Patients, clinicians, researchers, and the general public commonly assume that depression is inexorably intertwined with the material and social worlds of the person with depression. There can be little doubt that when bad things happen, people become distressed and unhappy. When very bad things happen, some people become clinically depressed. Once a person has developed depression, his or her social and material worlds are altered, often in adverse ways that compound and perpetuate the original problem, outlast the depressive episode, and perhaps contribute to future recurrences of the disorder. A better understanding of depression, its origins and long-term course, requires enlarging the scope of inquiry to take into account the interplay of social-environmental factors and life stress with depression over the course of an episode, as well as over the lifetime of the individual.

We begin this chapter with an overview of issues involving concepts and measures of life stress. This discussion provides a platform from which we then review research that addresses how life stress relates to onset of depression and subsequently how life stress is associated with the clinical course, lifetime course, and heterogeneity of depression. We focus on key theoretical debates, unresolved issues, and empirical gaps, along with the methodological implications for research on life stress and depression. We conclude with a discussion of directions for future research.

**CONCEPTUALIZATION AND MEASUREMENT OF LIFE STRESS**

Psychological stress represents an intuitively attractive and socially legitimated explanation for all varieties of unwanted emotional and physical conditions. Biases toward stress explanations confound research practices, permitting seemingly plausible but incorrect
results to be enthusiastically embraced and elude critical commentary. The challenge is to translate the potentially productive ideas about psychological stress into more precise concepts, definitions, and operational procedures, thereby preventing such biases and providing an appropriate empirical basis for scientific inquiry (Monroe & Slavich, 2007). We illustrate how these concerns can influence measurement practices in the next two sections.

**Self-Report Scales**

Research on life stress proliferated in the late 1960s and 1970s as a result of innovations in the assessment of life changes and the development of life event self-report checklists (Holmes & Rahe, 1967; Monroe & Yoder, in press). This novel approach promised the potential to measure stress in a standardized and objective manner and, in this format, to do so simply, with relatively little time, expense, or investigator effort.

Innovation and expediency, however, outweighed wisdom in the early development of these methods, and serious deficiencies in the self-report checklist approach became increasingly recognized. These deficiencies included the aforementioned potential bias of respondents to “explain away” (i.e., incorrectly attribute) their mental or medical problems to stress. However, the deficiencies also included the confounding between life events and symptoms of depression (e.g., inclusion of items such as change in sleeping and eating habits) and confounding between life events as consequences (as opposed to causes) of depression (e.g., trouble with boss, divorce, being fired from a job). With such approaches, too, it was difficult to accurately establish the objective severity of the event. Despite early recognition of these major limitations by some in the field (Brown, 1974; Paykel, 2001), as well as of the mounting evidence documenting other fundamental problems with self-report checklists (Dohrenwend, 2006), measures of this type continue to predominate in research on life stress and depression (Monroe, 2008).

**Interview-Based Systems**

Other investigators appreciated the promise of measuring stress by focusing on recent life events and developed methods for doing so with more scientifically sound procedures (Brown & Harris, 1978; Dohrenwend, 2006; Hammen, 1991; Paykel, 2001). Probably the most elaborate system for assessing, defining, and rating life stress is the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978). The LEDS incorporates explicit rules and operational criteria for defining acute and chronic stressors, for distinguishing between complex constellations of such stressors, and for rating these experiences using a comprehensive manual. This system provides “contextual ratings” for each life event, wherein the individual’s unique biographical circumstances are taken into account to evaluate the likely meaning of the event for that particular individual. The information from the interview can be presented in a separate meeting to independent raters who are blind to other clinical and study data and possible respondent biases. This is an important methodological procedure to prevent confounding of the severity ratings with depression status or with other known risk factors for depression (e.g., whether the person became depressed following the event or has other vulnerabilities for depression, such as a personal history of depression or family history of depression). The approach yields consensually agreed-upon objective ratings of the person’s recent life events and chronic difficulties that are informed by his or her biographical circumstances and not dependent on his or her perceptions of stress or current mental health status.
Alternative investigator-based systems have been developed that are consistent with the LEDS philosophy and that incorporate many of the same procedural advantages (Dohrenwend, 2006; Hammen, 1991; Paykel, 2001). Importantly, these investigator-based approaches have been found to be superior to self-report measures with respect to their psychometric properties, ability to control potential sources of bias, and capacity to predict depression (Brown & Harris, 1989; Hammen, 2005; Mazure, 1998; Paykel, 2003; Tennant, 2002). Given the resource-intensive nature of these systems, recent efforts have also been aimed at developing automated interviewing systems for assessing life stress (Slavich & Epel, 2010). These systems are not substitutes for intensive investigator-based procedures but rather are intended to combine the sophistication of an interview-based measure of stress with the simplicity of a self-report instrument. One such instrument, the Stress and Adversity Inventory (STRAIN), inquires about 96 different types of acute and chronic stress that are assessed by the LEDS. The online “interview” takes 25–35 minutes to complete and generates more than 115 stress exposure scores and life charts that summarize respondents’ exposure to stress over the lifespan (Slavich & Epel, 2010).

LIFE STRESS AND THE ONSET OF DEPRESSION

Reviews of research on life stress and depression unequivocally conclude that major life events precede the onset of many, if not most, depressive episodes. Depending on the type of sample under study (e.g., inpatient, outpatient, community cases), approximately 50–80% of individuals with depression report an acute, severe life event prior to onset (Brown & Harris, 1989; Hammen, 2005; Mazure, 1998; Paykel, 2003). A conservative estimate, based on a patient sample and restricted to events that are entirely independent of the person’s actions (“fateful” severe events), is that persons with depression have a 2.5-fold greater likelihood of having experienced a severe life event prior to onset compared with controls (Mazure, 1998; Shrout et al., 1989). A more liberal estimate based on a nonclinical sample raises the risk of depression onset following a severe life event severalfold (e.g., odds ratio of 9.38 for a first lifetime onset of depression; Kendler, Thornton, & Gardner, 2000). Most intriguing, multifactorial research that simultaneously evaluates a number of risk factors indicates that recent severe life events emerge as the most powerful indicator (Kendler, Gardner, & Prescott, 2002). Substantial evidence, too, indicates that these associations reflect causal influences for the onset of depression (Kendler & Gardner, 2010; Kendler, Karkowksi, & Prescott, 1999).

The Significance of Life Event Severity

It is important to emphasize that these findings are based on research involving acute, highly aversive life events occurring within about 3 months prior to onset of depression. In a review of more than 20 studies on the topic, Mazure (1998) observed that the consistency and strength of the association between life stress and depression is not simply a generic stress effect but is specifically related to “occurrences that are defined as undesirable, major life events” (p. 294; original emphasis). Kessler (1997) came to a similar conclusion, stating that “There is a consistently documented association between exposure to major stressful life events and subsequent onset of episodes of major depression” (p. 193). Kessler further noted that associations between life stress and depression are “generally stronger when ‘contextual’ measures are used rather than simple life event checklists” (p. 193).
One class of life events that has been found to be most strongly associated with depression onset is specifically termed “severe events” (Brown & Harris, 1978, 1989). These are major life events that are rated high on long-term contextual threat (i.e., events likely to have an enduring negative impact). This class of events represents intensely negative experiences, involving events such as serious threats to or losses of core relationships or occupations, acute adverse economic or health changes, humiliation and entrapment (Brown, Harris, & Hepworth, 1995; Kendler, Hettema, Butera, Gardner, & Prescott, 2003), and targeted rejection and social exclusion (Slavich, Thornton, Torres, Monroe, & Gotlib, 2009). Several studies have found that risk for depression increases dramatically for life events with the highest ratings on long-term contextual threat (see Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). As such, severe life events represent a very significant focal point for advancing theory and research (Kendler et al., 2002; Monroe & Hadjiyan-nakis, 2002).

Theoretical Debates, Unresolved Issues, and Empirical Gaps

The empirical picture is consistent and robust in demonstrating that many, if not most, individuals who develop an episode of major depression do so following a severe life event. What it might be about severe events in particular that potentiates the risk for depression, however, remains unclear. There are several issues for research that may help fill this gap.

Major Life Stress and Onset of Depression

Why is there a lack of interest in how this class of severe events is particularly strongly associated with onset of a depressive episode? Although there is great interest in the cognitive and biological correlates of stress, there has been relatively little specific interest or research using severe events as a focal point for investigating cognitive or biological aspects of depression (cf. Monroe, Slavich, Torres, & Gotlib, 2007b). Perhaps researchers in the field are inclined to interpret this finding as an obvious outcome; such an association makes convincing intuitive sense. Although many if not most people with depression (i.e., 50–80%) have had recent (i.e., pre-onset) severe life stress, only about 20% of individuals who are exposed to severe life events subsequently develop depression (Brown & Harris, 1978). Thus depression is not an obvious or normative outcome—it is a relatively infrequent one. Very little is known, too, about the 80% of people exposed to severe stressors who do not become depressed. Perhaps “stress” has been too readily embraced as a sufficient, self-contained explanation, without probing more deeply into the matter (Monroe, 2008).

One way to stimulate discussion would be for investigators to refine the types of severe events that are particularly virulent and often lead to depression. As indicated previously, research suggests that specific types of contextually rated adverse experiences are especially potent for precipitating a depressive episode. What might it be about this class of events that makes them so potentially depressogenic? Might there be contextual factors that are particularly influential (e.g., lack of support, past failures with similar experiences)? By deepening understanding of the psychological potency of these key markers for depression, it may help to elucidate the cognitive and biological consequences that collectively precipitate depression.

The “downstream” consequences and mediators of severe events represent other topics with potential to help understand why some people with these experiences become depressed whereas others do not. Although both psychosocial and biological approaches
VULNERABILITY, RISK, AND MODELS OF DEPRESSION

300

to depression invoke the importance of stress as a key mechanism translating environmental adversity into biological processes involved with depression, there is remarkably little research with severe events that attempts to link the two domains. What biological processes initiated by severe events might be important for initiating depression? Three promising areas of research involve regulation of the hypothalamic–pituitary–adrenal (HPA) axis, regulation of the immune system, and genetic influences.

Severe Life Events and the Biology of Depression

HPA-AXIS REGULATION.

One of the most consistently replicated biological findings in psychiatry is the overactivity of the HPA axis in patients with depression (see Goodwin & Jamison, 2007; Jarcho, Slavich, Tyllova-Stein, Wolkowitz, & Burke, 2013). At a general level, research on human life stress and the human neuroendocrine system appear to converge: One might expect cortisol, a major stress hormone, to be elevated in persons with depression suffering from recent major stress. Indeed, estimates of the proportion of the depressed samples reporting prior stress (50–80%) aligns nicely with the proportion of patients with HPA-axis dysregulation and excessively elevated cortisol levels (20–80%; Stetler & Miller, 2011). However, the literature on naturally occurring severe life events and HPA-axis function in depression provides little clarity on the matter (van Praag, de Kloet, & van Os, 2004). In fact, very few studies have directly examined the association between severe life events and cortisol function in patients with depression. At least one study reported cortisol to be elevated for persons with depression and with recent major stress (Dolan, Calloway, Fonagy, De Souza, & Wakeling, 1985). In contrast, at least one study reported HPA-axis dysfunction for persons with depression without recent stress (Roy, Pickar, Linnoila, Doran, & Paul, 1986). Other, more recent research also has yielded discrepant findings regarding cortisol’s relation to life events and depression onset (Hammen, 2005). Inconsistencies in this literature could be attributable to several factors, including differences across studies in how life stress was assessed, how HPA functioning was assessed, the types of individuals with depression who were sampled (e.g., community cases vs. inpatients), or in the timing of the index episode in the life course of the individual (e.g., first onset vs. fourth recurrence; Stetler & Miller, 2011).

Clarifying how severe life events and HPA-axis disturbances are related represents an obvious next step for research. For example, if individuals with a severe life event exhibit a more dysregulated pattern of HPA-axis functioning, is this due to continuation of the environmental stress or due to a centrally mediated “breakdown” in regulation of the HPA axis? Alternatively, if the high-stress group exhibits fewer HPA irregularities, conventional thinking on the stress–biology relations in depression would be challenged and require explanation. Because HPA-axis hyperactivity is often found to be greater among melancholic and endogenous subtypes of depression that often appear to report less stress, such an outcome is reasonable to entertain (Stetler & Miller, 2011). Given the theoretical importance of stress and cortisol, as well as the adverse effects of excessive cortisol on the brain structure and function, all possible contributing factors to HPA-axis overdrive merit exploration (Sapolsky, 2000).

IMMUNE SYSTEM FUNCTION AND INFLAMMATION

One of the most recent and potentially important insights on the biology of stress and depression concerns the recognition that components of the immune system involved in
inflammation may promote depression (Slavich & Irwin, in press). Although inflammation is typically thought of as the body’s primary response to tissue damage or bacterial infection, a large body of research has now accumulated demonstrating that stress can also trigger significant increases in systemic inflammatory activity (i.e., in the absence of illness or injury; Segerstrom & Miller, 2004). Markers of inflammation that have been found to be influenced by stress include the pro-inflammatory cytokines interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor-α, which are key mediators of inflammation, and C-reactive protein, a key biomarker of inflammation that is synthesized in the liver in response to IL-6. In addition, one study has also shown that recent severe life stress is associated with the activation of intracellular signaling pathways that regulate inflammation (Murphy, Slavich, Rohleder, & Miller, 2013). Levels of inflammation, in turn, have been found to be elevated in individuals with depression compared to those without depression (who are otherwise healthy; Dowlati et al., 2010). In addition, experimental studies in animal models and in humans have shown that immunological challenges that acutely upregulate inflammation (e.g., endotoxin administration) can evoke clinically significant episodes of depression (DellaGioia & Hannestad, 2010). As a result, there exists (at least in principle) a biologically plausible pathway by which life stress may evoke depression.

Given the recency of these findings, many unanswered questions remain. For example, does inflammation mediate the link between severe life stress and depression? Is inflammation relevant for all depressive symptoms or forms of depression, or only for certain symptoms or depressive subtypes? And are elevated levels of inflammation sufficient for onset of depression, or do other vulnerability factors need to be present for depression to occur? Given that inflammation has been implicated in a variety of physical disease conditions—including obesity, diabetes, arthritis, and cardiovascular disease—there also exists the possibility that inflammation may serve as a common biological mechanism linking stress with both major depression and other disorders that frequently co-occur with depression (Slavich & Irwin, 2014). However, much more research is needed to examine this hypothesis.

GENETIC FACTORS

One explanation for the fact that some people develop depression in the face of life stress whereas others do not involves specific vulnerability genes. Gene–environment research has become quite popular over the past decade, given advances in mapping of the human genome and the development of powerful molecular genetics techniques for detecting specific allelic variations in genes. In a landmark study, Caspi and colleagues (2003) reported that individuals with one or two copies of the short allele of the serotonin transporter gene (i.e., 5-HTTLPR) were especially susceptible to developing depression following stressful life events. As a result of these findings, a new generation of studies was spawned on life stress, genes, and depression.

Unfortunately, the majority of studies attempting to replicate the original study of Caspi and colleagues (2003) have used varied and often questionable procedures for assessing and defining life stress (Monroe & Reid, 2008). Recent reviews and meta-analyses arrive at opposing conclusions depending on how the quality of stress measurement is taken into consideration (Risch et al., 2009; Uher & McGuffin, 2010). At present, it appears that studies with high-quality stress measures that assess major (i.e., severe) life events often replicate the gene–environment interaction, whereas studies without such quality measures and indicators of stress do not (Karg, Burmeister, Shedden, &
Sen, 2011). Progress in gene–environment research will depend on proper specification of both the genetic and environmental components of the proposed interaction.

Although focusing on severe types of life events represents one promising approach for future research on life stress and depression, it begs the question of why some people become depressed without apparent major stress prior to onset. How are these cases to be explained? This next topic may be the singularly most pressing unresolved issue at the present time for research on life stress and depression.

Nonsevere Life Stress and Onset of Depression

Without question, not all people who become depressed do so following an acute, severe life event (Monroe & Harkness, 2011). Two lines of evidence substantiate this point: (1) major life stress does not always precede onset of a depressive episode, and (2) major life stress frequently precedes first or early lifetime episodes, and less often recurrences of depression. Specifically, it is estimated that about 20–50% of people with depression overall do not report recent severe stress and that an even greater percentage of people with recurrent episodes of depression do not report recent severe stress (Mazure, 1998; Monroe & Harkness, 2005). These data indicate that a substantial proportion of major depressive episodes cannot be accounted for by a severe life event.

In the absence of severe stress prior to onset of depression, investigators commonly have inferred that some individuals are especially sensitive to stress and, consequently, that less severe forms of stress trigger onset of depression for these highly vulnerable individuals (see Monroe & Harkness, 2005). Sensitization to stress can be conceptualized in terms of many factors, including influences of genes, early adversity, cognitive predisposition, and prior experiences of depression. For example, some people may be cognitively prone to perceive relatively benign or ambiguous life events as if the events were more severe (Abramson, Metalsky, & Alloy, 1989). A key assumption is that, for the complement of people who become depressed without a severe stress prior to onset of depression, some form of stress is still believed to be of causal importance, albeit at lower degrees of severity and in conjunction with particular vulnerabilities. This is a pivotal assumption, and to our knowledge an assumption that has not been addressed directly. It is also a very challenging assumption to test scientifically, and if the research is not properly conducted, progress could be impeded by inconsistent findings for years to come.

Unlike the situation concerning severe life events that are defined objectively by interview-based methods and for which there is a theoretically credible and empirically well-established reference point, no such clear reference point exists for life events that fall beneath this severity threshold. And the domain of nonsevere stress is vast. There are no guiding principles as to how to carve out the particular life events and chronic life conditions that might be capable of triggering depression in the purportedly predisposed. Most people have many stressors in their lives of varied types and levels of severity. People move, change jobs, make friends, lose friends, get raises, lose money, have altercations at home or at work, go on vacations, are robbed, become ill, renovate homes, have babies, get traffic tickets, have accidents, have pets that come and go, and so on. Respondents also are acquainted with many other people who may have similar experiences and may even have severe events (e.g., a brother’s divorce, a sister’s brain tumor, a best friend’s loss of work, a spouse fired from a job), all of which the respondents themselves may report upon, too. The sheer number of life events in people’s lives that are likely unrelated to depression almost certainly will compromise the ability to detect any meaningful
associations between nonsevere stress and depression. As a consequence, conceptualizations of stress in this nonsevere domain are generic, nonspecific, and inconsistent.

These conceptual shortcomings represent methodological obstacles for operationalizing nonsevere life stress. Without theoretical guidance, it will prove challenging to reliably unpack or meaningfully aggregate the flow of daily experiences involving nonsevere stressors, which vary in timing, degree, duration, and psychological content. The problem is compounded by the tendency of many researchers to opt for expedient methods and employ ad hoc measures that are neither reliable nor validated (Monroe & Reid, 2008). This situation could yield a patchwork of published findings that are loosely linked only by the most generic underlying notion of “stress.” One needs only to turn to the depression literature on life stress and the serotonin transporter gene to appreciate that these concerns are not unfounded (Monroe & Reid, 2008; Uher & McGuffin, 2010).

Promising leads have recently appeared that point to the potential of productively investigating nonsevere forms of stress in relation to heightened susceptibility to depression (e.g., Espejo et al., 2006; Hammen, Henry, & Daley, 2000; Kendler et al., 2005; Monroe et al., 2006; Slavich, Monroe, & Gotlib, 2011; Stroud, Davila, Hamm, & Vrshek-Schallhorn, 2011). Although these efforts are in the early stages of development, they have already demonstrated alternatives in how stress is conceptualized, assessed, and operationalized in relation to depression. Research on nonsevere forms of stress will require hard thinking to avoid soft measurement practices and ultimately unproductive outcomes. We discuss these matters further in the section titled “Future Directions.”

**When Stress Is Absent and Depression Occurs**

Not all people who become clinically depressed necessarily experience any changes in their life circumstances prior to onset. Furthermore, some of these people do not appear to have any detectable adversity—at all. In other words, people who do not have recent severe stress do not ipso facto have moderate or even necessarily even mild stress. Yet research practices have tended to treat them as such, as if they are hyperresponsive to stress. Depression for people without any detectable stress appears to come “out of the blue.” Such cases have a venerable clinical history but a correspondingly uneven research record with regard to validating a distinctive subtype of depression (see the upcoming subsection titled “Life Stress and Subtypes of Depression”). The field may have mistakenly forced some cases of depression to fit within a stress framework. Biases toward invoking stress foster creative thinking about how moderate or relatively minor experiences “could” have major consequences for highly sensitized individuals. Inclusion of cases without any stress in research, too, would impede the ability of the study design to detect stress sensitization. Stress in its absence may represent as important a finding and useful focal point for enlarging understanding of depression as is severe life stress (Monroe & Reid, 2009).

It is likely, though, that after examining the preceding discussion, many readers will conjure up thoughts of how a pleasant vacation, a nice raise in pay (without added effort or responsibilities), or a child graduating from the eighth grade (and/or all three) just might work its inimical way into some predisposed person’s psyche and set the stage for depression’s onset. (Or perhaps a severe event went undetected. Or perhaps it was the stress of boredom reflected by no events whatsoever. Perhaps . . .) We hope readers will give equal and impartial thought to how unproductive such extended and unbounded mental meanderings to resurrect stress explanations might be and to how prone we may be to think along such lines.
A general challenge facing depression researchers is how to explain why individuals with depression often exhibit such varied constellations of signs and symptoms and why only some individuals have a persistent, or recurrent, long-term course. A full account of depression should be capable of explaining these core questions. These concerns are the subject of studies of: (1) symptom severity, symptom profiles, and depression subtypes; and (2) the course of depression over an episode and a lifetime.

**Life Stress, Symptom Severity, Symptom Profiles, and Depression Subtypes**

**Life Stress, Symptom Severity, and Symptom Profiles**

People with depression with recent severe stress prior to onset of depression have greater levels of depressive symptoms compared to people with depression without such stress (e.g., Monroe, Harkness, Simons, & Thase, 2001; Muscatell, Slavich, Monroe, & Gotlib, 2009; Tennant, 2002). Research suggests that stress-severity associations often hold for symptoms assessed with the Beck Depression Inventory (BDI; Beck et al., 1988), but not for symptoms assessed with the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Due to the different loadings of cognitive (BDI) versus somatic (HRSD) symptoms on these two instruments, the findings suggest some degree of symptom specificity.

Monroe and colleagues (2001) found life stress to be associated principally with cognitive-affective symptoms. Across different assessment methods, there also was a consistent positive association between severe life events and suicidal ideation. Muscatell and colleagues (2009) examined both acute and chronic stressors in relation to BDI scores in a sample of participants with depression. They found that the acute, severe events predicted symptom severity in general and, more specifically, severity of cognitive and somatic symptoms (as well as lower levels of global functioning); importantly, chronic difficulties were not predictive of the current depressive symptomatology. Overall, research on life stress and the symptoms of depression is relatively sparse. However, existing work suggests that it may be a useful approach for clarifying the role of life stress in the expression of depression and more generally in explaining some of the heterogeneity of depressive signs and symptoms.

**Life Stress and Subtypes of Depression**

Historically, many early accounts of depression refer to a syndrome of “sadness without reason” (Klibansky, Panofsky, & Saxl, 1979; Monroe & Depue, 1991). Kraepelin (1921) suggested that some forms of depression “may be to an astonishing degree largely independent of external influences” (p. 181, italics in the original). Still others, invoking similar concepts, employ terms such as excessive depression, unjustified depression, and depression disproportionate to causative factors (Jackson, 1986, p. 316). All of these observations reflect the same central theme that some forms of depression appear to arise independent of social circumstances and life stress. As a result of these ideas, it is often assumed that an “endogenous” or “melancholic” subtype of depression exists that is fundamentally biologically driven, arising unconnected with environmental circumstances. This type of depression is typically contrasted with depressions that are presumed to
result from adverse social circumstances, indicative of a separate “reactive” form of the disorder (Jackson, 1986).

Several reviews of the literature from the past 25 years have indicated that life stress is more commonly present prior to the onset of almost any depressive subtype based on symptomatic differences (relative to the rate for nondepressed populations; Mazure, 1998). Some of these studies also suggest that there is a weak relationship between life stress and a particular depressive subtype (Mazure, 1998; Monroe & Depue, 1991; Tennant, 2002). Although most recent attempts to validate the endogenous or melancholic subtype have not provided promising leads (Hadzi-Pavlovic & Boyce, 2012; Wakefield, 2012), these questions have typically been posed without due attention to the lifetime course of depression. There are good reasons to suspect that by taking into account the lifetime course of depression (rather than focusing on the “index” episode), greater clarity regarding life stress and depressive subtypes might be attained (e.g., Brown, Harris, & Hepworth, 1994; Monroe & Harkness, 2005). We examine this topic further in the next section.

**Life Stress and Clinical Course of Depression**

A number of studies have examined associations between life stress, the short-term course of a depressive episode, and the long-term course of the disorder over a lifetime. Whereas research on life stress and onset of depression has one focal point (i.e., onset), research on life stress and the clinical and life course of depression has many points of interest over time (e.g., remission, relapse, recurrence, chronicity). And whereas the timing of life stress with regard to depression onset is fixed by the nature of the question (i.e., stress precedes onset), questions about the clinical course of a depressive episode involve ongoing stress at any point in time, pre- and post-onset. In contrast to the large literature on stress and depression onset, research on these related topics in relation to life stress is sparse. Although relatively unexplored, these topics could have great clinical utility and potential theoretical value.

**Recovery**

Given that major stress often precedes onset of a depressive episode, the question arises as to whether or not such circumstances might have prognostic utility with regard to differences in timing or rates of recovery. Although some research has addressed this topic, the variability in methods and the heterogeneity of depressed populations involved complicates the picture. Methodological differences in the timing of life stress (e.g., pre-onset vs. post-onset), the type of life stress (e.g., severe life events vs. other indices of stress), the population of participants studied (e.g., first onset, recurrences, severity, age), and treatment status (e.g., natural course, psychotherapy, pharmacotherapy) contribute to the discrepant findings.

With regard to time to recovery, some research suggests a more rapid resolution of depression following recent pre-onset stress (e.g., Kendler, Walters, & Kessler, 1997; Parker & Blignault, 1985), whereas other research suggests a slower response time to remission (Karp et al., 1993). With respect to life stress after onset, major life events exacerbate symptomatology (Brown & Harris, 1978), and recovery can be delayed considerably when stressors occur during treatment (e.g., Monroe, Roberts, Kupfer, & Frank, 1996). Again, however, caution is warranted owing to the relatively few studies on the topic and the diversity of methods, definitions, designs, and patient samples employed.
Research on life stress and the overall likelihood of eventual recovery has been somewhat more plentiful, but not necessarily more consistent. Some studies report that life events prior to onset forecast a better clinical prognosis, yet other studies suggest a worse outcome (Mazure, 1998; Paykel, 2003; Tennant, 2002). Major events occurring during the course of the episode may interfere with recovery (Mazure, 1998). Some of the discrepancies in this literature again are likely due to differences in methods and populations studied. For example, some studies suggest that life stress prior to onset forecasts a lower likelihood of recovery for people with severe forms of depression (e.g., recurrent depression) compared with those with less severe forms (e.g., first onset; Monroe et al., 1996). Also, although the presence of chronic stressors has rarely been taken into account (Hammen, 2005), such stressors have been found to impair improvement and make timely recovery less likely (Brown & Rosellini, 2011; Tennant, 2002). Overall, many questions about pre-onset events, chronic stressors, and the clinical course of depression remain unanswered, whereas there is more consistency about the adverse effects of concurrent stressors on overall recovery.

Relapse

Once recovery is attained, the person with a history of depression is at high risk for developing depression again. When this happens shortly following recovery, it is assumed that the person is slipping back into the prior episode (Monroe & Harkness, 2011). Can life stress help to explain why some individuals relapse whereas others do not during this vulnerable period? For example, does a stress-related episode imply that, while recovering, the psychobiological system is more or less susceptible to depression reemerging? Or can stress occurring after onset of depression be a factor in falling back into depression? With regard to pre-onset stressors, the evidence is once again mixed (Mazure, 1998; Paykel, 2003; Tennant, 2002). Life stress prior to the onset of a depressive episode, though, may forecast continuing stress, particularly given that persons with depression often generate life events (even when not actively depressed; Hammen, 2005). Thus the continuation of pre-onset stressors, the occurrence of new stressors, or the presence of chronic stressors all could be factors in promoting relapse. Research to date has not taken into consideration these different processes over time, even though such information could be of considerable clinical and theoretical value.

Recurrence

Over the past 25 years, attention to the long-term course of depression has shifted from the periphery to the center stage of clinical and research interest. Previously viewed as an acute, time-limited condition, major depression is presently seen as a recurrent, persistent disorder over the life course. For example, in the recently released DSM-5 (American Psychiatric Association, 2013), it is stated, “A diagnosis based on a single episode is possible, although the disorder is a recurrent one in the majority of cases” (p. 155).

The latest research, however, suggests that the pendulum has swung too far toward viewing depression as primarily a recurrent condition (Monroe & Harkness, 2011). Recent longitudinal research on population-based samples indicates that approximately 50%, perhaps up to 60%, of individuals who become depressed for the first time never suffer another episode and certainly do not suffer a lifetime riven by repeated recurrences (Eaton et al., 2008; Moffitt et al., 2010). One of the most intriguing questions and major gaps in the literature pertains to the role of life stress in relation to these two dramatically
different trajectories over the life course for people who develop depression for the first time.

A consistent finding from research on life stress and recurrence of depression is that major life events precede onset of initial and early lifetime episodes more commonly than later recurrences of depression (Monroe & Harkness, 2005; Monroe, Slavich, Torres, & Gotlib, 2007a; Stroud, Davila, & Moyer, 2008). Post (1992) proposed the “kindling” hypothesis to explain these observations, arguing that the relations of major stress to subsequent episodes of depression changes over time, such that progressively less severe doses of stress are required to bring about onset. Eventually, after many episodes, recurrences may appear spontaneously, independent of psychosocial origins. These intriguing ideas are derived from animal laboratory studies on electrophysiological kindling and behavioral sensitization, paradigms that demonstrate the plausibility of transitions from precipitated episodes to episodes apparently arising independent, or autonomous, of the original triggering stimulus conditions.

Awareness that depression is not always a chronic and recurrent condition and that major stress plays a different role in the initiation of first episodes versus recurrences raises intriguing questions and reveals important gaps in our understanding of these complex matters. These two issues, also, are intertwined with the previously discussed concepts and concerns regarding measurement of nonsevere life stress. We turn to these timely topics next.

**THEORETICAL DEBATES, UNRESOLVED ISSUES, AND EMPIRICAL GAPS**

As noted, the emphasis upon recurrence and chronicity of depression over the past decades has diverted attention from the corollary statistic indicating that not all incident cases of depression are followed by recurrences (minimum estimates, 40–50%), and, indeed, perhaps even the majority of people who become depressed for the first time never suffer a recurrence (maximum estimate, 60%). This realization points directly to a very important empirical gap: Who are these people who become depressed once, but apparently never again? How can someone who is proven to be capable of depression escape further episodes? How might these people with a single lifetime episode of depression differ from less fortunate individuals who experience an initial episode but who go on to suffer multiple recurrences (Monroe & Harkness, 2011)?

One obvious empirical gap pertains to possible initial difference between these two groups, particularly with regard to life stress. Might they differ in terms of the type or degree of stress prior to the initial onset? Might they differ in terms of ongoing stressors that are not resolved and that perpetuate problems or propagate new problems (Hammen, 2006)? Or might they differ in terms of early adversity and genetics (Brown, 2012; Brown & Harris, 2008)? It would appear that life stress, in its presence or absence, may be a key component for beginning to understand why some people may have but one lifetime episode and others many.

Another theoretical distinction and unresolved issue complicates this quest to understand differences between those who are recurrence prone and those who are not at the time of their first lifetime onset of depression. This concerns what the “changing role” of life stress over repeated recurrences signifies. Because almost all research on this topic has been cross-sectional, two interpretations currently are tenable: (1) A person becomes more and more susceptible to stress and recurrences with repeated stress and recurrences...
VULNERABILITY, RISK, AND MODELS OF DEPRESSION

of depression; and (2) a recurrence-prone person develops depression for the first and subsequent episodes without any major stress (and may or may not require nonsevere stress to develop depression again). With regard to the latter hypothesis, the role of major stress appears to change only as these recurrent-prone cases become increasingly represented in the recurrence distribution as lifetime total number of recurrences rises. In essence, this hypothesis maintains that there is a distinct recurrent subtype of depression that is detectable very early on in the life course of depression and that stress—either in its presence or absence—may be an important tool for detecting individuals with and without high propensity to recurrence (Burcusa & Iacono, 2007; Monroe & Harkness, 2011).

FUTURE DIRECTIONS, QUESTIONS, AND RECOMMENDATIONS

Life stress can play many roles in furthering understanding of the origins and course of major depression. Given the numerous possibilities, what might be the best way to prioritize the future research agenda? We suggest that new insights are most likely to be gained with a continued focus on severe life events. By using these types of experiences as a cornerstone for research, the role of stress and its importance in the context of other risk factors can be systematically probed in relation to the causes, consequences, and long-term course of major depression.

With respect to etiology, it is firmly established that major, severe life events represent one of the strongest available indicators of an impending depressive episode. The risk of depression increases dramatically at the highest levels of ratings for long-term contextual threat. There are reasonably well-established procedures available for defining and assessing these potentially uniquely informative types of stress. Although these interview-based assessment procedures are more costly in terms of labor, time, and expense, they are indispensable. It does not make scientific sense to adopt unreliable methods simply for the sake of expediency. (Otherwise, the research literature would be awash with self-report measures of genetic polymorphisms, amygdala activity, HPA-axis function, and so on!) Investigators interested in the causes of depression and its recurrences are well advised to use this empirical reference point in developing better models of the causes of depression.

For example, there are many risk factors for depression that need to be integrated with the findings on severe life events. We suspect that individual differences in, for instance, genetic predisposition, early adversity, cognitive vulnerability, personality, and social support will be of great value in explaining why some people develop depression following a severe life event and others do not. But if investigators in these related areas are interested in life stress, it is very important to evaluate their predictions in the specific context of severe life events first (before turning to less well-established stress indices such as moderate or minor stressors). The current debates about gene–environment interactions with the serotonin transporter polymorphisms might have been avoided had such a recommendation been adopted initially (Karg et al., 2011; Risch et al., 2009; Uber & McGuffin, 2010).

Adopting such integrative approaches with severe life events can help address contemporary questions about multicausality and concerns about the heterogeneity of major depression. How the different risk indicators “go with” severe events can inform investigators about the additive or multiplicative nature of the proposed models (Kendler & Eaves, 1986; Monroe & Simons, 1991). For example, are genetic or family history factors
more or less influential given the presence of a severe life event (Monroe, Slavich, & Gotlib, 2014)? Do cognitive vulnerabilities “build on” a severe event to distinguish those who go on to develop depression, or does greater cognitive vulnerability amplify lower degrees of stress to cause depression (Abramson et al., 1989)? Is HPA-axis dysregulation during an episode of depression characteristic of people who do or do not have a severe life event prior to onset? Does the role of severe life events change over successive episodes of depression, or is there a distinctive recurrent subtype in which people becomes depressed independent of life stress (Burcusa & Iacono, 2007; Monroe & Harkness, 2011)? These questions, guided by a focus on severe life events, we believe are of pressing importance and in theory can be addressed in the coming years.

We view severe events as the bright side of current stress theory and research in depression, the best present starting point from which to move forward. But obviously there is much more to “stress” than severe events, and, as we have emphasized, not all persons with depression have experienced severe life events just prior to onset of their condition. A core challenge remains in explaining depression’s origins for people who do not have a severe event prior to onset. This is where the empirical literature on severe stress leaves off and the theoretical premise of stress sensitization fills in.

Nonsevere forms of stress currently represent the dark side of stress theory and research in depression. Can moderate or low levels of stress contribute to the onset of a depressive episode? Might such forms of stress be particularly relevant for recurrences? There is optimism about what stress sensitization has to offer the field, and there are promising leads. But at present, theory on stress sensitization and nonsevere forms of stress for individuals with depression has been presumed more than affirmed. The framework of ideas involved has not been fully articulated or scrutinized, and the methods required to test them have not been sufficiently developed. As a consequence, nonsevere forms of stress are dark in the sense that they are relatively unknown, but also in the sense that there is something vaguely foreboding about them.

As we have indicated, a major challenge is how to extract the potentially nonsevere forms of stress from the “sea” of stress that might contribute to onset of a depressive episode. One place to start would be to take clues from the literature on severe life events and prioritize life events of lesser magnitude that possess similar potentially depressogenic themes for the participant. For example, there are a number of experiences that are consistent with a depressogenic motif, events that might harbor particular meanings of relevance for depression (e.g., loss, hopelessness, humiliation, interpersonal rejection; Abramson et al., 1989; Beck, 1983; Brown & Harris, 1978; Slavich et al., 2009). Life events that are “fateful,” that are beyond the control of the individual, also may be of particular interest (Monroe et al., 2006; Shrout et al., 1989). But there are likely to be other substantial methodological issues for researchers to attend to and work through that do not translate directly from the research on severe life events. For example, the time scale for an event to trigger a depressive episode might well differ between severe and nonsevere life events (e.g., if sensitized, it is plausible that the depression would develop more quickly and implausible that an event 3 months prior would suddenly trigger an episode). Perhaps most foreboding, though, are questions about the limits of stress sensitization. At what point, under what circumstances, and for which people with depression might researchers refute or abandon the premise?

Stress sensitization represents a theoretical premise that could be important for understanding depression and its recurrences and worthy of continued research. Indeed, one of the most promising lines of future research on stress sensitization and depression involves identifying the range of mechanisms at different levels of analysis (e.g., neural,
physiological, molecular, genomic) that may become aberrant and underpin depressive symptoms, either in the face of minor stressors or, perhaps, in the absence of detectable life stress altogether (Cuthbert & Insel, 2013; Sanislow et al., 2010; Slavich & Irwin, 2014). Given the conceptual and practical challenges for conducting research on this topic just noted, however, investigators should be circumspect and proceed with caution.

In light of some 35 years of research documenting the special role of severe life events in relation to the onset of depression (Brown & Harris, 1978), we recommend that researchers maintain an active focus centered on these types of stressors. We hope that important advances may come from attention to severe life events as a window into the lives of persons with depression and a reference point for understanding the collective processes via which depression may take hold.

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