3The Etiology of Depression

SUMMARY

Timing and Course of Depression

- Age of onset of major depression may have both clinical and etiological implications. Clinically, earlier age of onset is associated with a worse course of depression with greater chances of recurrence, chronicity, and impairment. Etiologically, first onset of depression at different ages (e.g., childhood, adolescent, adult, and older adult) may reflect somewhat different causal factors.
- Many individuals may experience a single, major depressive episode following an acute stressor and recover with little implication for future vulnerability. However, most (50–80 percent) who have one significant episode will have recurrent episodes and intermittent subclinical symptoms, with the risk of recurrence progressively increasing with each episode of major depression.

Biological Factors

- Genetic, neurological, hormonal, immunological, and neuroendocrinological mechanisms appear to play a role in the development of major depression, and many of these factors center around reactions to stressors and the processing of emotional information. Etiological processes may be modified by gender and developmental factors.

Environmental and Personal Vulnerabilities

- Etiological models for depression are largely diathesis-stress models in which stressful experiences trigger depression in those who may be vulnerable due to biological and psychosocial characteristics and circumstances.
- Environmental stressors associated with depression include acute life events, chronic stress, and childhood exposure to adversity. Personal vulnerabilities associated with depression include cognitive, interpersonal, and personality factors.
- Biological, environmental, and personal vulnerabilities interact to contribute to the development of depression and also may be affected by depressive states in a bidirectional process.

Co-Occurring Disorders

- Depression rarely occurs independent of other psychological disorders, including anxiety, substance abuse, behavioral, and personality disorders, as well as other medical illnesses. The presence of co-occurring psychological and medical disorders exacerbates the clinical and social consequences of depression, and makes it more challenging to treat.

Resilience and Protective Factors

- Certain biological, environmental, and personal factors have also been associated with the protection from or the overcoming of risk factors and adverse conditions related to the development of depression.

The purpose of this chapter is to review what is known or suspected about the causes of depression. Fundamentally, such depressive symptoms as sad mood, pessimism, and lethargy, are universal human experiences and are considered normal reactions to the struggles, disappointments, and losses of everyday life. However, for some individuals, the intensity and persistence of depressive symptoms are not typical, and a challenge for researchers has been to understand why some individuals experience marked and enduring depressive reactions and others do not. This chapter discusses some of the characteristics of individuals that may make them vulnerable, as well as the features of environments that are particularly likely to provoke depression. The chapter also emphasizes the interplay between persons and environments—the ways in which, for example, stressors may provoke depression but depression further influences social environments, often a vicious cycle that promotes chronic or recurrent depression. A further aspect of this bidirectional influence is the frequent co-occurrence of depression and other disorders, which may complicate its course and treatment. It is noted that some individuals are remarkably resilient in the face of adversity, and a further challenge to the field is to understand such processes.

The first topic to address is that not all depressions are alike; therefore, different etiological models and perspectives are likely to apply to different expressions of depressive disorder.

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TIMING AND COURSE OF DEPRESSIVE DISORDERS

Age of onset of major depressive disorder and lifetime course are two factors that have etiological as well as treatment and outcome implications.

Age of First Onset

First onset can occur at any time. Diagnoses of childhood depression are relatively rare (Birmaher et al., 1996; Egger and Angold, 2006), although many preadolescents including preschoolers have significant internalizing symptoms of dysphoria and distress (e.g., Cole et al., 2002; DuBois et al., 1995; Gross et al., 2006). Most diagnosed depressions first appear in adolescence and early adulthood (Andrade et al., 2003; Burke et al., 1990; Kessler et al., 2005)—especially among those born in more recent decades (e.g., Kessler et al., 2003). For example, in recent community studies up to one-third of adolescents met criteria for major depressive disorder (Kessler and Walters, 1998; Lewinsohn, Rohde, and Seeley, 1998).

Age of first onset has both clinical and etiological implications. Clinically, earlier age of onset of depression is generally thought to be associated with a worse course of depression, with greater chances of recurrence, chronicity, and impairment in role functioning (e.g., Hollon et al., 2006; Zisook et al., 2004). Those with adolescent-onset depression include a significant proportion among both treatment and community samples who go on to have recurrent episodes and significant impairment (e.g., Hammen, Brennan, and Keenan-Miller, 2008; Lewinsohn et al., 1999, 2000; Pine et al., 1998; Weissman et al., 1999a).

Evidence increasingly suggests that childhood, adolescent, adult, and older adult first onsets may reflect different causal factors. Childhood depressions may be a mixture of subgroups: those with true genetically familial early-onset recurrent depression; those exposed to significant psychosocial adversity, such as abuse, parental disorder, criminality, and family disruption who continue to experience social maladjustment and other problem behaviors but not depression into adulthood; and some with eventual bipolar disorder (e.g., Harrington et al., 1990; Weissman et al., 1999b).

Adolescent-onset depressions are noteworthy for several factors. One is that increasing rates of adolescent depression in recent years (e.g., Kessler et al., 2003) imply, among other things, that the etiology is substantially psychosocial, with significant cultural shifts in recent decades that have created stressful experiences and reduced resources and contribute to depressive experiences (e.g., Seligman et al., 1995). Another issue is the enormous divergence in rates of depression for girls and boys beginning in adolescence (e.g., reviewed in Hankin and Abramson, 2001). The dramatic increases in girls' rates of depression compared with boys' rates clearly requires etiological models that can explain such differences. For example, different models emphasize genetic (e.g., Silberg, Rutter, and Eaves, 2001), hormonal (e.g., Angold et al., 1999), stress exposure and stress processes (e.g., Rudolph, 2002; Shih et al., 2006), cultural shaping of values and vulnerabilities (Seligman et al., 1995), and gender-based coping strategies (e.g., Nolen-Hoeksema, 1991).

Perinatal Depression

The childbearing years in general, and those around pregnancy in particular, have attracted special attention with respect to the occurrence of depression and its potential effects on children's development. A large majority of women experience mild "blues" following delivery of an infant, and between 10 and 20 percent of new mothers experience clinical depression lasting anywhere from several weeks to a year. A smaller proportion, less than 0.5 percent, experience acute psychosis associated with the depression. A recent large-scale epidemiological survey that examined rates of diagnoses in nonpregnant women compared with past-year pregnant women found no differences overall in mood disorders (Vesga-Lopez et al., 2008). However, the rates of major depression were higher in postpartum women compared with nonpregnant women. For all women pregnant in the past year, their depression was associated with not being married, exposure to trauma and stressful life events in the past year, and overall poor health.

The dramatic hormonal changes a woman experiences during and after pregnancy have focused much attention on the biological and hormonal etiological factors of postpartum depression. However, there is widespread agreement that postpartum major depression is not distinct in terms of etiology from depression at other times. In addition to biological risk factors, social stressors, family composition, levels of social support, and especially poorer economic circumstances all contribute to the risk of developing postpartum depression (Bloch et al., 2005; Crouch, 1999; Grigoriadis and Romans, 2006; Hayes, Roberts, and Davare, 2000; Robertson et al., 2004; Segre et al., 2007).

Although relatively little research has focused on paternal postpartum depression, the few studies that have report rates among new fathers as lower but not too dissimilar to that of new mothers. Paulson, Dauber, and Lieferman (2006), reporting on depression among two-parent households in a national random sample of over 5,000 families, found rates of depression at 14 percent for mothers and 10 percent for fathers. Fathers' elevated rates of depressive symptoms and disorders after the birth of a child are associated with stressful adjustments and the quality of their relationship with the mother; mothers' depression is also a significant predictor of increased depression in postpartum fathers (Huang and Warner, 2005; Kim and Swain, 2007).

Course of Depression

The course of depression may shed light on both treatment and prevention concerns and etiological issues. Some individuals may experience a single, major depressive episode in response to an acute stressor, never seek treatment, and, except for impairment associated with the acute episode, recover with little implication for future vulnerability. However, many others, especially those with sufficient distress and impairment who seek (or should seek) treatment, will have recurrent episodes and possibly significant residual symptoms (e.g., Judd, 1997; Judd et al., 1998; Keller, 1985). Judd (1997) found that 80 percent of patients had at least one recurrence (with an average of 4 episodes) over a few years' follow-up, and many others had significant even if nondiagnosable symptoms. In an epidemiological study of first episode of depression, more than 50 percent had a recurrence over the multiyear follow-up (Eaton et al., 2008). Moreover, there is evidence that the risk for recurrence progressively increases with each episode of major depression—and decreases as the period of recovery is longer (Solomon et al., 2000). Episodes come closer together over time (Bockting et al., 2006; Kessing et al., 2004; Solomon et al., 2000). As Judd et al. (1998) have documented, impaired functioning in work, family, social, and marital roles persists to a considerable extent even when the individual does not meet the full criteria for a major depressive episode. Thus, recurrent depressive disorders and continuing symptoms are likely to be disruptive of lives and families.

Early-onset recurrent depression may reflect a genetic etiology (Holmans et al., 2007), but its progressive nature has also been speculated to indicate a neurobiological process in which early and successive episodes of depression alter the brain and neuroregulatory processes (e.g., Post, 1992). The "kindling" model postulates that successive episodes change the brain in ways that reduce the threshold at which stressors may trigger a further episode—possibly to the point of autonomous episodes of depression. A review of studies of stress-depression associations in first and later episodes found some support for the model (Monroe and Harkness, 2005). Truly longitudinal within-person studies to test this hypothesis are quite rare, although one such investigation by Kendler, Thornton, and Gardner (2000) studied nearly 2,400 female twins over 4 waves separated by at least 13 months each. They found evidence of a diminishing association between life events and depression as the person experienced increasing numbers of episodes (up to about 6–8 episodes). They suggested that whether the involved mechanism is biological or psychological, it appears to occur intensively in the first few episodes after initial onset, and then the kindling process slows or stops. The stress-depression relationship not only may vary over time with increasing numbers of episodes but also may differ according to genetic risk for depression (Kendler, Thornton, and Gardner, 2001).

Mild, chronic depression—termed dysthymic disorder—may also be very disruptive and enduring. It may be highly predictive of major depressive episodes, and, especially if its onset is early in life, it is associated with slow recovery and high rates of relapse or continuing symptoms (Klein, Shankman, and Rose, 2006). Early-onset dysthymic patients had relatively high rates of poor-quality early home environments (Lizardi et al., 1995) and a relatively elevated exposure to early adverse conditions, including physical and sexual abuse, as well as ongoing stressful life conditions (Riso, Miyaktake, and Thase, 2002). Chronic depression is also associated with higher rates of familial depression than is episodic major depression (Klein et al., 2004), which suggests an etiological subtype.

Key features of the course of depression have significant implications for families. Most depressions first occur in adolescence and young adulthood, periods during which critical developmental accomplishments may be disrupted, such as academic attainment and job planning, peer integration and acquisition of effective social skills, and romantic relationship formation. Obviously, childbearing years are affected as well. Young people who are depressed may select into, or default into, problematic environments that are stressful and may further overwhelm impaired coping capabilities. Depression may become recurrent for

biological as well as social and psychological reasons, and thus it may become harder to manage and treat. All members of the family are affected, and children are the most vulnerable to the negative impact of parental depression. Another important observation that comes from this evidence is that prevention programs may be particularly valuable and are probably best targeted at those most vulnerable to depression: those with extensive family history, those with symptoms of depression, and those with multiple risk factors for depression (e.g., poverty, exposure to violence, social isolation).

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BIOLOGICAL PERSPECTIVES ON THE ETIOLOGY OF DEPRESSION

A complex set of biological processes has been implicated in the etiology and course of depression—although such research has not always clarified whether such processes are underlying causal factors, correlates, or consequences of depression. These include interrelated mechanisms of genetic vulnerabilities, brain structure and function, neurotransmitter and neuroendocrine processes, and immune system processes. Discussion of the details and transactions among these processes given the vastly expanding research literature in recent years is beyond the scope of this report (but see Thase, 2008, for a review). Advances have been made in each of these areas as well as in studies of interactions among these biological mechanisms and environmental and personal factors that confer increased risk for depression. In light of the heterogeneity of depression, it is not surprising that the research evidence to date has failed to converge on a single set of biological processes that is related to the onset and course of depression. However, evidence supports the role of several important aspects of functioning in the brain, the central nervous system, and the periphery. A theme throughout these various lines of research is the importance of considering the interaction between biology and exposure to stress, particularly chronic or recurring stress, in the etiology and course of depression.

Genetic Vulnerability

It is well known that depression runs in families, a phenomenon implicating both genetic and environmental processes. A review of twin studies finds that about one-third of the risk for major depression in adults derives from genetic differences between individuals (Kendler et al., 2006; Sullivan, Neale, and Kendler, 2000). This figure is substantially lower than for some other psychological disorders, such as schizophrenia or bipolar disorder (McGuffin et al., 2003; Sullivan, Kendler, and Neale, 2003). Similarly, the risk of developing major depression increases about 2.5–3 times for those who have a first-degree relative with depression, whereas having a highly threatening life event increases risk from 5 to 16 times in a few months after the event (Kendler, Karkowski, and Prescott, 1998; Sullivan, Neale, and Kendler, 2000). Genetic influences appear to be modified by gender and developmental phase, and they may influence not only internal biological and psychological characteristics but also the nature of the person's effects on the environment (Kendler et al., 2001, 2006; Kendler and Karkowski-Shuman, 1997; Kendler, Gardner, and Prescott, 2003; Kendler, Gardner, and Lichtenstein, 2008).

Several genetic polymorphisms have been linked to increased risk of depression in response to stress. Foremost among these are genes of the serotonin system (5-HT). The neurotransmitter serotonin exerts effects on a broad range of physiological functions, such as emotions, sleep, circadian rhythm, thermoregulation, appetite, aggression, sexual behavior, pain sensitivity, and sensorimotor reactivity (e.g., Lucki, 1998; Neumeister, Young, and Strastny, 2004). Deficits in the central 5-HT system, such as reduced 5-HT concentrations, impaired uptake function of the 5-HT transporter, altered 5-HT receptor binding, and tryptophan depletion, have been linked to a number of psychological problems and psychiatric disorders, including depression (Neumeister, Young, and Strastny, 2004).

A number of studies have investigated the role of genetic polymorphisms in the serotonin-related genes in the etiology of depression. Currently, the serotonin transporter (5-HTTLPR) gene is the most promising one. Importantly, Caspi et al. (2003) and Kendler et al. (2005) found that individuals with one or two copies of the short allele of 5-HTTLPR experienced more depressive symptoms and higher rates of major depressive disorder in response to stressful life events than individuals who are homozygous for the long allele. These studies are especially noteworthy for their indication that genetic effects on depression may be observed only under conditions of exposure to stressors (see reviews by Uher and McGuffin, 2008; Zammit and Owen, 2006). The effects of the serotonin transporter polymorphism implicated in depression in response to stressful life events may be manifested behaviorally as dysfunctional emotionality in response to stress.

As an illustration of the complex transactions among brain functions, genes, and neurotransmitter systems, Hariri et al. (2005) used neuroimaging techniques to explore how individuals with different polymorphisms of the 5-HTTLPR gene responded to an amygdala activation task involving perception of fearful and angry faces. They found that normal, never-depressed individuals who had the short allele form of the 5-HTTLPR gene showed amygdala hyperreactivity in response to the emotion-arousing stimuli compared with other groups. The results suggest that the serotonin transporter polymorphism is linked to the brain's processing of emotional threat information. The study is noteworthy for helping to shed further light on neurobiological mechanisms by which stressful environmental experiences eventuate in depression in some people but not others.

In addition to the 5-HTTLPR polymorphisms, numerous other serotonin system genes have been studied as well as those known to affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and other brain regions. Meta-analytic studies of candidate genes and molecular genetic genome-wide association studies are increasing throughout the world, but it has been noted by a recent large-sample genome-wide association study of the high heritable human trait of height that they are likely to show what has long been predicted in quantitative genetics: Any relevant gene will have very small effects, and summing risk across multiple identified genes will yield limited explication of the effects (Weedon et al., 2008). Thus, in view of relatively modest overall heritability of depression, strong environmental effects, and tiny effects of individual genes, it is unlikely that genetic testing will prove to be an effective way to identify those at risk for depression. It has been speculated that "old-fashioned" methods of identifying risk through individual differences in a family history of depression or the personality trait of neuroticism will prove to be superior to molecular genetics (personal communication, Kenneth Kendler, Medical College of Virginia and Virginia Commonwealth University, August 8, 2008). That said, continuing analysis of genetic correlates of depression will doubtlessly contribute valuable information to fuller understanding of the neurobiological mechanisms underlying depression, and it may play a role in the development of pharmacotherapeutic agents.

A final note about genetic contributions to depression is the important acknowledgment not only that genetic factors have an impact on internal depressogenic processes but also that gene-environment correlations contribute to outcomes. For example, genetic factors may influence a depressed person's parenting styles as well as the offspring's heritable traits, so that the child's genotype and rearing environment are correlated (D'Onofrio et al., 2005, 2006, 2007; Rice, Harold, and Thapar, 2005). Similarly, youth with particular heritable characteristics evoke reactions from others and select or create experiences that are congruent with their heritable characteristics—processes that might increase the likelihood of depressive outcomes under relevant conditions. Although critically important to full understanding of genetic influences there is relatively sparse research on such mechanisms (personal communication, Sara Jaffe, King's College London, August 4, 2008).

Neuroendocrine Functioning

A dominant model of the neurobiology of depression that has emerged in recent years emphasizes the underlying dysregulation of the body's response to stress, involving the neuroendocrine system and brain responses (Thase, 2008). Key components are the HPA axis and the related corticotrophin-releasing hormone (CRH) and locus coeruleus-norepinephrine (LC-NE) systems, which include limbic and cortical pathways bidirectionally interconnected through various neurotransmitter and hormonal circuits (Boyce and Ellis, 2005; Meyer, Chrousos, and Gold, 2001). The primary glucocorticoid hormone is cortisol, which triggers a cascade of functions that are adaptive in the acute phases of response to stress and which normally resolve quickly through inhibitory feedback processes in the HPA axis. However, failure to normalize, resulting in sustained high cortisol, has deleterious effects, giving rise to physiological changes thought to promote a variety of illnesses.

Depression has been linked with elevated cortisol and related neurohormones. Numerous studies have indicated higher levels of cortisol and abnormalities in cortisol regulation among depressed compared with nondepressed individuals (e.g., reviewed in Plotsky, Owens, and Nemeroff, 1998; Ribeiro et al., 1993). Furthermore, depressed patients show slower recovery of cortisol levels in response to psychological stress than controls (see meta-analysis by Burke et al., 2005). Individuals who display evidence of abnormal cortisol regulation even after treatment are more likely to relapse and generally have a poorer clinical prognosis than patients whose cortisol functions returned to normal after treatment (e.g., Ribeiro et al., 1993). It appears that sustained hypercortisolism damages the stress system, including death of cells in the hippocampus (Sapolsky, 1996) with generalized effects on the circuits underlying emotion regulation.

It is hypothesized that both genetic and environmental factors account for individual differences in how individuals respond to (and recover from) HPA system activation. Genetic differences in species of animals and nonhuman primates have been shown to be associated with differences in emotional behavior and glucocorticoid responses to stress (e.g., Boyce and Ellis, 2005; Meyer, Chrousos, and Gold, 2001). Human genetic polymorphisms in the glucocorticoid receptor (GR) have been hypothesized as a source of impaired negative feedback regulation contributing to hyperactivity of the HPA-axis in depression (e.g., Holsboer, 2000). Evidence is emerging of GR polymorphisms associated with increased risk of developing major depression (van Rossum et al., 2006) and differences in response to treatment for depression (e.g., Brouwer et al., 2006; van Rossum et al., 2006).

Adverse environmental factors, especially those associated with early childhood development (or even prenatal exposure), have attracted considerable interest as possible contributors to abnormal biological stress regulation. Gold, Goodwin, and Chrousos (1988) speculated that brain circuits associated with stress reactions may have been sensitized as a result of early, acute exposure to stressors, so that in adulthood, depressive reactions to stress may be readily activated by even mild or symbolic representations of early stress precipitants. Evidence supports the impact of prenatal and postnatal stress, as well as disruptions of the parent-child bond, on abnormalities of HPA functioning in animal and human subjects (reviewed in Heim and Nemeroff, 2001; Kaufman et al., 2000; Meyer, Chrousos, and Gold, 2001; Plotsky, Owens, and Nemeroff, 1998). Meaney, Szyf, and Seckl (2007) also propose epigenetic processes by which maternal adversities affect fetal development mediated by adrenal hormone activity, and glucocorticoid levels program gene expression in the direction of impaired HPA function and health in offspring. While not specific to depression, the effects of environmental effects on gene expression in offspring have important implications for depression.

Limited but increasing evidence draws links between early adversity, abnormalities of the HPA, CRH, and LC-NE systems, and depression. For example, Essex et al. (2002) assessed cortisol levels in 4.5-year-olds and found that children who had been exposed to maternal stress both in infancy and concurrently had significantly higher levels of cortisol than nonstressed children or those exposed to either but not both periods of maternal stress. Moreover, the children with elevated cortisol had higher rates of behavioral and emotional symptoms (especially internalizing symptoms) approximately 2 years later. Although not specifically about depression, the results are consistent with the idea that early stress exposure predicts elevated cortisol when stress occurs later in life, and the pattern is predictive of later symptomatology (see also Heim et al., 2000, on early abuse experiences, depression, and adult HPA axis functioning). Preventing adverse environmental factors in children warrants further attention.

Immune System Processes and Depression

Spurred in part by the evidence of the strong association between depression and coronary heart disease, researchers have begun to examine the potential role of the immune system, and particularly proinflammatory cytokines, in the link between stress and depression (e.g., Danese et al., 2008; Miller and Blackwell, 2006). Recent models have proposed that chronic stress activates the immune system in a way that leads to inflammation, and that chronic inflammation in turn leads to symptoms of depression as well as pathological processes underlying heart disease (Miller and Blackwell, 2006). Cytokines are signaling molecules that coordinate inflammation in response to pathogens and include interleukin-1β, interleukin-6 (IL-6), and tumor necrosis factor-α. Among other functions, they direct white blood cells toward infections, signaling them to divide and activating their killing mechanisms. Downstream products of this process, including C-reactive protein (CRP), a molecule produced by the liver in response to IL-6, are used as an index of the inflammatory response.

Although the directions of these effects are yet to be disentangled, evidence indicates that chronic stress is associated with increased levels of both CRP and depression. Levels of IL-6 and CRP are elevated in individuals exposed to chronic stress (Segerstrom and Miller, 2004). Chronic stressors may prime the immune system to make a heightened response to stress. Alternatively, chronic stress may interfere with the capacity of the immune system to return to baseline after termination of a stressor, perhaps due to dysregulation of the HPA response and the production of glucocorticoids in response to stress (Miller and Blackwell, 2006). The inflammatory re sponse may also contribute to symptoms of depression by triggering sickness behaviors, including disruptions in appetite, sleep, and social activity. These processes may be involved in depression in general, or only in those individuals in which depression is comorbid with a medical condition, such as heart disease. Alternatively, depression may be involved in provoking inflammation. A recent meta-analysis reports some support for three causal models: depression to inflammation, inflammation to depression, and bidirectional associations (Howren, Lamkin, and Suls, 2009). Further research using prospective longitudinal designs is needed to clarify the directions of the relations among stress, depression, and inflammation.

Evidence from one longitudinal study has shed some additional light on the possible role of inflammatory processes in depression. Danese et al. (2008) examined the role of early life stress (childhood maltreatment) and later depression and inflammatory response processes (as measured by levels of CRP) as part of the longitudinal study of a birth cohort in Dunedin, New Zealand, followed into young adulthood. Specifically, they were able to compare young adults with no history of childhood maltreatment and no current depression, those with current depression and no maltreatment history, those with a positive history of maltreatment but no current depression, and those with both current depression and a history of maltreatment. It appeared that depressed individuals with a history of maltreatment were more likely to have high levels of CRP when compared to depressed-only individuals. Thus, maltreatment history seems to be an important modifier of the association between depression and inflammatory markers.

Although in its early stages, research on inflammatory responses suggests an additional biological process that may help to explain the link between stress and depression. And inflammatory processes may be especially important in elucidating important medical comorbidities of depression, most notably coronary heart disease.

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Environmental Factors

Depression is commonly construed as a reaction to negative environmental circumstances. Etiological models are largely diathesis-stress perspectives. A diathesis is a risk factor or vulnerability process, such as people's biological, personality, or cognitive characteristics, that accounts for individual differences in how they respond to similar stressful challenges. In order to illustrate key points—as well as to draw attention to circumstances that help to identify populations at particular risk for depression—in this section we focus on three kinds of stressful (environmental) conditions: (1) acute negative life events, (2) chronically stressful life circumstances, and (3) exposure to adversity in childhood.

Acute Life Events

A major risk factor for depression is the experience of undesirable, negative life events. There is ample evidence that most major depressive episodes are triggered by stressful life events (see reviews by Hammen, 2005; Kessler, 1997; Mazure, 1998). According to Mazure (1998) recent stressors were 2.5 times more likely in depressed patients compared with controls, and, in community samples, 80 percent of depressed cases were preceded by major negative life events. Most assessment methods survey the occurrence of stressors within the past 3 to 6 months in relation to depression, but Kendler, Karkowski, and Prescott (1998) found that the great majority of major depression onsets occurred within the first month after a significant negative life event. There is some evidence of a generally linear association between severity and number of negative events and the probability of depression onset (Kendler, Karkowski, and Prescott, 1998). However, the "severity" of the impact of an acute life event depends not only on the actual circumstances of the event but also on its subjective meaning to the individual. Thus, one person might become depressed only under extreme conditions of loss and deprivation, but another might become depressed because his or her personal vulnerabilities lead to exaggeration of the meaning of an acute event that is objectively minor.

It has been generally observed throughout the ages that depression is most likely to occur following the loss of something important to the sense of self, such as the loss of significant others or relationships or of a sense of worth and competence. Interpersonal losses or "exits" have been shown to be more associated with depression than with other forms of disorder (Tennant, 2002; see also Kendler et al., 1995)—perhaps especially for women.

For immigrant and refugee populations, experiences of loss and isolation are pervasive (Heilemann, Coffey-Love, and Frutos, 2004). Many immigrants and refugees experience lengthy or permanent separation from immediate and extended family. Loss of home, property, cultural ties, and customs may be significant for these communities. For many refugees and immigrants, these losses are also experienced in the context of the trauma of migration or the trauma of war. The impact of these experiences on the psychological functioning of individuals in these communities is profound. Rates of depression are reportedly high among these groups (Aguilar-Gaxiola et al., 2008). Owing to both biological and socialization processes, women are likely to be more attuned to and concerned about others' reactions to them, as well as reactive to the needs of others (e.g., Cyranowski et al., 2000). This seems to be particularly the case for immigrant women. For example, Hiott and colleagues (2006) reported that immigrant women may experience significant losses of social support and a sense of isolation on moving to a different country, and this loss may be manifested in a grieving process. The isolation may be related to unfulfilled relationships, or it may result from separation from or loss of family. These findings suggest that conflictual family relationships, unmet expectations in familial relationships, and isolation may be risk factors for depression in immigrant women who reside in the United States (Shatell et al., 2008). Thus, women may be especially likely to be depressed in response to stressful social loss experiences and even to the negative experiences of those in their social networks.

Gender differences in depression may be accounted for in part by women's greater exposure to interpersonal life events, as well as their greater likelihood, compared with men, of reacting to such events with depression. Results of studies of adults have been mixed with regard to whether or not women experience more overall recent stressors (e.g., Kendler, Thornton, and Prescott, 2001; McGonagle and Kessler, 1990; Spangler et al., 1996), but several studies have found that adolescent females have higher levels of exposure to recent stressors than do males (Ge et al., 1994; Shih et al., 2006). Moreover, several studies have shown that at comparable levels of acute stressors, women had higher levels of depressive symptoms than did men (Maciejewski, Prigerson, and Mazure, 2001; Rudolph and Hammen, 1999; Shih et al., 2006; van Os and Jones, 1999). Gender differences in exposure and reactivity may also reflect women's higher levels of certain diatheses, such as neuroticism or ruminative response styles, and meaning attached to interpersonal circumstances. In general, however, the risk factors for depression in men are likely to be very similar to those of women, involving complex interactions among environmental and neurobiological factors at different developmental stages (Kendler, Gardner, and Prescott, 2002, 2006). However, examination of gender differences in mechanisms underlying depressive responses to stress is sparse.

Although acute stress may precipitate depression in vulnerable individuals, the relationship is bidirectional: Those with depression or a history of depression experience significantly more acute stressors than those with no depression. This pattern ("stress generation"; Hammen, 1991b) applies particularly to events that are at least partly caused by the characteristics or behaviors of the person, such as interpersonal conflicts (reviewed in Hammen, 2006). One of the true calamities of depression is the vicious cycle of stress-depression-stress-depression that portends recurring or chronic depression.

Chronic Stress

Acute, episodic life events tell only part of the depression story. Another source of depression—although not as commonly studied—is exposure to enduring, long-term stressful circumstances. Many studies of stress-depression associations have not adequately distinguished between the effects of ongoing and acute stressors (e.g., Brown and Harris, 1978; Caspi et al., 2003), and failure to do so makes it difficult to fully explicate the mechanisms by which stressors have their effects on depression. An important feature of chronic stress, as with acute stress, is the bidirectional effect of stressful chronic conditions and depression on each other. The strains of poverty or unemployment or displacement in the case of immigrants and refugees, for example, may trigger depression, but depression erodes the individual's ability to cope with or change his or her circumstances.

Another notable feature of chronic stress is that for many individuals there are multiple, related areas of chronic stress. Consider, for example, the association of several demographic predictors of major depression. Hasin et al. (2005) found that a major depressive episode was associated with being female, having low income, and being widowed, divorced, or separated. In addition, low educational attainment and being unemployed, disabled, or a homemaker are also associated with major depression (e.g., Kessler et al., 2003). Commonly, many of these conditions co-occur, with low educational attainment, low income, and disadvantaged work status related to each other, and being a widowed, divorced, or separated woman is likely to be associated with lower income.

A specific example of a chronically stressful condition amplified by co-occurring adverse conditions is single-mother status. Single mothers have been found to have higher rates of major depression than married mothers (e.g., Davies, Avison, and McApline, 1997; Wang, 2004), especially for separated or divorced compared with never-married mothers (Afifi, Cox, and Enns, 2006). Two large-scale studies have shown that the association between single-parent status and depression is entirely or largely mediated by higher chronic and acute stress and low social support (Cairney et al., 2003; Targosz et al., 2003). Yet the role of chronic stressors is neither simple nor straightforward. Lone mothers have higher risk of depression not only because of the presence of higher levels of chronic social stressors compared with two-parent families or even single parents residing with extended family but also because of their lower socioeconomic position.

Furthermore, socioeconomic position might moderate the relationship between social stress and depression. For example, Barrett and Turner (2005) reported that among those with higher socioeconomic position, the adverse impact of racial discrimination and recent life events were more marked than that seen for those with lower socioeconomic position.

Low socioeconomic position is the source of a host of chronic stressors, including chronic strain and uncertainty surrounding a lack of adequate financial and other instrumental resources necessary to make ends meet (Malik et al., 2007; Muntaner et al., 2004). Given that racial and ethnic minorities are overrepresented among low-income populations, another chronic stressor that has been examined extensively in relation to depression is racial discrimination (Gee et al., 2007). While racial and other forms of discrimination are stressors, and, depending on the type of discrimination, such as racial, gender, age, or even social class, they can be either chronic or acute stressors (Banks and Kohn-Wood, 2007) and can increase risk of depression as such. Discrimination, however, can also impact beliefs, self-concept, and coping in ways that increase risk for mood disorders, including depression (Gee et al., 2007).

A number of institutional and sociocultural barriers are responsible for causing and maintaining existing disparities in access to and quality of mental health services received by minority groups. A succinct summary of the complex constellation of barriers is that "disparities result from ongoing interactions among factors at the levels of the health care environment, health care organization, community, provider, and person throughout the course of the depression development and treatment-seeking process (Chin et al., 2007)" (Van Voorhees et al., 2007, pp. 160S–161S). Social exclusion, which has played a key role in rendering these populations disproportionately vulnerable to and affected by incidence of depression, extends its adverse impact by limiting the engagement of and treatment in these historically unserved and underserved communities (Aguilar-Gaxiola et al., 2008). These groups' isolation from mainstream society because of linguistic barriers, geographic isolation, history of oppression, racism, discrimination, poverty, and immigration status plays a key role in creating and perpetuating their social exclusion and challenges to receiving treatment.

The environment can act as a source of chronic stressors as well. Extensive research has been devoted to the area of residential neighborhoods and mental well-being (Muntaner et al., 2004; O'Campo, Salmon, and Burke, 2009; O'Campo and Yonas, 2005). While not the only context or environment known to influence mental well-being—workplace organization and characteristics, for example, have also been studied in relation to major mental disorders—residential neighborhoods have been shown to be the source of multiple stressors, including physical incivilities (such as trash, graffiti), high levels of noise, traffic, crime, and delinquency, to name a few (O'Campo, Salmon, and Burke, 2009; Rajaratnam et al., 2008). These stressors should be considered to contribute to the risk of depression independently of, and may even interact with, any family or individual stressors that may place individuals at risk, including but not limited to economic strain and family and parenting stress (Cutrona, Wallace, and Wesner, 2006; Rajaratnam et al., 2008). In a randomized trial in which residents residing in neighborhoods characterized by concentrated poverty were given the opportunity to move to higher income neighborhoods, those who moved experienced declines in mental health problems, including depression, supporting the importance of residential context in shaping mental well-being (Del Conte and Kling, 2001; Goering et al., 1999). Efforts to prevent depression should focus not only on individuals and families but also on those larger structural interventions that can make profound differences (e.g., alleviating poverty, moving to a better neighborhood).

Finally, brief mention should be made of stressful parenting circumstances and their contribution to depression. Many parents are challenged by infants' and children's medical illnesses, developmental disabilities, and psychological disturbances, and the stress associated with such circumstances may result in depression. For example, a meta-analysis of 18 studies of mothers of children with and without developmental disabilities found that the former had higher rates of elevated symptoms of depression, falling above suggested clinical cutoffs compared with mothers of children without disabilities (29 versus 19 percent) (Singer, 2006). A further review of a broad array of samples, including mothers with children with mental retardation, autism, and other forms of developmental delay, found similar rates of elevated depressive symptoms and also noted a limited number of studies that reported on depressive diagnoses (Bailey et al., 2007). While limited in number, the findings suggest that depressive diagnoses were more frequent among mothers with disabled children. The study also noted that higher rates of depression were associated with multiple stressors in the family: higher levels of mother-reported stress, less effective coping styles, poorer health, low family support or cohesion, and presence of more than one child with a disability. Similarly, custodial care of children by grandparents (including both three-generation and "skipped-generation" households) is well-known to be associated with elevated depression symptoms and increased medical problems (e.g., Blustein, Chan, and Guanais, 2004; Hughes et al., 2007). Such chronically stressful circumstances are often compounded by low income, disadvantaged social status, and grandchildren with special needs (Blustein, Chan, and Guanais, 2004). Adolescent mothers are another group known to be at substantial risk for significant depression, often compounded by multiple chronic stressors such as low income, relationship difficulties, and reduced social support (Panzarine, Slater, and Sharps, 1995; Reid and Meadows-Oliver, 2007).

Exposure to Early Adversity

In addition to recent negative events and chronically stressful conditions, increasing evidence focuses on the link between childhood exposure to adversity and the development of depression in adolescence or adulthood. One research strategy studies associations between a single specific experience, such as sexual abuse or physical or emotional maltreatment, and depression. There is ample evidence from mostly retrospective community and clinical studies of a significant association between childhood sexual or physical abuse and adult depression particularly among women (e.g., Brown et al., 1999; Kendler et al., 2000; MacMillan et al., 2001) and similar results from prospective studies (e.g., Bifulco et al., 1998; Brown and Harris, 1993). Some studies suggest that abuse experiences are especially predictive of chronic or recurrent depression (Bifulco et al., 2002a; Lizardi et al., 1995). However, several studies suggest that physical and sexual abuse are related to diverse adult psychological disorders, not specifically to depression. Many of the studies have not distinguished among the specific types of abuse, nor have they controlled for factors in the environment that are correlated with abuse, which could themselves influence the likelihood of depression (such as parental psychopathology). In a large study of psychiatric outpatients, Gibb, Butler, and Beck (2003) found that childhood emotional abuse was most specifically related to depression compared with sexual or physical abuse (see also Alloy et al., 2006).

Using a different research strategy, Kessler and Magee (1993) examined associations among one or more from a diverse list of adverse experiences and depression. Their large-scale retrospective epidemiological study of community residents who met criteria for major depression found that several childhood adversities (parental drinking, parental mental illness, family violence, parental marital problems, death of mother or father, and lack of a close relationship with an adult) were predictive of later onset of depression. Three early adversities—parental mental illness, violence, and parental divorce—were significantly predictive of recurrence of depression. In a later similar study, Kessler, Davis, and Kendler (1997), examining 26 adversities occurring by age 16, found that although many of the events were associated with adult major depressive disorder, the adversities were also related to a broad array of psychological disorders besides depression. The investigators also noted that exposure to one or more adversities is common, occurring to three-fourths of respondents, and that the adversities tend to overlap or cluster with each other. Furthermore, they noted that no claim to causal relationships between adversity and disorders is possible, since there may be unmeasured common variables responsible for both adversity exposure and later disorder. Thus, while childhood traumas and early stressful conditions may contribute to depression, more study of the complex pathways is needed.

The mechanisms by which specific childhood stressors, such as physical or sexual abuse, have their effects on later depression are not known directly. However, such experiences are highly likely to occur in the context of parental lack of care, plus exposure to high levels of chronic and episodic stressors. Such environments contribute to dysfunctional cognitions and coping skills that increase vulnerability to depression. Neurobiological mechanisms may also be implicated, with the speculation that severe stress early in life alters the brain's neuroregulatory processes, which promote susceptibility to depression (e.g., Heim and Nemeroff, 2001). Exposure to adverse conditions in childhood may sensitize the youth to stress, so that it may take minimal exposure to later stressful

life events to precipitate depression in them compared with those without childhood adversity (e.g., Hammen, Henry, and Daley, 2000; Harkness, Bruce, and Lumley, 2006).

Personal Vulnerabilities to Depression

As noted earlier, etiological approaches to depression commonly invoke diathesis-stress models, in which stress precipitates depressive reactions among those with particular vulnerabilities. In this section, several nonbiological vulnerabilities are discussed: cognitive, interpersonal, and personality factors. As with biological factors, psychosocial vulnerabilities may contribute to the development of depression and also may be consequences of depressive states in a bidirectional process.

Cognitive Vulnerability to Depression

Considerable research on depression in the past 40 years has focused on three variants of cognitive models of depression—the classical cognitive triad model (negative views of the self, world, and future) of Aaron Beck (e.g., 1967, 1976), the versions of the helplessness/hopelessness cognitive style models of Seligman, Abramson, Alloy, and colleagues (e.g., Abramson, Metalsky, and Alloy, 1989; Abramson, Seligman, and Teasdale, 1978), and information-processing perspectives (e.g., reviewed in Joorman, 2008).

The Beck and cognitive style models emphasize the role of distortion in the content of thinking of depressed people. Those at risk for depression are hypothesized to have characteristic ways of interpreting events and circumstances that are excessively pessimistic and self-critical, with perceptions of helplessness and hopelessness about changing or improving their situations. Such underlying beliefs may be activated in the face of undesirable events, so that life events—even minor or fairly neutral experiences—are seen as reflections on one's underlying lack of worth and competence. Such views lead to the exacerbation and maintenance of symptoms of dysphoria and futility, sometimes to the extent of major depressive episodes and suicidality. Ample evidence has accumulated that verifies that, when experiencing depressed moods or episodes, a person's thinking is considerably more negative than he or she would display when not in a depressed mood (e.g., reviewed in Clark, Beck, and Alford, 1999). Moreover, prospective studies have verified that those considered at risk because of characteristic negative thinking are indeed likely to develop depressive reactions (Alloy et al., 2006; Gibb et al., 2006), especially in the face of stress (Hankin et al., 2004; Scher, Ingram, and Segal, 2005).

The information-processing approach to cognitive vulnerability refers to dysfunctional cognitive processes, such as biases in attention and memory, and overgeneralized thinking style (e.g., reviewed in Joorman, 2008; Mathews and MacLeod, 2005). Such biases may result in selective attention to negative information and reduced access to positive memories, increasing the likelihood of dysphoric reactions to negative events.

An interesting recent development in cognitive theories of depression is the study of the origins of depressogenic cognitive styles. Hypothesizing that they are acquired in childhood, several studies have found that children's negative cognitive styles are associated with parent-child communications characterized by criticism and disconfirmation, poor relationship quality, and modeling and learning of the parent's own negative cognitive style. Studies have also shown that negative cognitions are associated with histories of child abuse and maltreatment (e.g., reviewed in Alloy et al., 2006). The committee's review of the literature on the role of genetic factors in child outcomes notes that there is also evidence of heritability of depressogenic attributional style and other indicators of cognitive vulnerability to depression in youth (e.g., Abramson, Seligman, and Teasdale, 1978; Lau, Rijsdijk, and Eley, 2006; McGuire et al., 1999; Neiderhiser and McGuire, 1994; Neiss, Sedikides, and Stevenson, 2006).

Interpersonal Vulnerabilities to Depression

Depressive disorders are known to be associated with considerable impairment in interpersonal functioning—marital discord, intimate partner violence, parenting difficulties, insecure attachment, and low social support, to mention several specific areas. The symptoms of depression may contribute to difficulties in close relationships. Irritability, loss of energy and enjoyment, sensitivity to criticism, and pessimistic or even suicidal thoughts may initially elicit concern from others, but eventually they may seem burdensome, unreasonable, or even willful—sometimes eroding the support of spouses, friends, and family (Coyne, 1976). There is also increasing evidence that enduring maladaptive characteristics of the person's interpersonal style and cognitions about relationships may be observed when the person is not in a depressive state, and may serve as risk factors for the development of depression—perhaps in part because of their contribution to stressful conflict and loss events (Eberhart and Hammen, 2009; Hammen and Brennan, 2002).

A prominent issue in depression is marital discord. Meta-analyses across multiple studies have indicated significant associations between depression and self-reported poor marital satisfaction (Whisman, 2001). Rates of divorce and never-married status are elevated among those with depression (e.g., Coryell et al., 1993). One informative study found that depression, compared with other disorders, is uniquely associated with marital dissatisfaction. Zlotnick et al. (2000) found that depressed individuals—both men and women—reported significantly fewer positive and more negative interactions with their partners than did the nondisorder and nondepressive disorder groups.

Longitudinal studies show that depression may result from marital difficulties (Whisman and Bruce, 1999). Also, depression may cause marital difficulties. Whisman, Uebelacker, and Weinstock (2004) found that not only did current depressed mood predict marital dissatisfaction for the self, but also the spouse's depressed mood predicted the partner's dissatisfaction. Other studies also show bidirectional effects of depression and marital dissatisfaction (Coyne, Thompson, and Palmer, 2002; Davila et al., 2003). The romantic relationships of young women assessed over a 5-year period indicated that lower quality of the relationships at the end of the follow-up, as well as the boyfriend's dissatisfaction, were significantly correlated with the amount of time the woman had spent in major depressive episodes (Rao, Hammen, and Daley, 1999).

Intimate partner violence is a major risk factor for psychopathology, including depression, among abuse survivors (Campbell, 2002; O'Campo, Ahmad, and Cyriac, 2008). Numerous studies have reported high levels of depression among survivors of abuse. In a meta-analysis by Golding (1999), the weighted mean rate for depression among survivors of partner violence was 47 percent. Not only is partner violence a major stressor that increases the risk of depression, but also experiences of violence affect the victim's trust in others, levels of isolation, and coping styles, which further increase the risk of becoming depressed (Calvete, Corral, and Estevez, 2007). A strong predictor of maternal depression in home visiting samples is a maternal history of trauma, especially a maternal history of child abuse, domestic violence, or both (Boris et al., 2006).

Several mechanisms are likely to underlie the association between depression and difficulties in intimate relationships, including maladaptive cognitions and attachment insecurities leading to dependency, distrust, excessive reassurance-seeking, and other behaviors that provoke conflict. Certainly one general mechanism that is likely to affect marital behaviors is experience in one's own family of origin. Depressed individuals commonly report histories of violence and marital disruption in their early lives, as well as poor quality of care and relationships with their own parents. As a result of their early family histories, for example, insecure attachment representations may develop that make them vulnerable both to development of depression (Bifulco et al., 2002b; Kobak, Sudler, and Gamble, 1991) and to poorer quality of relationships (Carnelley, Pietromonaco, and Jaffe, 1994). Individuals exposed to ineffective parental role models are also likely to fail to acquire the social problem-solving skills needed to resolve conflicts in close relationships.

An additional pathway to discord is that depressed people tend to marry other people with psychological problems, thus increasing the chances of marital disharmony. A review and meta-analysis of several studies of patients with mood disorders confirmed the significant likelihood that individuals with depressive disorders marry others with depression (Mathews and Reus, 2001). Depressed women patients have also been found to have higher rates of marriage to men with antisocial and substance use disorders (e.g., Hammen, 1991a). Research on nonpatient samples also shows spouse similarity for depressive disorders (e.g., Galbaud du Fort et al., 1998; Hammen and Brennan, 2002) and wives' major depression associated with husbands' antisocial personality disorder (Galbaud du Fort et al., 1998). While the possible reasons for "nonrandom mating" are beyond the scope of this report, the implications of such marital patterns are clear: Marriages in which both partners experience symptoms and vulnerabilities to disorder may give rise to marital discord and instability by contributing to stressful home environments and potentially to limited skills for resolving interpersonal disputes.

Parenting problems and conflicts between parents and children are commonly associated with depression. Chapter 4, on the effects of parental depression on children, details the nature, extent, and consequences of dysfunctional parenting. Despite the desire of most depressed parents to provide nurturing, consistent, and responsive parenting, many are significantly likely to be negative, critical, or withdrawn in their interactions with their children (e.g., Lovejoy et al., 2000). Notably, intergenerational patterns of parenting problems are evident, with depressed adults highly likely to report that they had difficulties with their own parents (e.g., reviewed in Parker and Gladstone, 1996).

Related findings have been reported in community samples, in which depressed individuals reported more negative views of their parents (e.g., Blatt et al., 1979; Holmes and Robins, 1987, 1988). Andrews and Brown (1988), for example, found that women who became clinically depressed following occurrence of major life events were more likely to report lack of adequate parental care or hostility from their mothers, compared with those who did not become depressed (see also Brown and Harris, 1993). When dealing with vulnerable populations, it is important to consider that parenting style may differ by ethnicity as well as by views on what constitutes appropriate parenting and parenting values (Pinderhughes et al., 2000).

Intergenerational conflict is common among immigrant parents (Phinney, Ong, and Madden, 2000). Children tend to acculturate and learn new languages faster (Kwak, 2003). This creates conflict in families and may contribute to parental depression or exacerbate difficulties related to parental depression. In reviewing the extensive literature on depressed individuals' recollections of parents, Gerlsma, Emmelkamp, and Arrindell (1990) and Alloy et al. (2006) concluded that parental child rearing styles that include low affection and more control (overprotection) were most consistently related to depression.

In addition to difficulties in intimate family relationships, depressed people and those at risk for depression report problems with social support. They appear to have problems with the availability—or the perception of availability—of supportive relationships with others, including friends and associates. Perceived support helps to reduce depression and its likelihood of recurrence (Sherbourne, Hays, and Wells, 1995). However, depression is associated with low levels of perceived support (Burton, Stice, and Seeley, 2004; Dalgard et al., 2006; Wade and Kendler, 2000). Research evidence suggests that reduced availability of supportive relations with others may be "real" in terms of actual social isolation due to behaviors and traits that discourage sustained and helpful relations with others, such as introversion and behavioral inhibition (Gladstone and Parker, 2006) or poor social skills (Tse and Bond, 2004). Also, depressive states may result in negative and distorted cognitions about one's worthiness and perceptions of the unlikelihood of receiving effective help from others. Such perceptions may cause failure to seek help and support even if it does exist.

Personality Vulnerabilities

Space prevents the elaboration of the many candidates for personality traits and habits that might constitute vulnerability to depression, but we mention two factors that have received considerable recent attention: neuroticism and ruminative response style.

The construct of neuroticism has had a long history in psychology. Neuroticism is a higher order personality dimension, defined by negative emotionality and high reactivity to real and perceived stress. Neuroticism is a powerful predictor of depressive episodes, according to a review by Enns and Cox (1997; see also Fanous et al., 2002; Schmitz, Kugler, and Rollnik, 2003). Although the level of neuroticism may decline with reductions in depressive symptoms, recent longitudinal studies have supported the idea that relatively higher levels of neuroticism persist independent of depressive states (e.g., Clark et al., 2003; Kendler, Karkowski, and Prescott, 1999; Kendler and Karkowski-Shuman, 1997; Santor, Babgy, and Joffe, 1997). It is suggested that neuroticism may be one of the genetically transmitted traits that predisposes an individual to both stressful life events and depression, and to tendencies to respond to stressors with depression (Kendler et al., 1995; Kendler, Gardner, and Prescott, 2003). Kendler, Gardner, and Prescott (2003), for example, found that neuroticism was a strong predictor of stressful life events, particularly those related to interpersonal relationships. In other analyses, Kendler, Kuhn, and Prescott (2004) found that neuroticism moderated the effects of stress on depression, particularly potentiating its effects at the highest levels of stress exposure.

Neuroticism is highly correlated with trait anxiety (Watson and Clark, 1984), harm avoidance (Zuckerman and Cloninger, 1996), and measures of the behavioral inhibition system. Watson and Clark (1984) suggested that these are interchangeable measures of the same stable and pervasive trait, which they label *negative affectivity*. It is defined as the disposition to experience aversive emotional states, including nervousness, tension, worry, anger, scorn, revulsion, guilt, rejection, self-dissatisfaction, and sadness—especially in response to perceived stress.

A related construct, ruminative response style, refers to a cognitive and behavioral coping strategy, employed mainly by women, for responding to negative emotions, particularly dysphoria. Nolen-Hoeksema (1991) proposed that, when experiencing emotional distress, women display a response style that emphasizes rumination, self-focus, and overanalysis of the problem and excessive focus on their own emotions. In contrast, men use more distraction and problem resolution. When ruminative responses are employed, they tend to intensify negative, self-focused thinking and to interfere with active problem solving, hence deepening or prolonging the symptoms of depression. A series of studies has demonstrated support for these hypotheses, including gender differences in coping style and the association of ruminative coping with depression (e.g., Nolen-Hoeksema, Morrow, and Fredrickson, 1993; reviewed in Nolen-Hoeksema and Girgus, 1994; Nolen-Hoeksema, 2000).

Integrative Research

In view of the multiple biological, environmental, social, and personality risk factors for depression, research on risk for depression will be advanced by integrative, multivariable models that link biological factors with environmental and personal characteristics. To date, however, the field is marked mainly by complex models that have not been empirically evaluated or by empirical tests of fairly limited integrative models. Many of the theoretical models have been focused on a particular subtopic, such as predicting outcomes and their mechanisms in children of depressed parents (e.g., Goodman, 2007; Goodman and Gotlib, 1999) or gender differences in adolescent depression (Alloy and Abramson, 2007; Hankin and Abramson, 2001). Broader models linking stress, HPA axis, and neurocognitive as well as cognitive and interpersonal factors, for example, are urgently needed. Limited integrative empirical approaches that include biological factors are emerging, including complex quantitative genetic, environmental, and personal factors (e.g., Kendler, Gardner, and Prescott, 2002, 2006) and gene-environment analyses (e.g., Caspi et al., 2003). Studies that link neuroendocrine, stress, and social-cognitive factors are particularly needed.

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CO-OCCURRING DISORDERS

As this chapter has indicated, depression co-occurs with a host of stressful life events, early adversities, and ongoing strains, and it is also commonly associated with a variety of interpersonal difficulties and problematic traits and behavioral tendencies. A further complexity is introduced by the reality that depression typically does not occur in a "pure" form, independent of the effects of additional psychological disorders. In both the original U.S. National Comorbidity Study and the recent replication, of all the community residents who met the criteria for lifetime or 12-month major depression or both, approximately 75 percent had at least one other diagnosis, with only a minority having pure cases of depression (Kessler et al., 2003). For patients with a diagnosis of current major depression, only 40–45 percent had depression in isolation, and 60–65 percent had at least one comorbid diagnosis; similar rates have been reported in different countries (e.g., Blazer et al., 1994; De Graaf et al., 2002; Rush et al., 2005; Zimmerman, Chelminski, and McDermut, 2002).

Approximately 60 percent of comorbid disorders are anxiety disorders, particularly generalized anxiety disorder, panic disorder, social phobia, and posttraumatic stress disorders (Mineka, Watson, and Clark, 1998). Among patients with anxiety disorders, approximately 30 percent have a comorbid mood disorder (Brown et al., 2001). The onset of anxiety disorders typically precedes the onset of depression, with earlier-onset anxiety disorders (panic, social anxiety, generalized anxiety disorder) predicting the subsequent first onset of depression (Andrade et al., 2003; Kessler et al., 1996; Stein et al., 2001; but see Moffitt et al., 2007). So common is the overlap between depressive and anxiety disorders that some have argued that major depression and generalized anxiety disorder may virtually be the same disorder or closely associated, genetically mediated distress disorders (e.g., Kendler et al., 2007; Moffitt et al., 2007).

Besides anxiety disorders, substance abuse and alcoholism and eating disorders are frequently accompanied by depressive disorders, in both clinical and community samples (Rohde, Lewinsohn, and Seeley, 1991; Sanderson, Beck, and Beck, 1990; Swendsen and Merikangas, 2000). Several recent large epidemiological studies found rates of 25–30 percent for comorbid substance or alcohol abuse (Davis et al., 2005; Melartin et al., 2002). In their analysis of the origins of the comorbidity of substance use disorders, Swendsen and Merikangas (2000) considered whether they share a causal relationship (e.g., alcoholism causes depression or the reverse) or are related because of a shared etiological factor. Their data and review suggest a causal association, rather than shared etiology, for alcohol and depression, with evidence both for depression causing alcohol abuse and abuse causing depression. However, for other substance abuse, the patterns were inconsistent, suggesting that multiple mechanisms may be contributing to the comorbidity.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, not only are Axis I disorders (i.e., clinical disorders, including major mental disorders, as well as developmental and learning disorders) highly likely to co-occur with depression, but also personality disorders are more the rule than the exception with depressed patients. Personality disorders refer to a set of patterns of dysfunctional conduct and attitudes that start early in life, are persistent, and affect all areas of a person's functioning. Depending on the study, rates of personality disorders among depressed people range between 23 and 87 percent (Shea et al., 1990; Shea, Widiger, and Klein, 1992). Most studies have found that personality disorders in the "dramatic/erratic" cluster (such as borderline personality disorder) and in the "anxious/fearful" cluster (such as avoidant personality disorder) predominate (e.g., Alpert et al., 1997; Brieger, Ehrt, and Marneros, 2003; Rossi et al., 2001; Shea et al., 1990).

One of the crucial problems with depression co-occurrence with other disorders is that the combinations may greatly complicate both the clinical course of depression and the efficacy of typical treatments. For example, the presence of a comorbid anxiety disorder predicts a significantly worse course of depression and dysthymia (Brown et al., 1996; Gaynes et al., 1999; Shankman and Klein, 2002). Likewise, a comorbid personality disorder predicts a poorer outcome (Daley et al., 1999; Klein, 2003; Klein and Shih, 1998; see the review by Newton-Howes, Tyrer, and Johnson, 2006).

Depression is also a ubiquitous presence in medical illnesses, and a recent large depression treatment study (Sequence Treatment Alternatives to Relieve Depression: STAR*D) found that 53 percent of depressed patients had significant medical comorbidity (Yates et al., 2004). Serious acute and chronic diseases are highly stressful, and depression may be a reaction to the challenges associated with such problems; it can even result from the pathophysiological processes of certain diseases.

Of particular note is the role that depression may play as a contributor to ill health (Katon, 2003). For example, depression may interfere with healthy lifestyle choices, such as regular exercise, smoking cessation, good nutrition, and compliance with medical treatments; dysfunctional self-care behaviors may play a causal role in the onset of certain diseases or in the course of disease and recovery (e.g., Evans et al., 2005). Furthermore, as noted earlier, depression has been linked with inflammatory processes that underlie several major diseases. Depression is associated with biological abnormalities, such as insulin resistance and secretion of inflammatory cytokines, which might contribute to diabetes onset (Musselman et al., 2003). Depression has been shown to be a predictor of heart disease progression or death in longitudinal studies of both initially healthy patients or in follow-up after first heart attack (Frasure-Smith and Lesperance, 2003; Rugulies, 2002; Suls and Bunde, 2005). Depression with medical illness comorbidity is significantly more common among those with lower income, divorced or widowed, less educated, unemployed, and nonwhite (Yates et al., 2004), and it predicts longer and more frequent episodes of major depression.

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RESILIENCE AND PROTECTIVE FACTORS

The rich literature on biological, environmental, and personal risk factors for depression also indicates a striking finding: not all individuals who have been exposed to risk factors for depression develop the disorder. As a result, researchers have attempted to identify possible protective factors that serve as sources of resilience in the face of known risk. A protective factor is a feature of the individual or the environment that is associated with a decreased probability of the development of a disorder among individuals exposed to factors that increase risk for the disorder. Resilience refers to the processes through which individuals overcome risk factors and adverse conditions and achieve positive outcomes. Similar to risk research, the investigation of sources of resilience has included biological, environmental, and psychological processes. One of the challenges for researchers has been to avoid the pitfall of defining protective factors and processes of resilience as merely the absence of risk factors. That is, protective factors and evidence for resilience must be found in the presence of risk, not as a consequence of the absence of exposure to risk.

The resilience research literature has focused largely on children exposed to adverse environmental conditions, with relatively less study devoted to depression specifically. However, two key themes in the broader literature are important to note. One is that, across the range of resilience research over three decades, several variables appear universally to promote positive adaptation in children (Masten, 2007). Among these are secure attachment and connection to competent and caring adults and positive family systems (such as parental supervision), normal cognitive development and IQ, competent self-regulatory systems (including agreeable personality traits, effortful control of attention and impulses, healthy executive functioning), positive outlook and achievement motivation, and peer, school, and community systems that promote positive values and opportunities. The second theme in resilience science is an increasing emphasis on integrative, multilevel research on resilience in developing systems, drawing on biological, personality, cognitive, social, family, and environmental constructs that work together to promote adaptation and self-regulatory processes (Masten, 2007).

As specifically applied to resilience in the face of risk for developing depression, researchers have focused on biological factors, such as neuro-chemical, neuropeptide, and hormonal processes that mediate and moderate the relation between stress and depression (e.g., Charney, 2004; Davidson, 2003; Robbins,

2005; Southwick, Vythilingam, and Charney, 2005). For example, brain structure, brain function, and neurotransmitters related to the ability to sustain positive affect in the face of stress and adversity may be characteristic of individuals who are exposed to chronic stress but who do not develop depression. Dopamine levels in the prefrontal cortex and the nucleus accumbens; serotonin levels in the prefrontal cortex, amygdala, hippocampus, and dorsal raphe; and levels of neuropeptide-Y in several cortical and subcortical regions have been implicated as protective factors against the risk for depression (Charney, 2004; Southwick, Vythilingham, and Charney, 2005). Davidson et al. (2003) have shown that the relative activation of the left versus the right prefrontal cortex is related to the ability to not only dampen negative emotions but also to upregulate positive emotions.

In an interesting animal model of the role of controllable and uncontrollable stress, Amat et al. (2006) found that experience with controllable stressors early in development may have an effect on subsequent responses to uncontrollable stressors that have been implicated in learned helplessness and depression. These researchers found that initial experience with controllable stress blocks intense activation of serotonergic cells in the dorsal raphe nucleus that would typically be produced by uncontrollable stress. Furthermore, activity in the ventral medial prefrontal cortex (PFC) during initial controllable stress was required for the later protective effect to occur. This suggests that the ventral medial PFC is needed to process information about the controllability of stressors and to use such information to regulate responses to subsequent stressors. This finding is consistent with work by Davidson (2000) suggesting that the ventral medial PFC is involved in the representation of positive and negative affective states in the absence of immediately present incentives.

Research on biological processes related to resilience has been complemented by evidence for psychological and behavioral features of resilience—that is, research concerned with what resilient individuals think and do in response to exposure to risk factors that reduce the likelihood that they will develop depression. Research has examined the psychological processes that are linked to these underlying neurobiological processes. Resilient individuals are not passive respondents to stress and adversity. Rather, those who are resilient are able to bring into action a set of skills to regulate thoughts and emotions and engage in behaviors that can resolve controllable sources of stress. Active forms of coping are associated with resilience in response to controllable stressors. In contrast, accommodative or secondary control coping, including emotion regulation skills, are related to better outcomes in response to uncontrollable stress (Compas et al., 2001).

Cognitive reappraisal, or the ability to view a stressful or threatening situation in a more positive light, is an example of an emotion-regulation or coping process that is related to resilience to stress in adolescents and adults (e.g., Compas, Jaser, and Benson, 2008; Gross, 2001). The ability to use cognitive reappraisal to manage stress and emotions develops during adolescence along with the development of basic cognitive executive function skills. Cognitive reappraisal and other forms of secondary control coping skills, including acceptance and the ability to use positive activities as a form of distraction, are a source of resilience in adolescents of parents with a history of depression (Jaser et al., 2005).

In a further study of adolescents whose parents have a history of depression, good-quality parenting despite depression and having a non-depressed parent or other adult to turn to were found to predict resilient outcomes (Brennan, LeBrocque, and Hammen, 2003). Although limited, the research on resilience in the face of risk factors for depression points in the direction of early interventions to improve parenting and children's emotion regulation, and stress management as ways to reduce the negative impact of parental depression and other adverse conditions. Further integrative research on resilience mechanisms—as well as on interventions—is needed to support efforts to break the chain of intergenerational transmission of disorder and impairment.

Go to:

RESEARCH GAPS

Much is known about risk factors for depression, but further research is needed to test models of how multiple biological and psychosocial factors work together and to clarify the mechanisms by which stressful experiences lead to depressive reactions in individuals and in the family context. Similarly, the processes by which resilient outcomes occur despite exposure to parental depression and other adverse conditions are vastly complex, and research will benefit from developmentally sensitive and integrative models that can be tested over a longitudinal course. We need to know more about optimal timing and methods of intervention to prevent the development and escalation of depression in those at greatest risk—especially young people during their formative family and career years.

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CONCLUSION

Depression is highly prevalent and, for many, a chronic or recurring problem that interferes with work and family. It erodes the motivation, energy, and enjoyment needed to nurture and sustain marital, parenting, and social relationships. It is a disorder with many faces—starting at different ages, possibly chronic or waxing and waning, and typically mixed with a variety of other complicating problems, such as anxiety disorders, substance abuse, and behavioral disorders. It frequently occurs as a causal factor or contributor to medical illnesses. There is considerable information on depression prevalence and manifestations in the general population, but less information specifically about depression in adults who are parents and caregivers. However, it is clear that depression's negative and enduring effects on personal functioning also have adverse effects on those living with a depressed person. Children of depressed parents are at great risk for depression and maladjustment in academic, social, and intimate roles, and depressed parents have difficulty functioning effectively in their parenting and marital roles.

Risk factors and causal mechanisms involved in depression have implicated a wide range of biological (genetic, neurological, hormonal, and endocrinological) factors that may play a role in underlying vulnerability or in the processes by which stressors trigger depression in some people. Fundamentally, etiological models are diathesis-stress models, in which stressful experiences—whether early childhood trauma, acute recent life events, or ongoing chronic strains—trigger depression. Finding depression "genes"—or another simple chemical marker—is an illusory goal, and it is not likely to be of practical help in identifying those at risk. Depression will most commonly be found among those facing chronically stressful conditions, such as social disadvantage and distressed relationships or lack of supportive and intimate relationships. There are numerous individual characteristics that moderate or mediate the effects of stress on depression, including personality traits that reflect emotional reactivity and negativity, as well as styles of thinking about self and the world that emphasize beliefs about worthlessness, helplessness, and futility. Skills for coping with adversity that are passive, avoidant, and ineffective may perpetuate depression. Unraveling the complex and interlocking contributors to depression requires more integrative and long-term study than has yet been conducted or supported. Substantial gaps occur in the application of knowledge about etiology to the detection and early treatment of depression.

Because of depression's varying clinical manifestations and co-occurring mental health and medical conditions, its different symptom and course profiles, and its likelihood of recurrence, depression is very difficult to treat effectively in a universal way and over long periods of time. What may help a depressed teenage mother could be very different from what is needed by an adult depressed father—or by the same young woman after several bouts of major depression. Treatments or preventive interventions that are effective for reducing depressive symptoms may not resolve the underlying family or economic difficulties that

erode sustained mental health. Thus, no simple prescriptions for treatment or prevention are realistic, and different individuals and settings will need different but multifaceted, flexible, and long-term care that recognizes that depression affects the whole family and that supports recovery rather than cure.

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