and nest building in mice. The medial preoptic area, the olfactory bulb, the bed nucleus of the stria terminalis, and the ventral tegmental area all have been implicated in the initiation and maintenance of maternal care (Corodimas et al. 1992, Numan & Sheehan 1997, Pedersen et al. 1994). Prior experience appears to interact with these neuroendocrine mediators, as a previous history of parental care enhances CNS oxytocin release (Kendrick et al. 1997). In addition, oxytocin and vasopressin are critically involved in another important form of social behavior, adult pair bonding.

Finally, oxytocin appears to have behavioral and physiological stress-attenuating and anxiolytic effects (Heinrichs et al. 2003). Fear and stress-induced release of oxytocin has been shown to reduce anxiety and stress-related behaviors in rodents (Carter & Altemus 1997, Heinrichs et al. 2003), and has been associated with attenuated secretion of ACTH, corticosterone, and catecholamines in lactating rats (Heinrichs et al. 2003). Similarly, in humans, Altemus et al. (1994) found reduced plasma ACTH, cortisol, and glucose responses to physical stress, and Heinrichs et al. (2003) reported attenuated reactivity of the pituitary adrenal axis to psychosocial stress in postpartum lactating women compared with nonlactating women.

In a recent study (Heinrichs et al. 2003) of healthy men who underwent the Trier Social Stress Test, subjects who received oxytocin, social support, or both oxytocin and social support experienced an increase in calmness during the test procedure, whereas subjects who received neither oxytocin nor social support experienced a decrease in calmness and an increase in anxiety. Subjects who received the combination of social support and oxytocin exhibited the lowest cortisol responses to stress and the greatest increases in calmness and decreases in anxiety.

Taken together, preclinical and clinical studies suggest that social support enhances multiple aspects of physical health and plays a key role in reducing stress and depression. These effects of social support appear to be mediated, in part, through effects on other psychosocial factors, such as optimism, and through effects on multiple neurobiological factors. Oxytocin appears to be of particular importance because of its effects on prosocial behavior and its inhibitory effects on multiple stress-activated neuroendocrine systems.

ROLE MODELS Strong role models and mentors serve an important educational and developmental function for resilient individuals. At every stage of life, observation and imitation constitute powerful forms of learning that can alter the course of one's development. This is particularly true for childhood and adolescence, when the nervous system is changing rapidly and when habitual styles of thinking and behavior are becoming consolidated.

In the lives of children and adolescents, nonparental adults may play formative roles in development by conveying knowledge and skills, challenging youth with new perspectives, providing dependable support, motivating and inspiring hard work, promoting moral values, nourishing self-esteem, and facilitating occupational ambitions (Hirsch et al. 2002). This is particularly true for natural mentors (i.e., nonparental adults including kin, neighbors, teachers, and coaches who are members of the mentored youth's natural social network). For example, in a study by Rhodes et al. (2002) of 770 adolescents from a large city in the Midwest, 52% reported having a natural mentor. Those with a natural mentor reported less marijuana use, less nonviolent delinquency, more positive attitudes toward school, higher school attachment and school efficacy, and a stronger belief in the importance of doing well in school. Natural mentors had a direct effect on reducing problem behaviors and increasing positive school attitudes, as well as an indirect effect in helping their mentored youths avoid negative peers.

Having a nonparental natural mentor can also help to buffer against the development of depression. Among 129 young African American mothers, those with natural mentors had lower levels of depression and benefited more from social support than did mothers without natural mentors (Rhodes et al. 1992). Having a mentor appeared to moderate the relationship between depression and social support and relationship problems. Similar findings have been reported in Latino adolescent mothers.

The lasting effect of role models and mentors undoubtedly depends on complex neurobiological circuitry involved in learning and memory as well as reward and attachment. From resilient role models one may learn a host of strategies to diminish the likelihood of developing stress-induced depression and/or to manage symptoms if they develop. Strategies include the fostering of psychosocial resilience factors, many of which are discussed in this review, including positive emotions, cognitive flexibility, optimism, meaning, social support, and active coping.

Active Coping Style (Including Exercise)

ACTIVE COPING At least 400 ways of coping have been identified in the scientific literature (Skinner et al. 2003). Two common categorical approaches to classifying coping mechanisms include problem- versus emotion-focused coping and approach versus avoidance coping. In this section, we discuss the relationship between depression and passive (avoidance, emotion-focused) coping and between resilience and active (approach, problem-focused) coping.

In general, resilient or hardy individuals have been described as using active coping mechanisms when dealing with stressful life situations (Moos & Schaefer 1993). In a study of undergraduate students, Maddi (1999a,b) found that high scores in hardiness were positively correlated with active coping and planning, whereas low scores in hardiness were associated with denial, behavioral and mental disengagement, and proneness to cope with stress by using alcohol (Maddi 1999a,b). Active coping (seeking social support, adopting a fighting spirit,

reframing stressors in a positive light) has also been associated with improved well-being, fewer psychological symptoms, and the ability to manage stressful circumstances among college students (Valentiner 1994), at-risk children (Werner & Smith 1992), traumatized adults and depressed adults (Fondacaro & Moos 1989), and patients with medical conditions such as cardiac illness (Holahan et al. 1995).

Depression has been associated with passive coping style in clinical mental health populations, in community populations, and in patients with medical conditions. Studies of both clinical and community samples have shown passive, avoidant, and emotion-oriented coping strategies to be associated with higher levels of depressive symptoms, and active strategies (which directly address stressors and modulate emotional reactions) to be associated with lower levels of depression (Billings & Moos 1984, Endler & Parker 1990, Folkman & Lazarus 1980). For example, among 373 normal adolescents, Muris and colleagues (Muris et al. 2001) found that depression was associated with high levels of parental rejection, negative attributions, and passive coping, as well as low levels of active coping and self-efficacy. Furthermore, evidence suggests that coping style not only predicts the development of depression but also that depression may influence coping style.

From a neurobiological perspective, active coping at the time of stress or trauma may decrease the likelihood of developing fear-conditioned associations to the trauma (reviewed in LeDoux & Gorman 2001). In addition, active coping at the time of re-exposure to already established fear-conditioned stimuli may decrease the intensity of fear-conditioned memories and responses. Conditioned stimuli become integrated with unconditioned stimuli in the lateral nucleus of the amygdala. Later, when the organism is re-exposed to the fear-arousing conditioned stimulus, this stimulus is encoded in the lateral nucleus. The lateral nucleus then activates the central nucleus, which in turn activates brainstem-mediated fear responses, including passive freezing behavior as well as autonomic and endocrine responses. However, animal studies have shown that if rats are active (i.e., move to another place) during re-exposure to the conditioned stimulus, the conditioned stimulus is terminated and information flow is redirected from the lateral nucleus to the basal nucleus instead of to the central nucleus. The basal nucleus then relays information to motor circuits in the ventral striatum. LeDoux & Gorman (2001) have suggested that this redirection of information only takes place if the organism is active and not passive. It is possible, then, that active coping may prevent fear conditioning or decrease the intensity of already established fear-conditioned memories and responses and, in so doing, may decrease the likelihood of developing trauma-related anxiety and mood disorders as well as trauma-related functional impairment.

EXERCISE In both cross-sectional and prospective studies, individuals who exercise consistently have been found to report lower depression scores than those of individuals who do not exercise (Brosse et al. 2002, Camacho et al. 1991). Exercise training has been shown to improve depressive symptoms in healthy

subjects (DiLorenzo et al. 1999) and in patients with cancer (Segar et al. 1998), neuromuscular disorders (Brosse et al. 2002), cardiac conditions (Beniamini et al. 1997), and chronic pulmonary obstructive disease (Emery et al. 1998).

Exercise training has been effective in treating clinical depression among young adults (Martinsen et al. 1985) and middle- as well as older-age adults (Blumenthal et al. 1999, Singh et al. 2001). For example, in a randomized controlled study of 156 middle-aged adults with MDD, Blumenthal et al. (1999) reported similar and significant reductions in depression scores among subjects treated with 16 weeks of aerobic exercise, sertraline, or the combination of aerobic exercise and sertraline. Rates of remission in the three groups ranged from 60% to 69%. Response rate was significantly faster for sertraline; relapse rate 10 months after remission was significantly lower in the exercise alone group (Babyak et al. 2000, Salmon 2001). In addition, during the follow-up period those who exercised on their own had a nearly 50% reduction in probability of relapse.

In meta-analyses of studies involving the relationship between exercise and depression, subjects who exercised reported reductions in depressive symptoms equal to subjects treated with cognitive behavioral therapy, and substantially greater than reductions in subjects receiving no treatment (Lawlor & Hopker 2001, Manber et al. 2002). It is important to note that many of the published studies reporting positive effects of exercise on depression have problematic methodological flaws. Nevertheless, the scientific literature overall supports a positive relationship between exercise and psychological well-being and between exercise and reduction in symptoms of depression.

A number of mechanisms have been proposed to explain the antidepressant effects of exercise. Exercise has been associated with increases in plasma monoamines and free tryptophan levels. It is possible that exercise affects alterations in monoamine functioning commonly seen in depression (Brosse et al. 2002). It is also possible that the antidepressant effects of aerobic exercise are mediated, at least in part, by the HPA axis and/or B-endorphins. As noted above, a substantial subgroup of individuals with major depression exhibit hyperactivity of the HPA axis, as evidenced by elevated CSF, CRH, and plasma cortisol, and nonsuppression of endogenous cortisol following dexamethasone challenge. Exercise-trained individuals, on the other hand, tend to display attenuated HPA axis responses to exercise and mental stress (Dienstbier 1991, Luger et al. 1987, Wittert et al. 1996). Exercise also leads to a rapid increase in B-endorphins and an associated elevation in mood that is attenuated by administration of the opiate antagonist naloxone (Hoffmann et al. 1990, Janal et al. 1984).

From a genetic standpoint, aerobic exercise induces expression of multiple genes known to be involved in plasticity and neurogenesis (Cotman & Berchtold 2002). For example, increased levels of hippocampal neurotrophic factors BDNF, BDNF mRNA, NGF, and 2(FGF-2) have been reported in rodents after days to weeks of wheel-running (reviewed in Cotman & Berchtold 2002). BDNF, in particular, is considered an important mediator of synaptic efficacy, use-dependent plasticity, connectivity, cell survival, neurogenesis, and learning (Cotman &

Berchtold 2002). Acute and chronic stress decrease expression of neurotrophic factors, such as BDNF, in the hippocampus, and deficiencies in neurotrophic factors may contribute to states of depression (Smith et al. 1995). Thus, it has been hypothesized that exercise reverses neurotrophic deficiencies in depression and improves clinical symptoms by increasing gene expression of hippocampal neurotrophic factors, with a subsequent strengthening of neuronal structure and facilitation of synaptic transmission.

Of particular interest for the study of resilience is the preclinical finding that stress-induced decreases in hippocampal BDNF mRNA can be prevented by one week of voluntary wheel-running exercise (Russo-Neustadt et al. 2001). The capacity for aerobic exercise to prevent stress-induced anxiety and depression is an important area of study in both animals and humans. In research related to exercise and its effect on anxiety and depression, it will also be important to study interactions between CNS neurotransmitters (e.g., monoamines) and peripheral factors (e.g., estrogen, corticosterone) known to have relevance for gene expression of neurotrophic factors and for symptoms of major depression.

INTERACTIONS INVOLVING RISK AND RESILIENCE FACTORS

It is important to emphasize that the neurobiological and psychosocial risk and resilience factors we have discussed do not operate in isolation. Instead, they interact with and influence multiple other risk and resilience factors. For example, LC/NE hyperactivity, which is commonly seen in anxiety disorders and in a subgroup of patients with major depression, is regulated by a variety of neurotransmitters and neuropeptides, with CRF and glutamate having stimulatory effects, and norepinephrine, epinephrine, NPY, endogenous opiates, GABA, benzodiazepines, and serotonin having inhibitory effects (Morgan et al. 2003). Similarly, the relationship between religion/spirituality and stress resilience or stress-induced depression is mediated, in large part, through multiple other resilience factors. Religion/spirituality is typically associated with optimism and positive emotions, purpose and meaning in life, a deep and broad form of social support, rest and rejuvenation, greater access to resources (through regular attendance at church/services), and a healthy lifestyle, all of which have been associated with stress resilience.

Of note, bolstering one resilience factor often has positive effects on other resilience factors. Using a time-lag model for the prediction of depression, Holahan et al. (1995) found that high social support predicted less subsequent depression in patients with acute and chronic cardiac illness, and that this relationship was partly mediated by the use of an active coping style. Importantly, in this cohort of patients, social support preceded and facilitated the use of active coping mechanisms. Similarly, administering a CRF antagonist to a chronically stressed individual would likely enhance resilience and lessen the chances of developing an anxiety or mood

disorder, partly through its influence on multiple neurobiological systems that are known to be involved in depression and anxiety (e.g., cortisol, NPY, NE, 5-HT).

CONCLUSIONS AND IMPLICATIONS

Numerous brain regions, neurotransmitter systems, genetic factors, and developmental influences are involved in stress resilience and stress-induced alterations in mood and anxiety. Important neurobiological resilience factors related to positive emotions, optimism, humor, spirituality, finding meaning, social support, and active coping likely include a highly functional dopamine-mediated reward system, absence of the short allele of the 5-HT transporter gene promoter polymorphism, and a serotonin system that remains effective during prolonged periods of high stress (without marked 5-HT depletion and 5-HT1A downregulation). Resilience factors also likely include a noradrenergic system that does not hyperrespond to stress and that returns rapidly to baseline as a result of factors such as robust NYP responsivity, absence of alpha-2cDel322-325-AR adrenoreceptor gene polymorphism, capacity to contain stress-induced CRF overdrive, and appropriate balance of neuromodulators and receptors (e.g., DHEA and cortisol, oxytocin and vasopressin, alpha-2a and alpha-2c adrenergic receptors, CRH-1 and CRH-2 receptors) in critical brain regions. Functional capacity of brain regions (e.g., prefrontal cortex, amygdala, hippocampus, dorsal raphe nucleus, and locus coeruleus) and neural pathways involved in the regulation of stress, fear, and mood are also a critical determinant of stress resilience versus stress-induced anxiety and depression. Numerous other factors that have not been included in this review, such as GABA-benzodiazepine receptor density and function, galanin responsivity to stress, and stress-induced release of estrogen and testosterone, have also been identified as potential resilience factors (Charney 2004).

The ability to recover rapidly after negative events is characteristic of most resilient individuals. Although hardy/resilient individuals experience event-related negative affect, they do not allow negative affect to persist, and many have the capacity to find meaning in adversity. This capacity to profit from information acquired as a result of negative events and to find meaning in these events may be important factors in facilitating rapid return of neurobiological stress systems to baseline. Analogously, Davidson et al. (2000) have suggested that failure to rapidly recover from aversive events can be an important risk factor for vulnerability to anxiety and mood disorders. This may be especially true when the failure to rapidly recover is accompanied by frequent or prolonged exposure to negative events, during which multiple neurobiological stress systems remain activated for lengthy periods.

In this chapter, we did not discuss the role of childhood stress in promoting future vulnerability or resilience to stress. Preclinical and clinical work suggests that moderate childhood stressors that can be successfully managed or mastered are likely to cause stress inoculation and stress resilience to subsequent stressors.

On the other hand, severe childhood stressors that cannot be managed or mastered are more likely to lead to stress sensitization and vulnerability to future stressors. Thus, although children should not be exposed to stressors that are overwhelming, they are likely to benefit from moderate stressors that they can successfully master.

Our brief review of the literature on neurobiological and psychosocial factors associated with stress resilience and stress-induced depression points to a number of possible interventions for individuals suffering from, or at risk for developing, stress-induced depression. Potential interventions include psychological, social, spiritual, and neurobiological approaches, or a combination of these approaches.

The most promising psychological approaches involve cognitive behavioral therapies that explore thoughts and feelings as they relate to behaviors. These therapies can teach individuals to become more optimistic, use more positive emotions, alter pessimistic explanatory styles of thinking, cognitively reappraise negative events, and find positive meaning in adverse circumstances. For example, individuals suffering with depression typically use explanatory styles of thinking that evaluate difficult problems as permanent, pervasive, and unsolvable. Resilient nondepressed individuals, on the other hand, view difficult problems as temporary, specific to the situation, and solvable. Cognitive-behavioral therapies help depressed patients recognize chronic pessimistic and depressive explanatory styles of thinking and to systematically change those styles of thinking. Cognitive-behavioral therapies also teach the patient to reappraise adverse events in less-threatening terms and to increase their appraisal of the likelihood for successful coping.

Social interventions also have the potential to enhance stress resilience. As noted earlier, low social support has been strongly associated with level of stress, anxiety, depression, posttraumatic stress disorder, and medical morbidity and mortality. On the other hand, increased social support appears to have protective and buffering effects on mental and physical health. Taken together, the literature on social support strongly suggests that interventions designed to enrich social networks and emotional support will enhance stress resilience and decrease the likelihood of developing stress-induced depression. Through effects on multiple neurobiological systems, enhanced emotional support also decreases medical morbidity.

In working with patients, it is important for therapists to thoroughly assess the extent of social network and the level of emotion support. Encouraging and facilitating expansion of positive and emotionally meaningful sources of social support (relationship with family, friends, and coworkers; membership in supportive organizations such as religious institutions) should be a priority for therapists who are working with depressed patients or those at risk for stress-induced disorders. Whenever possible, support should come from others within the individual's natural environment. For those who need outside support from volunteers, programs such as Project Head Start and Big Brothers Big Sisters have proven to be excellent models for promoting positive social support and resilience.

Although mental health workers typically shy away from discussions with patients about religion/spirituality, these practices are clearly associated with resilience and depression. It may be helpful for therapists to recommend and

encourage regular religious/spiritual practices in patients who are so inclined. For those who do not formally observe religious and/or spiritual traditions but who are drawn in this direction, the therapist might recommend serious exploration of one or more such practices. Furthermore, for all individuals, whether or not they participate in religious and/or spiritual practices, altruism can safely be recommended as an effective resilience factor. Altruism consistently has been related to resilience in both children and adults. Finally, other nontraditional therapies may also prove to be powerful tools for enhancing stress resilience, decreasing depression, and reducing the likelihood of developing stress-related symptoms of depression and anxiety. For example, aerobic exercise and meditation are both associated with resilience to stress and stress-related mental illness. Of note, many of the resilience factors that we have identified in this review can be enhanced through rigorous and systematic training.

Finally, interventions targeted at specific neurobiological risk and resilience factors may also prove to be effective for bolstering resilience against stress and stress-induced mood and anxiety disorders. For example, based on the literature cited in this review, one might hypothesize that SSRIs, tricyclic antidepressants, adrenergic blockers (i.e., clonidine, guanfacine, propranolol, prazosin), NPY, dopamine receptor agonists, monoamine oxidase inhibitors, dopamine reuptake inhibitors, CRF antagonists, and DHEA might each play a role in fostering stress resilience. Determining which pharmacological agents would be most helpful for particular at-risk or symptomatic individuals will be an important area for future investigation.

The study of stress resilience and the prevention of stress-induced anxiety and mood disorders is in its infancy. It is likely that the most effective strategies for promoting resilience will involve multiple coordinated psychosocial, spiritual, and neurobiological approaches. The bolstering of more than one resilience factor will likely have additive or synergistic effects on well-being. Furthermore, therapists who treat individuals suffering with depression are likely to experience greatest success when they actively focus on enhancing stress resilience as well as on reducing symptoms of psychopathology.

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CONTENTS