STRESS AND ITS SEQUELAE: DEPRESSION, SUICIDE, INFLAMMATION, AND PHYSICAL ILLNESS

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Life stress is a central construct in many contemporary models of mental and physical health. Consistent with these formulations, a large corpus of research has demonstrated that stress plays an influential role in the onset, maintenance, and recurrence of psychiatric illness, as well as in several major physical health problems that cause substantial morbidity and mortality (Cohen, Janicki-Deverts, & Miller, 2007; Harkness & Monroe, 2016; Kendler, Karkowski, & Prescott, 1999; Slavich, 2016b). In this chapter, we summarize key studies on these important topics with a focus on well-documented effects and lingering conceptual and methodological issues.

To accomplish these goals, we first summarize how stress has been conceptualized and assessed over the years. Second, we review links between different types of stress exposure and depression, focusing on contemporary models of these associations and hypothesized subtypes of depression. Third, we discuss research linking stress with suicidal thoughts and behaviors. Fourth, we examine recent theories and research on how stress increases risk for both depression and physical illness, with a focus on neural and immune system processes that might underlie these effects. Fifth, we describe new integrated theories of stress, depression, and physical illness that aim to provide a more complete account of the multilevel mechanisms underlying these associations. Finally, we provide some thoughts on future directions and concluding comments.

METHODOLOGICAL ISSUES IN THE ASSESSMENT OF STRESS

Although there is little debate about whether stress should be accorded a central role in etiological models of disease, many questions remain regarding how to best operationalize and assess life stress. Over the past century, researchers have relied most heavily on self-report checklist measures of stress that have advantages but also several limitations. As a result of these limitations, investigators began using interview-based systems to assess life stress that yield extensive information about the different contextual features of reported stressors. These stress assessment methods have been reviewed in detail elsewhere (e.g., Cohen, Kessler, & Gordon, 1997; Dohrenwend, 2006; Hammen, 2016; Harkness & Monroe, 2016; Monroe, 2008; Monroe & Slavich, 2016; Slavich, 2016a). Here, therefore, we provide only a brief overview of contemporary methods for assessing stress, first focusing on self-report checklist measures and then focusing on interview-based systems.

Self-Report Checklist Measures of Life Stress

The vast majority of studies on stress and health have used checklist measures of stress, which generally ask respondents to identify whether they have experienced a variety of typical stressors that may occur in the context of one's life. Sometimes these measures also assess the timing or perceived severity

of such exposures. These measures are expedient, inexpensive, and easy to administer, which has contributed to their widespread proliferation. Commonly used checklists for assessing stress in adults include the Social Readjustment and Rating Scale (Rahe, 1978), Life Experiences Survey (Sarason & Johnson, 1976), and List of Threatening Experiences (Brugha & Cragg, 1990). The Social Readjustment and Rating Scale inquires about a person's exposure to 42 different life events, and each event has a life change unit assigned to it that indicates the amount of stress experienced. The checklist thus attempts to objectively weight life events and to account for individual differences in stress reporting by assigning a life change (i.e., impact) score for each life event assessed. In contrast, the Life Experiences Survey provides a more extensive index of 60 life events, and relative to other checklists, there is greater item specificity, which reduces item ambiguity. This measure also includes criteria to guide respondents in determining whether a stressor is considered a life event, which reduces the likelihood of nonsignificant life events getting counted. Finally, the List of Threatening Experiences includes only 12 life events. The stressors assessed span several life domains (e.g., illness or injury, unemployment, financial problems, death), and they were selected given their known impact on psychological outcomes. The measure is thus very brief and, consequently, has been used in many studies to examine associations between stress and health.

A broader variety of self-report checklist measures have been used to assess stress in youth. The most commonly used measures include the Adolescent Perceived Events Scale (Grant, Compas, Thurm, McMahon, & Gipson, 2004) and Life Events Questionnaire (Coddington, 1972), which capture both positive and negative life events. Other frequently used scales that are more idiosyncratic in nature are the Adolescent Stress Questionnaire (Byrne, Byrne, & Reinhart, 1995; Byrne & Mazanov, 2002) and the Adolescent Life Change Event Scale (Waaktaar, Borge, Fundingsrud, Christie, & Torgersen, 2004). These measures are scored in a variety of different ways. Whereas some researchers have focused on the total number of negative life events that a person endorses on the checklist, others have

focused on the subjective impact of these stressors, as indexed by either the average or the total sum of the perceived severity of all self-reported stressors. Considered together, these instruments have been found to exhibit reasonable psychometric properties as assessed with test–retest reliability and concurrent validity (Grant et al., 2004; Hammen, 2009).

Although self-report checklist measures are appealing given that they are inexpensive and quick to administer, researchers have identified several limitations that influence the types of research question that can be addressed using such instruments. These limitations include three key problems. First, self-report checklist measures do not provide respondents with adequate instructions for knowing what life stressors have sufficient impact so as to meet the severity threshold for being defined as a life stressor (e.g., as opposed to a daily hassle). In addition, typical self-report checklist items do not provide adequate contextual descriptions of stressors; consequently, interpretations of the same stressor can vary widely between participants. When combined, these two factors lead to *intracategory variability*, which occurs when a variety of different stressors may be reflected in each type of stressor category (e.g., cancer diagnosis and a broken toe both counting as a recent major health event). This blurring of operational boundaries causes respondents to report major life stressors as minor stressors and, conversely, minor life stressors as major ones, which can in turn lead to inaccurate or misleading results (Dohrenwend, 2006).

Second, a substantial body of work has shown that there is a poor concurrence between respondent- and investigator-defined life stressors (Gorman, 1993; Harkness & Monroe, 2016; Lewinsohn, Rohde, & Gau, 2003; McQuaid et al., 1992; Monroe, 2008). Most problematic is the fact that many checklist measures confound stressful life events with the psychiatric outcomes being investigated (e.g., changes in sleep or eating behavior). Moreover, because checklist measures are not sensitive to the exact timing of when life stressors occur, they usually cannot unpack whether an endorsed stressor is the cause versus the consequence of psychiatric illness (Monroe, Slavich, & Georgiades, 2014). Stress exposure and psychiatric symptoms might still be strongly correlated under

such circumstances, but that does not mean that the stress exposure caused the change in symptoms, which is frequently what investigators aim to demonstrate.

Third, many studies have now demonstrated that not all life stressors are created equal with respect to their impact on health (Hammen, 2005; Monroe & Slavich, 2016; Slavich, 2016a). Because of the methodological limitations described above, however, checklist measures are not sufficiently sensitive to enable investigators to study these effects or to make the types of fine-grained distinctions that would improve theory and advance the field. In the context of depression research, for example, interpersonal and noninterpersonal stressors are frequently combined into one overall index of stress exposure, but several studies have shown that these stressors can have very different effects (e.g., Brown, Harris, & Hepworth, 1995; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Slavich, Thornton, Torres, Monroe, & Gotlib, 2009). Depression research has also generally treated stressful life events that are dependent on an individual's characteristics or behavior (e.g., an argument with a friend) and independent of one's behavior (i.e., a fateful event; e.g., spouse illness, death of family member) as being conceptually equal, but this distinction may also be critical for understanding certain aspects of depression (e.g., Gershon et al., 2011; Harkness & Stewart, 2009; see Liu & Alloy, 2010). The point is that because the items on self-report checklist measures do not include sufficient contextual information for distinguishing between different types of stressors, these measures are not well equipped to address questions about stressor specificity. Ultimately, then, self-report checklist measures may still be useful—especially for assessing perceived stress—but as Harkness and Monroe (2016) described in detail, investigators must frame their research questions and intent in a manner that is consistent with the known limitations of these instruments.

Interview-Based Systems for Assessing Life Stress

To address limitations associated with self-report checklist measures, some researchers have developed rigorous interview-based measures of stress that yield higher quality data (Brown & Harris, 1978; Dohrenwend, 2006; Hammen, 1991). Although there are differences among these interviews, they generally use a semistructured approach to obtain extensive contextual information about each life stressor experienced and pertinent biographical details of the respondent. This information enables investigators to more accurately assess the meaning of a stressful life event for a particular person and the probable impact of the stressor on the person's life. Whereas self-report checklist measures suffer from definitional ambiguity, interview-based approaches often rely on elaborate and highly detailed life stress rating manuals, which codify the assessment approach and scoring criteria and provide clear operational definitions about what qualifies as a stressful life event or chronic difficulty. These manuals thus ensure consistency across assessments and systematize the rating of life stressors across the key dimensions mentioned previously (e.g., interpersonal vs. noninterpersonal stressors; dependent vs. independent stressors).

Presently, there are a number of different interview-based systems for assessing life stress. Several of these systems rely on an interviewer-scored approach in which the interviewer determines the nature of the stressors experienced and their objective severity or impact on the respondent's life. These systems include the Structured Life Events Inventory (Wetherington, Kessler, & Brown, 1993), Kendler Life Stress Interview (Kendler et al., 1995), Brief Life Event List (Paykel, 1997), and the UCLA Life Stress Interview (Hammen, 1991).

To add an additional layer of objectivity and independence to the stressor ratings, other systems have been developed that use a two-step process in which an interviewer first obtains extensive contextual information about each life stressor that a person experienced over the past 1 to 2 years, including how the stressor unfolded, whether the stressor was expected or unexpected, what resources were available, what other stressors the individual was concurrently experiencing, and whether the person previously experienced similar stressors. Then, after the interview is finished, the interviewer presents a detailed life stress narrative that includes

facts surrounding each reported stressor and relevant biographical details of the respondent to an independent team of raters who are blind to factors that could bias the ratings, such as how the respondent reacted emotionally to the stressor (e.g., with excessive tears or emotional distress) and his or her clinical status (e.g., psychiatric diagnoses, depressive symptoms). The goal of the rating team, in turn, is to determine the objective impact of each stressor, defined as how a typical person would experience the stressor given the same contextual details and biographical characteristics (Hammen, 2009). This two-step, idiographic, person-centered approach to assessing stress enables investigators to extract the meaning of each reported stressor for a particular individual, as well as to obtain an objective consensus rating of each stressor's severity, focus, independence, life domain, and social-psychological features (Monroe, Slavich, & Georgiades, 2014; Slavich, 2016a). Examples of this labor-intensive, two-step approach to assessing life stress include the Life Events and Difficulties Schedule (Brown & Harris, 1978), UCLA Life Stress Interview (Hammen, 1991), Standardized Event Rating System (Dohrenwend, Raphael, Schwartz, Stueve, & Skodol, 1993), and Stressful Life Events and Difficulties Interview (Leserman, 2003). When the self-report, interviewer-rated, and independent rater–scored assessment approaches are compared, the independent rater–scored method exhibits better psychometric properties than the interviewer-rated method, and both of these methods outperform the self-report checklist approach (Kendler et al., 1995; Paykel, 1983).

Online Systems for Assessing Lifetime Stress Exposure

Although interview-based systems for assessing stress have numerous advantages, they are extremely time intensive and costly. In addition, given the immense amount of time that it takes to identify, summarize, present, and rate every stressor, these systems are typically used to assess stress exposure that occurs only over short periods of time (e.g., past 1–2 years), even though many contemporary models posit that stressors that occur across the entire life course can exert a cumulative impact on

mental and physical health (Graham, Christian, & Kiecolt-Glaser, 2006; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 1998; Seo, Tsou, Ansell, Potenza, & Sinha, 2014; Slavich & Cole, 2013). To address these issues, researchers have recently developed automated systems for assessing stress that span the entire life course and that can be either self- or interviewer administered. Specifically, the Stress and Adversity Inventory (STRAIN) consists of an extensive online interview that queries about 55 different types of acute and chronic stressors that are known to affect health. There is an Adolescent STRAIN and an Adult STRAIN, and each interview takes 18 to 25 minutes to complete. Once an interview is completed, the system produces more than 115 stress exposure scores and life charts that summarize a respondent's exposure to many different types of stress. Given the high-resolution nature of the data generated, scores from the STRAIN have been shown to predict mental and physical health complaints in the general population (e.g., Shields, Moons, & Slavich, 2017; Slavich & Shields, in press; Toussaint, Shields, Dorn, & Slavich, 2016), as well as clinical outcomes in specific disease populations (e.g., Bower, Crosswell, & Slavich, 2014; Dooley, Slavich, Moreno, & Bower, 2017).

Although the STRAIN is not a substitute for time-intensive systems like the Life Events and Difficulties Schedule, it incorporates several advantages of traditional interview-based approaches, including the ability to classify each stressor's type (e.g., acute vs. chronic), life domain (e.g., housing, education, work, marital–partner), and core social-psychological characteristic (e.g., interpersonal loss, physical danger, humiliation, entrapment, role change or disruption). The system also enables investigators to identify the precise timing of when each stressor occurred, which can be used to generate time-limited stress exposure scores (e.g., early vs. adulthood life stress) and stress exposure groups or trajectories (Monroe, Slavich, & Georgiades, 2014). As a result, the STRAIN is a very useful tool for researchers or clinicians who are interested in assessing lifetime stress exposure or who want to assess recent stress exposure, but who do not have the time or resources needed to use traditional interview-based systems.

Summary

In summary, life stress has been conceptualized and assessed in many ways over the years. Self-report checklists are easier to use than interview-based measures, but they also yield data that are nonspecific at best and misleading at worst. These features have led some researchers to argue that "interview-derived measures of stress exposures are superior to self-report life event checklists" and that "it is preferable not to assess stress exposures at all than to assess them with psychometrically flawed measures that have the potential to produce misleading results" (Harkness & Monroe, 2016, p. 737). To address these issues, researchers have developed online, interview-based systems for assessing lifetime stress exposure, and these systems represent a significant step forward insofar as they combine the sophistication of an interview-based measure of stress with the simplicity of a self-report instrument. Notwithstanding these issues, a large literature exists that links stress exposure with mental and physical illness, and we turn to these associations next, with a particular focus on the role that stress plays in depression and related mental and physical health problems.

STRESS AND DEPRESSION

Although the effects of life stress have been examined in relation to numerous outcomes, the literature on stress and depression is the largest and most conceptually advanced. In this context, an abundance of research has examined the effects of both major life events and daily hassles on depression. Research has also examined not just how stress causes depression, but how depression may contribute to the generation of stressful life events and how individuals may become increasingly sensitive to stress over time. We examine each of these issues below.

Major Life Events and Depression

Approximately 50% to 80% of depressed individuals appear to experience a severe major life event before developing depression (Brown & Harris, 1986, 1989; Hammen, 2005; Mazure, 1998; Paykel, 2003), and in case–control studies, depressed individuals are at least 2.5 times more likely than nondepressed persons to have experienced a recent severe life event (Mazure, 1998; Shrout et al., 1989). These effects are even stronger when recent life events involve a combination of interpersonal loss and social rejection, which has been called *targeted rejection* (Brown et al., 1995; Kendler, Hettema, et al., 2003; Slavich, Tartter, Brennan, & Hammen, 2014; Slavich et al., 2009; for a review, see Slavich, O'Donovan, Epel, & Kemeny, 2010). Moreover, in comparative work examining the effects of stress and other known risk factors for depression, severe life events have emerged as the most robust prognostic marker of depression (Kendler, Gardner, & Prescott, 2002). Considered together, then, there is little doubt that major life events are among the strongest proximal precipitants of depression in adults, especially when life events involve interpersonal loss and social rejection (Hammen, 2005; Monroe, Slavich, & Georgiades, 2014; Slavich, 2016a, 2016b).

Although less researched, similar findings have emerged in studies of youth. In a study of high-risk youth selected for having experienced life adversity, for example, adolescents who developed depression were significantly more likely to have experienced a serious interpersonal loss or disappointment life event in the month before developing depression relative to nondepressed youth (Goodyer, Herbert, Tamplin, & Altham, 2000). Similarly, 62% of depressed youth recruited through outpatient services reported at least one stressful life event in the past year (again, as assessed by a life stress interview) compared with only 27% of psychiatrically healthy adolescents (Williamson, Birmaher, Anderson, al-Shabbout, & Ryan, 1995).

Self-reported levels of stress exposure have yielded similar findings. In one study, self-reported stressful life events predicted the development of clinically significant depressive symptoms in adolescent girls (Burton, Stice, & Seeley, 2004). In another study paralleling the aforementioned association between targeted rejection and depression in adults, self-reported romantic breakups predicted adolescents' first onset of depression over a 1-year period (Monroe, Rohde, Seeley, & Lewinsohn, 1999). Considered together, these findings provide substantial

empirical support for the formulation that major life events strongly precipitate onset of depression in adults and youth, especially when such stressors involve interpersonal loss and social rejection.

Daily Hassles and Depression

Given the relative importance of major life events in understanding risk for depression, minor stressors, sometimes called *hassles,* have received markedly less attention. Hassles are typically defined as life stressors that are likely to occur during the course of everyday life and include situations such as misplacing car keys or missing a ride to school or work. Although research linking hassles to depression has not been consistent (Harkness, 2008), depressed individuals have been found to report higher rates of daily hassles than healthy control participants (Lovejoy & Steuerwald, 1997; Ravindran, Matheson, Griffiths, Merali, & Anisman, 2002). Underscoring the potential importance of better understanding the role that hassles play in the onset and maintenance of depression, however, higher frequency of daily hassles has been found to be associated both with greater depression severity (Klein, Lewinsohn, & Seeley, 1997) and with depression recurrence (Bockting et al., 2006). Presently, it remains unknown whether daily hassles are an equivalently strong predictor of depression as major life events.

Stress Generation and Depression

Although early research was premised on the notion that stress contributed to depression, a large body of research has since revealed evidence of a reciprocal relationship between stress and depression. Specifically, it is now known that depression and depressogenic personality factors can contribute to the occurrence of stressors, in turn leading to a heightened risk for depression recurrence. Hammen (1991) coined this term *stress generation,* stemming from her seminal work in female adults with depression. In this line of research, Hammen found that women experiencing depression were not simply passive respondents to stressful life events, but, rather, that they possessed characteristics that led them to generate stressful events in their lives. Interestingly, these attributes also shaped the specific types of events that were generated. Specifically,

they tended to engender life events that were interpersonal in nature and at least partly dependent on their actions or behavior, such as getting fired from a job or having a major argument with a friend or spouse. In Hammen's initial study on this topic, she found that adult women with depression were more likely to experience dependent, interpersonal life events relative to bipolar patients, patients reporting medical illness, or healthy individuals. Moreover, dependent, interpersonal (but not independent) life events were associated with recurrence of depression. These effects were initially examined in adult women with depression but have since been explored and replicated in diverse samples, including adult men (Cui & Vaillant, 1997) and women (Hammen & Brennan, 2002; Harkness & Luther, 2001), as well as adolescents (Daley et al., 1997; Hammen & Brennan, 2001; Patton, Coffey, Posterino, Carlin, & Bowes, 2003). The main message emerging from this body of work is that depressed individuals can generate stressors in their lives that can in turn increase their risk for recurrence of depression and the development of comorbid disorders (Hammen, 2005, 2009).

A preponderance of research has tested the influence of depressive symptoms and major depressive episodes on stress generation. However, investigators have also examined several other predictors of stress generation, including personality factors, cognitive vulnerabilities, and interpersonal contexts (Hammen, 2005, 2006; Liu, 2013). This research has used both interview-based and self-report methodologies, and the results from this work have largely demonstrated that depressogenic factors and behaviors persist during remission from depression (Hammen, 2006).

Focusing first on personality and interpersonal factors, these processes have received significant attention as predictors of stress generation. In early work on this topic, for example, Kendler and colleagues found that neuroticism—which may be genetically transmitted from parent to child—was a robust predictor of the occurrence of stressful life events in general (Kendler, Gardner, & Prescott, 2003; Kendler et al., 1995) and interpersonal life events in particular (Fergusson & Horwood, 1987; Kendler, Gardner, & Prescott, 2003; Poulton &

Andrews, 1992). Autonomy and sociotropy have also been implicated in stress generation. For example, autonomy-consistent traits have been found to predict interpersonal conflict in women with a history of depression (Daley et al., 1997), and sociotropy has been associated with greater interpersonal (but not achievement-related) life events in women (Shih, 2006). Finally, research in college student samples has found that insecure attachment—specifically, anxious and avoidant attachment styles—is associated with the occurrence of interpersonal (but not achievement-related) stressors and, moreover, that these stressors mediate the link between dysfunctional attachment and subsequent depressive symptoms (Hankin, Kassel, & Abela, 2005).

A variety of cognitive vulnerability factors have also been implicated in stress generation. In adults, for example, depressogenic cognitive styles (as indexed by a composite of negative inferential styles and hopelessness) have been found to predict the subsequent occurrence of interpersonal stressors (Safford, Alloy, Abramson, & Crossfield, 2007), and in a cross-sectional study, exhibiting a more negative attributional style was associated with higher rates of dependent (but not independent) interpersonal stressors before onset of depression for individuals experiencing their first lifetime episode of the disorder (Simons, Angell, Monroe, & Thase, 1993). In addition, research has shown that negative inferential styles in children of parents with a history of depression predict the occurrence of dependent interpersonal life stressors over a 1-year period (Shih, Abela, & Starrs, 2009).

Research has also examined predictors of stress generation using self-report instruments for assessing stress. For example, Eberhart, Auerbach, Bigda-Peyton, and Abela (2011) showed that a variety of different depressogenic schemas (e.g., emotional deprivation, mistrust or abuse, social isolation, defectiveness, failure, and subjugation) predict interpersonal life stress, which in turn led to higher levels of depressive symptoms in university students. In a younger sample of adolescents, low perceived control (i.e., inability to exert influence over important outcomes in one's life) has been found to predict higher rates of dependent, interpersonal

life stressors and subsequent depressive symptoms (Auerbach, Eberhart, & Abela, 2010). Collectively, these findings demonstrate that cognitive factors may play an important role in stress generation processes.

Finally, some of the earliest research on stress generation found that women experiencing depression often live in environments that cultivate stressful life events (Hammen, 1992; Hammen & Brennan, 2002). For example, early studies showed that depressed women more often report stressful family environments, marriages characterized by interpersonal discord, partner mental illness, and psychiatrically ill children, which can each in turn lead to the generation of specific stressful life events. It is perhaps not surprising that socioemotional contexts play an important role in stress generation, with depressed women living in low-income environments or who have less education being more susceptible to the effects of stress generation than their less vulnerable counterparts (Fergusson & Horwood, 1987). Finally, child maltreatment and abuse have also been found to predict interpersonal stress in youth (Harkness, Lumley, & Truss, 2008), whereas in adults, stress generation appears to be most strongly associated with emotional abuse (Liu, Choi, Boland, Mastin, & Alloy, 2013).

In an attempt to organize the variety of different factors that could influence stress generation, Liu (2013) proposed an integrated framework that includes cognitive, environmental, behavioral, and genetic predictors of stress generation and the effects that resulting stressors could have on depression. In this model, stress generation is hypothesized to be influenced by both distal and proximal factors. Distal factors, such as child maltreatment, influence cognitive risk factors, such as how individuals perceive the world and make attributions and inferences for different life experiences. These cognitive factors are in turn hypothesized to influence behavioral and interpersonal styles (e.g., how individuals approach relationships; excessive reassurance seeking, attachment styles) that increase a person's likelihood of generating interpersonal stressors. Genetic factors that may affect stress reactivity (e.g., 5-HTTLPR genotype) are also included as processes that may moderate the effects

of behavioral vulnerabilities on stress generation susceptibility (e.g., Conway, Slavich, & Hammen, 2014; Starr, Hammen, Brennan, & Najman, 2013). Ultimately, although a vast number of studies have examined these various factors in isolation, no studies have yet been conducted that test the full integrated model.

Stress Sensitization and the Kindling Hypothesis

Given the twin findings that stress is strongly associated with depression and that individuals who experience a first depressive episode are at elevated risk for experiencing subsequent episodes, research has also examined whether stress plays a different role in the initial onset of depression versus in subsequent, recurrent episodes of the disorder (Monroe & Harkness, 2005). Consistent with this possibility, studies using interview-based measures have shown that major life stress is more strongly associated with the first onset of depression as compared with recurrent depressive episodes in adults (Mazure, 1998; Monroe & Harkness, 2005; Monroe, Slavich, & Gotlib, 2014). Moreover, there is some evidence that reductions in levels of pre-onset stress are unique to interpersonal loss, suggesting that adults experiencing early life adversity or prior depression may be especially sensitive to such stressors (Slavich, Monroe, & Gotlib, 2011). Comparatively less research has tested these patterns of associations in adolescents, and the findings in this literature are more mixed. For example, whereas one study that used a self-report checklist measure of stress found that major life events are a stronger predictor of first versus recurrent episodes of depression (Lewinsohn, Allen, Seeley, & Gotlib, 1999), a subsequent study using a more rigorous interview-based methodology found that life events were equally as important for predicting both initial and recurrent depression (Daley, Hammen, & Rao, 2000).

With these findings as the backdrop, researchers have attempted to understand mechanisms that might underlie recurrence in depression, and this work has yielded at least three schools of thought. The first possibility is that recurrent episodes of depression are triggered by a lower threshold of life

stress relative to first lifetime episodes of the disorder (e.g., Mazure, 1998). The second possibility is that recurrent episodes of depression are increasingly less reliant on environmental stressors, with biological processes playing an increasingly more important role over time (e.g., Kendler, Thornton, & Gardner, 2000). Finally, the third possibility is that individuals who experience recurrent forms of depression are highly sensitive to stress across the entire disease trajectory, perhaps because of biological differences that either emerge very early on in the lifetime course of depression or that are already present before individuals experience their first lifetime episode of the disorder (e.g., Anderson, Monroe, Rohde, & Lewinsohn, 2016).

These differing perspectives, which will be important to reconcile, stem from early, pioneering animal work in the domain of sensitization and kindling. In initial animal studies on this topic, *kindling* referred to the sensitization of limbic brain tissues, and researchers examining these effects demonstrated that after a sufficient number of trials, a progressively lower threshold of electrical current was needed to induce seizures (Goddard, McIntyre, & Leech, 1969). Therefore, it was believed that electrical kindling led to functional and structural alterations in brain regions that in turn caused increased sensitization and future seizures (M. Clark, Post, Weiss, Cain, & Nakajima, 1991). Researchers interested in understanding the pathophysiology of mood disorders subsequently applied these concepts to examine whether neurobiological kindling after a first depressive episode increases a person's sensitivity to stress and, therefore, the person's likelihood of experiencing recurrent episodes of depression, and the result of this work is now represented in a large literature on stress sensitization, the kindling hypothesis, and depression.

Although a complete examination of this literature is beyond the scope of this chapter, several excellent reviews have been written on this topic (e.g., Monroe & Harkness, 2005; Post, 2007). Generally speaking, the empirical basis for the stress sensitization perspective comes from findings suggesting that structural and functional neurobiological alterations may result from an individual's prior experiences with stress or depression. Consistent

with this formulation, reduced hippocampal volume has emerged as a consistent marker of both recurrent and chronic depression (e.g., Bremner et al., 2000; Shah, Ebmeier, Glabus, & Goodwin, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999), which could be caused by the toxic effects of glucocorticoids that are released in larger quantities during stress. These mechanisms may also explain the reduced amygdala volume sometimes seen in depression (Sheline, Gado, & Price, 1998). Along related lines, research on the neuroendocrine bases of depression has shown that depressed adults reporting high levels of traumatic early life stress exhibit a 6 times greater adrenocorticotrophic hormone response to mild stress than depressed adults with no history of abuse, suggesting that early life adversity may predispose individuals to exhibiting alterations in hypothalamic–pituitary–adrenal axis (HPA) functioning that may promote the recurrence of depression (Heim et al., 2000; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013). Given findings such as these, it has been hypothesized that neuroanatomical changes and HPA dysregulation (i.e., kindling) may evolve, at least in part, through exposure to prior life stress or depression and that such biological changes may render a person at elevated risk for recurrence of depression given the influence that these changes may have on stress sensitivity.

In addition to this biological account of stress sensitization and the kindling hypothesis, Segal, Williams, Teasdale, and Gemar (1996) proposed a nonbiological theory to explain depression recurrence. This model derives from the cognitive theory of depression (D. A. Clark, Beck, & Alford, 1999), which posits that maladaptive cognitive schemas, or negative beliefs that are formed by negative early life experiences, encompass an interrelated network of maladaptive beliefs, emotions, and memories that can be reactivated by negative life events in adulthood. To explain depression recurrence, Segal et al. (1996) posited that when components of this cognitive–emotional network become more tightly interconnected, which is thought to occur during depressive episodes, the depressogenic network may become activated by increasingly lower levels of stress. Similar to the neurobiological framework

described above, therefore, this model proposes that exposure to stress and depression can alter how depressotypic information is processed, which in turn increases a person's susceptibility to recurrent episodes of depression when the person is faced with increasingly more minor forms of stress over time.

Although Segal et al. (1996) viewed this framework as complementary to the neurobiological account of stress sensitization (e.g., Post, 1992; Post, Rubinow, & Ballenger, 1986), recent electrophysiology research leveraging event-related potentials (ERPs) has shown a potential pathophysiological basis for depressotypic self-referential processing biases. Specifically, several research groups have used a self-referential encoding task to probe implicit aspects of self-schema (e.g., Auerbach et al., 2016; Auerbach, Stanton, Proudfit, & Pizzagalli, 2015; Shestyuk & Deldin, 2010; Speed, Nelson, Auerbach, Klein, & Hajcak, 2016). In this task, individuals are presented with positive and negative adjectives that are matched on arousal and word length, and they are then asked whether each word is self-relevant. In the past, the task was used to capture negative biases, as indexed by the greater endorsement and recall of negative versus positive self-relevant adjectives (e.g., Goldstein, Hayden, & Klein, 2015; Kuiper & Derry, 1982). More recently, though, researchers have used ERPs to better understand the putative processes associated with depressotypic self-referential processing during the self-referential encoding task administration.

Researchers who have used this strategy have primarily focused on early ERP components (i.e., P1, P2), which reflect semantic monitoring of emotional information, and late ERP components (i.e., late positive potential), which index sustained engagement with emotion words (Fischler & Bradley, 2006) and images (Foti, Hajcak, & Dien, 2009). In adults, depressed individuals showed potentiated P2 and late positive potential effects to negative versus positive words, whereas healthy adults exhibited the opposite effect (Shestyuk & Deldin, 2010). Similar results have also been found in depressed adolescents (Auerbach, Stanton, et al., 2015) and in never-depressed, at-risk youth (Speed et al., 2016). Although these results are promising for

elucidating processes that may underlie depression, future research focusing on stress sensitization and kindling would benefit from exploring the extent to which depressogenic self-referent ERP severity may be associated with differential vulnerability to depression after a range of life events. Ultimately, the hope is that this line of research will help inform the development of novel strategies for preventing depression recurrence.

Summary

Taken together, this research demonstrates that stress plays an important role in depression onset, maintenance, and recurrence. In addition, studies have identified specific types of stressors (e.g., dependent, interpersonal stressors; targeted rejection) that have especially strong associations with depression and behavioral and neurobiological processes (e.g., stress generation, sensitization) that have improved etiological understanding of the disorder. Future research using psychobiological approaches may enhance investigation of integrated models of stress and depression (e.g., Liu, 2013), which may ultimately lead to key advancements in treatment.

DEPRESSION SUBTYPES AND SPECIFICITY

Although we have so far been talking about depression as a singular disorder, depression is actually characterized by an extraordinary amount of symptomatic heterogeneity. In fact, given the present-day *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013) criteria for depression, there are 945 possible combinations of symptoms that could lead an individual to be diagnosed with this disorder (van Loo, de Jonge, Romeijn, Kessler, & Schoevers, 2012). Also, although it is well established that preonset life stress is associated with greater symptom severity, whether stress influences the specific type of symptoms an individual is likely to experience remains unclear (Monroe, Harkness, Simons, & Thase, 2001; Muscatell, Slavich, Monroe, & Gotlib, 2009; Tennant, 2002). In one prototypic study on this topic, Monroe et al. (2001) found that experiencing more severe life events before onset of depression was strongly associated with exhibiting more cognitive and affective (but not somatic) symptoms of depression during the depressive episode and, moreover, that these effects were unique to preonset life stressors. In a second study, Muscatell et al. (2009) found that individuals who experienced a preonset severe life event endorsed more cognitive–emotional and somatic symptoms of depression, but that these effects did not extend to chronic forms of preonset life stress. Therefore, although it is clear that stress has a pronounced effect on severity of depression, additional research is needed to examine whether life stress contributes to specific depressive symptoms or symptom clusters and, if so, whether these effects are similar for different forms of stress (e.g., acute vs. chronic stress) or different types of stressors (e.g., interpersonal relationship vs. housing vs. financial stressors).

Depression Subtypes

Researchers have also examined whether life stress is associated with different subtypes of depression, given that such research has the potential to improve both the understanding of the etiology of depression and the development of better prevention and intervention approaches. Arguably, the most well-researched subtypes of depression are melancholic (i.e., endogenous, autonomous) depression and nonmelancholic (i.e., nonendogenous, reactive) depression. Melancholic depression is characterized by unreactive mood, anhedonia, psychomotor retardation, and mood disturbances in the morning. This form of the disorder is believed to have strong neurobiological and genetic underpinnings; therefore, depressive episodes characterized by this subtype are hypothesized to develop autonomously from life stress. In contrast, nonmelancholic depression, which often is less severe, typically develops in response to stressful life events, although these effects appear to differ on the basis of whether self-report checklist or interview-based measures of stress are used (Harkness, 2008).

In several checklist-based studies that examined associations between stress and melancholic and nonmelancholic depression, for example, stressful life events were found to be more strongly associated with nonmelancholic (vs. melancholic) forms

of the disorder (Kohn et al., 2001; Robins, Block, & Peselow, 1990; Türkçapar et al., 1999). However, a substantial number of null findings have also been published (e.g., Leff, Roatch, & Bunney, 1970; Monroe, Thase, Hersen, Himmelhoch, & Bellack, 1985; Thomson & Hendrie, 1972). Among the studies that have used interview-based measures of life stress, many found that greater stress exposure is associated with nonmelancholic depression (Frank, Anderson, Reynolds, Ritenour, & Kupfer, 1994; Harkness & Monroe, 2006; Paykel, Rao, & Taylor, 1984; Roy, Breier, Doran, & Pickar, 1985; Zimmerman, Coryell, Pfohl, & Stangl, 1986), but, again, nearly half of the studies in this literature found no evidence of differences in stress exposure between the subtypes (Bebbington et al., 1988; Brown, Harris, & Hepworth, 1994; Brown, Ní Bhrolcháin, & Harris, 1979; Brugha & Conroy, 1985; Dolan, Calloway, Fonagy, De Souza, & Wakeling, 1985). Thus, despite considerable attention to the matter, it remains unclear whether stress plays a differential role in nonmelancholic versus melancholic depression.

Depression Specificity

Finally, an abundance of research has shown that depression and anxiety disorders frequently co-occur (Kessler et al., 2007; Kessler, Berglund, Demler, et al., 2005). For this reason, researchers have investigated whether life stress is more strongly associated with depression versus anxiety, although only a few studies have directly compared these effects (Harkness, 2008). Among studies that have conducted this comparison, depressed individuals without a comorbid anxiety disorder reported higher levels of self-reported life stress relative to individuals with generalized anxiety disorder without a comorbid depressive disorder. However, the greatest overall levels of stress were reported by individuals exhibiting both depression and anxiety (Newman & Bland, 1994). In a more recent study that used an interview-based approach to assessing stress, Kendler, Karkowski, and Prescott (1998) found that depression and anxiety disorders were preceded by different types of major life events (Kendler et al., 1998). Specifically, whereas depression tended to be precipitated by major life events involving interpersonal loss, generalized anxiety

disorder tended to be precipitated by major life events involving danger (Kendler, Hettema, et al., 2003; cf. Brown, 1996; Finlay-Jones & Brown, 1981). Although these findings are intriguing, as noted above, very few studies to date have used sophisticated interview-based measures of stress and examined the different forms and specific types of life stress that are differentially associated with discrete psychiatric disorders and symptom profiles.

Summary

In summary, despite the strong desire to map specific life stressor domains onto depression, the mixed findings described underscore the need for much more research on this topic. The identification of specific stress–depression relationships is important for improving theories of depression pathogenesis. Perhaps more important, though, this work will have critical implications for strengthening early identification and prevention efforts.

STRESS AND SUICIDAL THOUGHTS AND BEHAVIORS

Thus far we have largely focused on the association between life stress and depression. Now, we turn to one of the most serious potential consequences of experiencing severe life stress and depression, namely suicidal thoughts and behaviors. Suicide is a leading cause of death worldwide and thus a very serious public health concern (World Health Organization, 2016). Among adolescents, it is the second leading cause of death (Centers for Disease Control and Prevention, 2013), and compared with nondepressed adolescents, those experiencing depression have a six-fold greater likelihood of making a suicide attempt (Nock et al., 2013). In response to these alarming statistics, there has been an increase in the availability of mental health services aimed at treating suicidal adolescents and adults. Unfortunately, however, these efforts have not succeeded in decreasing the prevalence of suicidal behaviors (Kessler, Berglund, Borges, Nock, & Wang, 2005). As a result, researchers have recently increased their efforts to identify distal and proximal factors that underlie risk for the onset and persistence of suicidal behaviors, and in this context,

life stress has received substantial attention (Liu & Miller, 2014).

Indeed, several etiological models and theories have strongly implicated life stress in potentiating suicidal thoughts and behaviors (e.g., Hawton, Saunders, & O'Connor, 2012; Joiner, 2005; Mann et al., 2005; Wenzel & Beck, 2008). In a recent review of this work, Liu and Miller (2014) systematically highlighted the impact of life stress on suicidal thoughts and behaviors. As these researchers noted, suicidal ideation and behaviors are closely related (and often highly correlated) and, at the same time, only one third of individuals transition from suicidal ideation to actually making a suicide attempt (Nock et al., 2008). Therefore, recent research has sought to identify mechanisms that might induce this transition from suicidal ideation to attempting suicide—or that might differentiate these different groups of individuals—to improve the early identification and prevention of life-threatening behaviors (Auerbach, Millner, Stewart, & Esposito, 2015; Auerbach, Stewart, & Johnson, 2017; Stewart et al., 2017).

In this context, a wealth of research conducted over the past three decades has begun unpacking the effects of life stress on suicidal thoughts, plans, and attempts. The majority of these studies have, perhaps not surprisingly, found a strong relationship between life stress exposure and suicidal ideation regardless of the population being examined (e.g., adolescents, adults, community samples, and clinical populations; Casey et al., 2006; Monroe et al., 2001; Waelde, Silvern, & Hodges, 1994). Paralleling the findings discussed above showing that interpersonal stressors are especially strongly related to depression (Brown et al., 1995; Kendler, Hettema, et al., 2003; Slavich et al., 2009), research examining the link between stress and suicidal ideation has shown that interpersonal stressors may play a particularly important role in promoting ideation (Adams, Overholser, & Spirito, 1994; Fanous, Prescott, & Kendler, 2004; Fergusson, Woodward, & Horwood, 2000; Joiner & Rudd, 1995; Stein et al., 2010). Although relatively less research has examined the relation between life stress exposure and suicide planning, the pattern of effects appears to be similar, with greater stress exposure being associated with a greater likelihood of suicidal planning (Borges et al., 2008; McKeown et al., 1998).

A substantial body of work has also shown that stressful life events (Kaslow et al., 2002; Stein et al., 2010) and interpersonal stressors (Baca-Garcia et al., 2007; Fergusson et al., 2000) are related to suicide attempts. In this context, though, a few studies have yielded null findings (Kirmayer, Boothroyd, & Hodgins, 1998; McKeown et al., 1998), especially when adjusting for covariates (Wong, Stewart, Ho, Rao, & Lam, 2005). Similar positive associations have been found for suicide deaths (e.g., Brent et al., 1988, 1993, 1994). Interestingly, research on this topic has revealed that legal stressors (Appleby, Cooper, Amos, & Faragher, 1999; Brent et al., 1993) and somatic illness (Cavanagh, Owens, & Johnstone, 1999; Duberstein, Conwell, Conner, Eberly, & Caine, 2004; Khan, Mahmud, Karim, Zaman, & Prince, 2008) may have a particularly strong relationship to suicide death.

In summary, research to date has shown that life stress increases risk for suicidal thoughts and behaviors, with these effects potentially being strongest for interpersonal stressors. At the same time, only a few studies have examined the effects of stressors occurring in different life domains (e.g., relationship, work, legal) or that have different social-psychological characteristics (e.g., interpersonal loss, humiliation, physical danger). In addition, it remains largely unknown whether stressors of different types predict different aspects of suicidality (i.e., ideation vs. plans vs. attempts). Ultimately, additional research using more sophisticated methods for assessing life stress is needed to improve our understanding of these more fine-grained associations and to develop intervention strategies that may serve to prevent the needless loss of life among at-risk patients.

STRESS, DEPRESSION, AND PHYSICAL ILLNESS

Major life stressors are not just associated with increased risk for depression and suicide, they also increase risk for a variety of somatic and physical disorders that frequently co-occur with depression. These diverse disease conditions include asthma,

rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, cardiovascular disease, and chronic pain (e.g., Cohen et al., 2007; Cutolo & Straub, 2006; Kivimäki et al., 2006; McEwen & Kalia, 2010). Over the years, researchers have proposed numerous explanations for why stress might increase risk for both depression and these various physical ailments, with a majority of these formulations focusing on personality, cognitive–emotional, or behavioral processes (e.g., neuroticism, hostility, threat sensitivity, poor health behaviors). More recently, however, research has revealed that life stress may activate immune system processes that increase risk for both depression and related physical health problems, and this work has paved the way for more sophisticated thinking on how stress may have such broad effects on mental and physical health.

Initial evidence for the notion that depression and certain physical conditions might be biologically linked and influenced by stress-related processes came from the observation that depression and poor physical health tend to be strongly associated over the lifespan. In a prospective study of more than 1,200 young adults, for example, asthma in adolescence and young adulthood was associated with a significantly increased likelihood of being diagnosed with depression later in life (odds ratio = 1.7; Goodwin, Fergusson, & Horwood, 2004). Likewise, research has shown that persons with rheumatoid arthritis and inflammatory bowel disease are 2 to 3 times more likely to be depressed than the general population (Graff, Walker, & Bernstein, 2009; Katz & Yelin, 1993; Regier et al., 1988) and that depression is approximately twice as likely in individuals with coronary heart disease and 3 times as likely in persons with congestive heart failure compared with prevalence rates in the general population (Whooley, 2006; see also Barth, Schumacher, & Herrmann-Lingen, 2004; Wulsin & Singal, 2003). Finally, metabolic syndrome has also been found to significantly increase a person's subsequent risk for depression (Pan et al., 2012), and as many as 72% of patients with chronic pain meet diagnostic criteria for concurrent major depressive disorder (Poole, White, Blake, Murphy, & Bramwell, 2009; see also Bair et al., 2004). Depression, therefore, is not just

associated with a few somatic complaints but rather with increased risk for several major physical health problems.

THE IMMUNE SYSTEM AND INFLAMMATION

In an attempt to explain these associations between depression and physical illness, researchers have recently begun examining biological processes that are activated by stress and that could in turn promote symptoms of depression, suicidal behavior, and the physical health problems described above. One of the most recent and potentially important discoveries in this line of work involves the realization that stress can activate immune system processes that increase levels of inflammation throughout the body (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Steptoe, Hamer, & Chida, 2007). Inflammation is known to induce several symptoms of depression, potentially promote suicidal thoughts, and likely cause other biological changes to occur that, if sustained, can lead to the emergence of somatic and physical health problems over time (Fagundes & Way, 2014; Slavich, 2015). In fact, inflammation is now widely recognized as a key mechanism linking stress and poor overall health (Calder, 2006; Couzin-Frankel, 2010; Slavich, 2015; Slavich & Irwin, 2014).

To understand how these effects occur, it is important to know that the immune system's primary purpose is to keep the body biologically safe, especially from viral and bacterial infections that could kill the host if left unaddressed (Barton, 2008; Medzhitov, 2008). To achieve this goal, the immune system responds to a variety of different physiological and chemical signals in the body that indicate the presence of microbes (e.g., bacteria, viruses, fungi) that could spread throughout the body and cause severe infection and even death (Medzhitov, 2007). Central to these dynamics is a family of receptors called toll-like receptors that are present on different immune cells and that upregulate inflammatory and antimicrobial innate immune responses when a microbial threat is detected (Medzhitov, 2001, 2007). When bacteria are detected, for example, toll-like receptors

respond by initiating a conserved signaling cascade that activates the intracellular transcription factors nuclear factor-κB and activator protein 1 (Barton, 2008; Medzhitov, 2001). These transcription factors in turn induce the expression of genes that promote inflammation, such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α; Irwin & Cole, 2011; Medzhitov, 2008).

As a result of these changes in gene expression, immune cells produce small protein molecules called *cytokines*, which coordinate cell-to-cell communication during threat and serve to regulate the inflammatory response (Karin, 2006; Raison, Capuron, & Miller, 2006). The pro-inflammatory cytokines IL-1β, IL-6, and TNF-α are among those most widely studied in research on stress and depression (Slavich & Irwin, 2014). These cytokines and others cause redness, heat, swelling, and pain at sites of infection as a way to promote wound healing and recovery, but they are most interesting to stress and depression researchers because they can communicate with the brain to induce widespread effects on mood, cognition, behavior, and physiology. For example, cytokines can increase body temperature, heart rate, and respiratory rate (Poon, Ho, Chiu, & Chang, 2013; Ricciotti & FitzGerald, 2011), and they can also promote the development of a constellation of depressotypic behaviors called *sickness behaviors,* which include sad mood, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal (Dantzer & Kelley, 2007; Hart, 1988; Slavich & Irwin, 2014).

Together, these local and systemic immune system effects help accelerate wound healing and limit the spread of infection while prompting a dramatic shift in motivation and behavior that favors energy conservation, recuperation, and recovery (Barton, 2008; Medzhitov, 2008). Generally speaking, then, these effects are adaptive when they occur in a time-limited fashion and in response to an actual threat. However, increases in inflammation can also become chronic (e.g., as a result of glucocorticoid resistance or sustained perceptions of social–environmental threat), and under these circumstances, inflammation can cause oxidative stress, accelerated biological aging (e.g., as indexed by telomere length), and

ultimately different inflammatory disease states that precipitate early mortality (Graham et al., 2006; Lupien et al., 2009).

As alluded to above, increases in inflammation can persist over time, in part because of sustained perceptions of social–environmental threat. These effects presume the existence of pathways linking the brain and immune system, and at least three such pathways have been identified to date (Irwin & Slavich, 2017). First, the sympathetic nervous system can regulate pro-inflammatory cytokine production by releasing the neurotransmitter norepinephrine, which modulates immune response gene transcription via stimulation of β-adrenergic and possibly α-adrenergic receptors (Grisanti et al., 2011; Irwin & Cole, 2011). This signaling cascade suppresses transcription of antiviral type I interferon genes and upregulates transcription of pro-inflammatory immune response genes, leading to reduced antiviral activity and increased pro-inflammatory cytokine activity (Cole, Korin, Fahey, & Zack, 1998). Second, the HPA axis can regulate pro-inflammatory cytokine production by stimulating the release of the glucocorticoid cortisol from the adrenal cortex (Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987). Although cortisol typically has anti-inflammatory effects, cortisol production can enhance inflammation under conditions of chronic social–environmental threat or when glucocorticoid resistance has developed (G. E. Miller, Cohen, & Ritchey, 2002). Finally, although the brain and immune system have historically been thought of as physically separate systems, a recent groundbreaking study revealed that the brain is directly connected to the peripheral immune system through the existence of previously unknown meningeal lymphatic vessels that serve as a "highway" on which immune cells can travel from the brain to the peripheral immune system and back again (Louveau et al., 2015).

LIFE STRESS AND INFLAMMATION

The existence of these three pathways linking the brain and immune system is important for research on stress, depression, and health because it provides evidence for the existence of biologically plausible

pathways by which different stressors occurring in the social environment may influence inflammatory activity and, in turn, health (Irwin & Cole, 2011; Irwin & Slavich, 2017; G. Miller, Chen, & Cole, 2009). In this vein, numerous studies have demonstrated that different forms of acute and chronic stress are associated with elevated inflammatory activity across the life course (Segerstrom & Miller, 2004; Slavich & Irwin, 2014; Steptoe et al., 2007). In a recent longitudinal study of more than 4,600 children, for example, Slopen, Kubzansky, McLaughlin, and Koenen (2013) found that greater cumulative stress exposure (e.g., being physically or sexually abused, separated from mother or father, taken into foster care) before age 8 predicted higher levels of the pro-inflammatory IL-6 and inflammatory marker C-reactive protein (CRP) at age 10, and higher levels of CRP at age 15. Similar findings have been found in adults, with negative social interactions and life events involving friends and family members in daily life predicting elevations in several markers of inflammatory activity, including CRP, IL-6, and a soluble receptor for TNF-α (e.g., Fuligni et al., 2009; Marin, Chen, Munch, & Miller, 2009).

Finally, paralleling the studies described previously that have demonstrated especially strong effects of targeted rejection on risk for depression, two studies to date have shown that experiencing only one major life event involving targeted rejection is sufficient to alter molecular signaling pathways that can lead to increased inflammatory activity. In the first study, 147 adolescent girls at elevated risk for depression were assessed every 6 months for 2.5 years, and participants were found to have significantly higher levels of messenger RNA for signaling molecules that increase systemic inflammation (i.e., nuclear factor-κB and inhibitor of κB) at study visits when they had experienced a recent targeted rejection life event as compared with visits when no such life event had occurred (Murphy, Slavich, Rohleder, & Miller, 2013). In the second study, 121 youths with elevated risk for asthma were assessed every 6 months for 2 years, and participants were found to have significantly lower levels of messenger RNA for signaling molecules that reduce airway inflammation and obstruction (i.e., the glucocorticoid and β2-adrenergic

receptor) at study visits when they had experienced a recent targeted rejection life event as compared with visits when no such life event had occurred (Murphy et al., 2015). Moreover, in this latter study, the effects of recent life stress on these molecular signaling pathways were specific to recent targeted rejection life events and did not extend to other categories of life stress, namely interpersonal or noninterpersonal life events.

INFLAMMATION, DEPRESSION, AND SUICIDE

Considered together, these studies provide evidence that life stress in general, and especially targeted rejection life events, have the ability to upregulate inflammatory activity. However, is inflammation related to depression and depression-related clinical phenomena, such as suicide? Although this question has been on researchers' minds since at least the early 1990s, the link between inflammation and depression has recently been the focus of enormous interest. Indeed, as reviewed in Slavich and Irwin (2014), at least five lines of work presently support the possibility that inflammation plays an important role in at least some forms of the disorder.

First, as noted above, several somatic disorders and physical disease conditions involving inflammation are known to frequently co-occur with depression. These conditions include rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, coronary heart disease, and chronic pain (e.g., Goodwin et al., 2004; Graff et al., 2009; Pan et al., 2012; Poole et al., 2009; Whooley, 2006). Second, multiple markers of inflammatory activity (e.g., IL-1, IL-6, TNF-α, and CRP) have been found to be elevated in individuals with depression compared with nondepressed participants, and, in addition, at least some studies have found that elevations in these biomarkers appear to precede onset of the disorder (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009). Third, immunological challenges that upregulate inflammatory activity, such as interferon-α treatment, typhoid vaccination, and endotoxin administration, have been found to trigger depressive-like behaviors in animal models of depression and diagnosable forms of major

depressive disorder in humans (Capuron & Miller, 2004; DellaGioia & Hannestad, 2010). Fourth, inflammatory challenges have also been shown to alter metabolic and neural activity in brain regions that have been implicated in the pathophysiology of depression—namely, the basal ganglia, cerebellum, anterior cingulate cortex, and ventral striatum (e.g., Capuron et al., 2005, 2012; see also Slavich, Way, Eisenberger, & Taylor, 2010). Finally, at least three anti-inflammatory agents—namely, celecoxib (Celebrex), etanercept (Enbrel), and infliximab (Remicade)—have been found in well-controlled studies to reduce depressive symptoms (see Köhler, Benros, Nordentoft, Mors, & Krogh, 2015). Considered together, these data provide converging correlational and experimental evidence that inflammation is involved in the pathogenesis of at least some forms of depression (Slavich & Irwin, 2014).

Although less research has focused on links between inflammation and suicide, some studies to date have implicated inflammatory processes in heightened risk for suicidal ideation and behavior, perhaps because of the role that cytokines play in undermining healthy self-regulation (Shields, Moons, & Slavich, in press). In psychiatric patients, for example, levels of inflammation have been found to be associated with individuals' self-reported severity of suicidal ideation (Brundin, Erhardt, Bryleva, Achtyes, & Postolache, 2015). In addition, a recent meta-analytic review of 18 studies found that levels of the pro-inflammatory cytokines IL-1β and IL-6 are consistently higher in the blood and postmortem brain samples of patients with suicidality relative to both patients without suicidality and healthy control subjects. In addition, patients who completed suicide consistently have lower levels of in vitro production of the inflammatory cytokine IL-2 (Black & Miller, 2015). Finally, in a recent prospective cohort study of 39,349 participants, those exhibiting the highest levels of the inflammatory marker CRP were 4 times more likely to die by suicide relative to persons in the lowest CRP group (Batty, Bell, Stamatakis, & Kivimäki, 2016). Considered together, these studies provide promising evidence that inflammation may play an important role in suicide. Given the limited number of studies on this topic, though, additional research is needed to clarify several issues, including how, exactly, inflammatory factors cause suicidal ideation or behavior; whether particular cytokines are more responsible for these effects than others; and whether cytokines actually increase risk for suicide (i.e., as opposed to the stress of contemplating suicide increasing levels of inflammation).

INTEGRATED THEORIES OF STRESS, DEPRESSION, AND PHYSICAL ILLNESS

Armed with data such as these on the biology of stress, depression, and suicide, researchers are for the first time in history poised to develop biologically plausible, multilevel theories that describe the full set of psychological, neural, physiological, molecular, and genomic mechanisms linking stress to increased risk for depression, suicide, and related physical health problems. According to Social Signal Transduction Theory of Depression, for example, social threat and adversity get represented in brain regions that process interoceptive cues and the distressing aspects of social and physical pain (e.g., anterior insula, dorsal anterior cingulate cortex). These regions in turn project to lower level structures, including the hypothalamus and brainstem autonomic control nuclei, which can modulate inflammatory activity via the HPA axis and sympathetic nervous system. Activation of these pathways leads to the release of cortisol, epinephrine, norepinephrine, and acetylcholine, which interact with receptors on cytokine-producing cells to initiate transcription factor activity that increases inflammatory gene expression and, ultimately, the production of pro-inflammatory cytokines. These cytokines in turn signal the brain to induce several symptoms of depression, including sad mood, anhedonia, fatigue, psychomotor retardation, altered appetite and sleep, and social-behavioral withdrawal. Although this highly conserved biological response to adversity is critical for survival during times of actual physical threat or injury, it also can be activated by modern-day social threats—including symbolic or imagined threats—leading to an increasingly pro-inflammatory phenotype that is hypothesized to be a key phenomenon driving depression pathogenesis and recurrence, as well as the overlap of depression with

several inflammation-related somatic conditions including asthma, rheumatoid arthritis, chronic pain, metabolic syndrome, cardiovascular disease, and neurodegeneration; see Slavich & Irwin, 2014).

Other biologically informed, multilevel theories have been proposed for understanding the pathogenesis of depression and physical health problems (see McLaughlin, Sheridan, & Lambert, 2014; A. H. Miller & Raison, 2016; Nusslock & Miller, 2016; O'Donovan, Slavich, Epel, & Neylan, 2013; Slavich & Cole, 2013). These formulations are similar insofar as they posit that neurocognitive threat detection and resulting physiological or immune activity can have short-term adaptive value but also promote mental and physical health problems if they are engaged too frequently over time. However, these models also differ on the basis of their conceptual focus and the specific mechanisms described. Ultimately, although such theories are important for guiding future research on multilevel pathways underlying risk for depression, suicide, and physical illness, additional research is needed to test these theories and examine their predictive utility.

FUTURE DIRECTIONS

Taking stock of what we have learned about stress, depression, suicide, and physical illness over recent decades, it is remarkable to see how much we now know about psychological, cognitive, emotional, and behavioral aspects of these phenomena and, in addition, how much we still do not know about the biology underlying these phenomena. Moreover, critical questions remain regarding how to best define, differentiate, and measure basic constructs in this area of work. With respect to life stress, we have now reached the point at which all serious studies on the effects of stress should consider using stress measurement systems that cover the entire lifespan and that enable investigators to distinguish between different forms and types of life stress. This work will be important for revealing the specific types of stressors that are most strongly related to different health outcomes, and it will also serve as the starting point for developing biologically plausible theories of depression, suicide, and physical health that begin with the social environment. With

respect to depression, we now know a lot about psychological and behavioral factors that promote increased risk for depression onset and recurrence but relatively little about the biological processes underlying these aspects of depression and how such processes may give rise to both depression and depression-related outcomes, such self-harm behavior and physical illness. Therefore, much more work is needed to elucidate links between psychological, cognitive–emotional, and behavioral aspects of these outcomes and the biological mechanisms that influence these phenomena. Studies examining these multilevel interactions in childhood and adolescence have the potential to be particularly effective because they can reveal risk processes that emerge before individuals become ill, which could be targeted to prevent a lifetime marked by depression and depression-related disease.

Finally, much remains to be learned about the role that the human brain and immune system play in the outcomes considered here and in mental and physical health more generally. Presently, we have very reasonable working models for how social stressors are represented in the brain, how the brain regulates peripheral immune system activity, and how central and peripheral immune system activity can in turn influence mood, cognition, and behavior. However, these models need to be refined, and additional information on multilevel risk and resilience factors is needed to reveal why stress sometimes leads to illness and why other times it does not. Presuming that altered immune system activity is a key process underlying the health outcomes described here, additional research is also needed to explain why stress is sometimes associated with mental health problems involving inflammation (e.g., anxiety, depression), other times with physical health problems involving inflammation (e.g., asthma, chronic pain), and yet other times with both mental and physical health problems that combine to affect clinical functioning and well-being.

CONCLUSION

In conclusion, at no time in history have researchers known more about the psychology of stress, depression, suicide, and physical illness. Given the

recent development of low-cost methods for assessing neural and immune system activity, we are now poised to extend this work and learn a great deal about the biology of major health problems that cause substantial disease burden and human suffering. This research has the potential to inform the development of novel strategies for treating and perhaps preventing stress-related illness, but much more research is needed to turn this potential into a reality.

References

Adams, D. M., Overholser, J. C., & Spirito, A. (1994). Stressful life events associated with adolescent suicide attempts. *Canadian Journal of Psychiatry*, *39,* 43–48. http://dx.doi.org/10.1177/070674379403900109

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Anderson, S. F., Monroe, S. M., Rohde, P., & Lewinsohn, P. M. (2016). Questioning kindling: An analysis of cycle acceleration in unipolar depression. *Clinical Psychological Science*, *4,* 229–238. http://dx.doi.org/10.1177/2167702615591951

Appleby, L., Cooper, J., Amos, T., & Faragher, B. (1999). Psychological autopsy study of suicides by people aged under 35. *British Journal of Psychiatry*, *175,* 168–174. http://dx.doi.org/10.1192/bjp.175.2.168

Auerbach, R. P., Bondy, E., Stanton, C. H., Webb, C. A., Shankman, S. A., & Pizzagalli, D. A. (2016). Self-referential processing in adolescents: Stability of behavioral and ERP markers. *Psychophysiology*, *53,* 1398–1406. http://dx.doi.org/10.1111/psyp.12686

Auerbach, R. P., Eberhart, N. K., & Abela, J. R. (2010). Cognitive vulnerability to depression in Canadian and Chinese adolescents. *Journal of Abnormal Child Psychology*, *38,* 57–68. http://dx.doi.org/10.1007/s10802-009-9344-y

Auerbach, R. P., Millner, A. J., Stewart, J. G., & Esposito, E. C. (2015). Identifying differences between depressed adolescent suicide ideators and attempters. *Journal of Affective Disorders*, *186,* 127–133. http://dx.doi.org/10.1016/j.jad.2015.06.031

Auerbach, R. P., Stanton, C. H., Proudfit, G. H., & Pizzagalli, D. A. (2015). Self-referential processing in depressed adolescents: A high-density event-related potential study. *Journal of Abnormal Psychology*, *124,* 233–245. http://dx.doi.org/10.1037/abn0000023

Auerbach, R. P., Stewart, J. G., & Johnson, S. L. (2017). Impulsivity and suicidality in adolescent inpatients. *Journal of Abnormal Child Psychology*, *45,* 91–103. http://dx.doi.org/10.1007/s10802-016-0146-8

Baca-Garcia, E., Parra, C. P., Perez-Rodriguez, M. M., Sastre, C. D., Torres, R. R., Saiz-Ruiz, J., & de Leon, J. (2007). Psychosocial stressors may be strongly associated with suicide attempts. *Stress and Health*, *23,* 191–198. http://dx.doi.org/10.1002/smi.1137

Bair, M. J., Robinson, R. L., Eckert, G. J., Stang, P. E., Croghan, T. W., & Kroenke, K. (2004). Impact of pain on depression treatment response in primary care. *Psychosomatic Medicine*, *66,* 17–22. http://dx.doi.org/10.1097/01.PSY.0000106883.94059.C5

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine*, *66,* 802–813. http://dx.doi.org/10.1097/01.psy.0000146332.53619.b2

Barton, G. M. (2008). A calculated response: Control of inflammation by the innate immune system. *Journal of Clinical Investigation*, *118,* 413–420. http://dx.doi.org/10.1172/JCI34431

Batty, G. D., Bell, S., Stamatakis, E., & Kivimäki, M. (2016). Association of systemic inflammation with risk of completed suicide in the general population. *JAMA Psychiatry*, *73,* 993–995. http://dx.doi.org/10.1001/jamapsychiatry.2016.1805

Bebbington, P. E., Brugha, T., MacCarthy, B., Potter, J., Sturt, E., Wykes, T., . . . McGuffin, P. (1988). The Camberwell Collaborative Depression Study. I. Depressed probands: Adversity and the form of depression. *British Journal of Psychiatry*, *152,* 754–765. http://dx.doi.org/10.1192/bjp.152.6.754

Black, C., & Miller, B. J. (2015). Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus nonsuicidal patients. *Biological Psychiatry*, *78,* 28–37. http://dx.doi.org/10.1016/j.biopsych.2014.10.014

Bockting, C. L., Spinhoven, P., Koeter, M. W., Wouters, L. F., Visser, I., & Schene, A. H. (2006). Differential predictors of response to preventive cognitive therapy in recurrent depression: A 2-year prospective study. *Psychotherapy and Psychosomatics*, *75,* 229–236. http://dx.doi.org/10.1159/000092893

Borges, G., Benjet, C., Medina-Mora, M. E., Orozco, R., Molnar, B. E., & Nock, M. K. (2008). Traumatic events and suicide-related outcomes among Mexico City adolescents. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49,* 654–666. http://dx.doi.org/10.1111/j.1469-7610.2007.01868.x

Bower, J. E., Crosswell, A. D., & Slavich, G. M. (2014). Childhood adversity and cumulative life stress: Risk factors for cancer-related fatigue. *Clinical Psychological Science*, *2,* 108–115. http://dx.doi.org/10.1177/2167702613496243

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in major depression. *American*

Journal of Psychiatry, *157,* 115–118. http://dx.doi.org/10.1176/ajp.157.1.115

Brent, D. A., Perper, J. A., Goldstein, C. E., Kolko, D. J., Allan, M. J., Allman, C. J., & Zelenak, J. P. (1988). Risk factors for adolescent suicide: A comparison of adolescent suicide victims with suicidal inpatients. *Archives of General Psychiatry*, *45,* 581–588. http://dx.doi.org/10.1001/archpsyc.1988.01800300079011

Brent, D. A., Perper, J. A., Moritz, G., Baugher, M., Roth, C., Balach, L., & Schweers, J. (1993). Stressful life events, psychopathology, and adolescent suicide: A case control study. *Suicide and Life-Threatening Behavior*, *23,* 179–187.

Brent, D. A., Perper, J. A., Moritz, G., Liotus, L., Schweers, J., Balach, L., & Roth, C. (1994). Familial risk factors for adolescent suicide: A case-control study. *Acta Psychiatrica Scandinavica*, *89,* 52–58. http://dx.doi.org/10.1111/j.1600-0447.1994.tb01485.x

Brown, G. W. (1996). Psychosocial factors and depression and anxiety disorders—some possible implications for biological research. *Journal of Psychopharmacology*, *10,* 23–30. http://dx.doi.org/10.1177/026988119601000105

Brown, G. W., & Harris, T. (1986). Stressor, vulnerability and depression: A question of replication. *Psychological Medicine*, *16,* 739–744. http://dx.doi.org/10.1017/S0033291700011740

Brown, G. W., & Harris, T. O. (1978). *Social origins of depression: A study of psychiatric disorder in women*. New York, NY: Free Press.

Brown, G. W., & Harris, T. O. (1989). *Life events and illness*. New York, NY: Guilford Press.

Brown, G. W., Harris, T. O., & Hepworth, C. (1994). Life events and endogenous depression: A puzzle reexamined. *Archives of General Psychiatry*, *51,* 525–534. http://dx.doi.org/10.1001/archpsyc.1994.03950070017006

Brown, G. W., Harris, T. O., & Hepworth, C. (1995). Loss, humiliation and entrapment among women developing depression: A patient and non-patient comparison. *Psychological Medicine*, *25,* 7–21. http://dx.doi.org/10.1017/S003329170002804X

Brown, G. W., Ní Bhrolcháin, M., & Harris, T. O. (1979). Psychotic and neurotic depression: Part 3. Aetiological and background factors. *Journal of Affective Disorders*, *1,* 195–211. http://dx.doi.org/10.1016/0165-0327(79)90005-3

Brugha, T. S., & Conroy, R. (1985). Categories of depression: Reported life events in a controlled design. *British Journal of Psychiatry*, *147,* 641–646. http://dx.doi.org/10.1192/bjp.147.6.641

Brugha, T. S., & Cragg, D. (1990). The List of Threatening Experiences: The reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica*, *82,* 77–81. http://dx.doi.org/10.1111/j.1600-0447.1990.tb01360.x

Brundin, L., Erhardt, S., Bryleva, E. Y., Achtyes, E. D., & Postolache, T. T. (2015). The role of inflammation in suicidal behaviour. *Acta Psychiatrica Scandinavica*, *132,* 192–203. http://dx.doi.org/10.1111/acps.12458

Burton, E., Stice, E., & Seeley, J. R. (2004). A prospective test of the stress-buffering model of depression in adolescent girls: No support once again. *Journal of Consulting and Clinical Psychology*, *72,* 689–697. http://dx.doi.org/10.1037/0022-006X.72.4.689

Byrne, D. G., Byrne, A. E., & Reinhart, M. I. (1995). Personality, stress and the decision to commence cigarette smoking in adolescence. *Journal of Psychosomatic Research*, *39,* 53–62. http://dx.doi.org/10.1016/0022-3999(94)00074-F

Byrne, D. G., & Mazanov, J. (2002). Sources of stress in Australian adolescents: Factor structure and stability over time. *Stress and Health*, *18,* 185–192. http://dx.doi.org/10.1002/smi.940

Calder, P. C. (2006). n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *American Journal of Clinical Nutrition, 83*(6, Suppl.), 1505S–1519S.

Capuron, L., & Miller, A. H. (2004). Cytokines and psychopathology: Lessons from interferon-alpha. *Biological Psychiatry*, *56,* 819–824. http://dx.doi.org/10.1016/j.biopsych.2004.02.009

Capuron, L., Pagnoni, G., Demetrashvili, M., Woolwine, B. J., Nemeroff, C. B., Berns, G. S., & Miller, A. H. (2005). Anterior cingulate activation and error processing during interferon-alpha treatment. *Biological Psychiatry*, *58,* 190–196. http://dx.doi.org/10.1016/j.biopsych.2005.03.033

Capuron, L., Pagnoni, G., Drake, D. F., Woolwine, B. J., Spivey, J. R., Crowe, R. J., . . . Miller, A. H. (2012). Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Archives of General Psychiatry*, *69,* 1044–1053. http://dx.doi.org/10.1001/archgenpsychiatry.2011.2094

Casey, P. R., Dunn, G., Kelly, B. D., Birkbeck, G., Dalgard, O. S., Lehtinen, V., . . . Dowrick, C. (2006). Factors associated with suicidal ideation in the general population: Five-centre analysis from the ODIN study. *British Journal of Psychiatry*, *189,* 410–415. http://dx.doi.org/10.1192/bjp.bp.105.017368

Cavanagh, J. T., Owens, D. G., & Johnstone, E. C. (1999). Life events in suicide and undetermined death in south-east Scotland: A case-control study using the method of psychological autopsy. *Social Psychiatry and Psychiatric Epidemiology*, *34,* 645–650. http://dx.doi.org/10.1007/s001270050187

Centers for Disease Control and Prevention. (2013). *Welcome to WISQARS.* Retrieved from http://www.cdc.gov/injury/wisqars/index.html

Clark, D. A., Beck, A. T., & Alford, B. A. (1999). *Scientific foundations of cognitive theory and therapy of depression.* Hoboken, NJ: Wiley.

Clark, M., Post, R. M., Weiss, S. R., Cain, C. J., & Nakajima, T. (1991). Regional expression of c-fos mRNA in rat brain during the evolution of amygdala kindled seizures. *Brain Research: Molecular Brain Research*, *11,* 55–64. http://dx.doi.org/10.1016/0169-328X(91)90021-O

Coddington, R. D. (1972). The significance of life events as etiologic factors in the diseases of children: II. A study of a normal population. *Journal of Psychosomatic Research*, *16,* 205–213. http://dx.doi.org/10.1016/0022-3999(72)90045-1

Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological stress and disease. *JAMA*, *298,* 1685–1687. http://dx.doi.org/10.1001/jama.298.14.1685

Cohen, S., Kessler, R. C., & Gordon, L. U. (1997). *Measuring stress: A guide for health and social scientists.* Oxford, England: Oxford University Press.

Cole, S. W., Korin, Y. D., Fahey, J. L., & Zack, J. A. (1998). Norepinephrine accelerates HIV replication via protein kinase A-dependent effects on cytokine production. *Journal of Immunology*, *161,* 610–616.

Conway, C. C., Slavich, G. M., & Hammen, C. (2014). Daily stress reactivity and serotonin transporter gene (5-HTTLPR) variation: Internalizing responses to everyday stress as a possible transdiagnostic phenotype. *Biology of Mood and Anxiety Disorders*, *4,* 2. http://dx.doi.org/10.1186/2045-5380-4-2

Couzin-Frankel, J. (2010). Inflammation bares a dark side. *Science*, *330,* 1621. http://dx.doi.org/10.1126/science.330.6011.1621

Cui, X.-J., & Vaillant, G. E. (1997). Does depression generate negative life events? *Journal of Nervous and Mental Disease*, *185,* 145–150. http://dx.doi.org/10.1097/00005053-199703000-00003

Cutolo, M., & Straub, R. H. (2006). Stress as a risk factor in the pathogenesis of rheumatoid arthritis. *Neuroimmunomodulation, 13,* 277–282. http://dx.doi.org/10.1159/000104855

Daley, S. E., Hammen, C., Burge, D., Davila, J., Paley, B., Lindberg, N., & Herzberg, D. S. (1997). Predictors of the generation of episodic stress: A longitudinal study of late adolescent women. *Journal of Abnormal Psychology*, *106,* 251–259. http://dx.doi.org/10.1037/0021-843X.106.2.251

Daley, S. E., Hammen, C., & Rao, U. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *Journal of Abnormal Psychology*, *109,* 525–533. http://dx.doi.org/10.1037/0021-843X.109.3.525

Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, *21,* 153–160. http://dx.doi.org/10.1016/j.bbi.2006.09.006

DellaGioia, N., & Hannestad, J. (2010). A critical review of human endotoxin administration as an experimental paradigm of depression. *Neuroscience and Biobehavioral Reviews*, *34,* 130–143. http://dx.doi.org/10.1016/j.neubiorev.2009.07.014

Dohrenwend, B. P. (2006). Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological Bulletin*, *132,* 477–495. http://dx.doi.org/10.1037/0033-2909.132.3.477

Dohrenwend, B. P., Raphael, K. G., Schwartz, S., Stueve, A., & Skodol, A. (1993). The structured event probe and narrative rating method for measuring stressful life events. In L. Goldberger, S. Breznitz, L. Goldberger, & S. Breznitz (Eds.), *Handbook of stress: Theoretical and clinical aspects* (2nd ed., pp. 174–199). New York, NY: Free Press.

Dolan, R. J., Calloway, S. P., Fonagy, P., De Souza, F. V., & Wakeling, A. (1985). Life events, depression and hypothalamic-pituitary-adrenal axis function. *British Journal of Psychiatry*, *147,* 429–433. http://dx.doi.org/10.1192/bjp.147.4.429

Dooley, L. N., Slavich, G. M., Moreno, P. I., & Bower, J. E. (2017). Strength through adversity: Moderate lifetime stress exposure is associated with psychological resilience in breast cancer survivors. *Stress and Health*. Advance online publication. http://dx.doi.org/10.1002/smi.2739

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67,* 446–457. http://dx.doi.org/10.1016/j.biopsych.2009.09.033

Duberstein, P. R., Conwell, Y., Conner, K. R., Eberly, S., & Caine, E. D. (2004). Suicide at 50 years of age and older: Perceived physical illness, family discord and financial strain. *Psychological Medicine*, *34,* 137–146. http://dx.doi.org/10.1017/S0033291703008584

Eberhart, N. K., Auerbach, R. P., Bigda-Peyton, J., & Abela, J. R. Z. (2011). Maladaptive schemas and depression: Tests of stress generation and diathesis-stress models. *Journal of Social and Clinical Psychology*, *30,* 75–104. http://dx.doi.org/10.1521/jscp.2011.30.1.75

Fagundes, C. P., & Way, B. (2014). Early-life stress and adult inflammation. *Current Directions in Psychological Science*, *23,* 277–283. http://dx.doi.org/10.1177/0963721414535603

Fanous, A. H., Prescott, C. A., & Kendler, K. S. (2004). The prediction of thoughts of death or self-harm in a population-based sample of female twins. *Psychological Medicine*, *34,* 301–312. http://dx.doi.org/10.1017/S0033291703008857

Fergusson, D. M., & Horwood, L. J. (1987). Vulnerability to life events exposure. *Psychological Medicine*, *17,* 739–749. http://dx.doi.org/10.1017/S0033291700025976

Fergusson, D. M., Woodward, L. J., & Horwood, L. J. (2000). Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychological Medicine*, *30,* 23–39. http://dx.doi.org/10.1017/S003329179900135X

Finlay-Jones, R., & Brown, G. W. (1981). Types of stressful life event and the onset of anxiety and depressive disorders. *Psychological Medicine*, *11,* 803–815. http://dx.doi.org/10.1017/S0033291700041301

Fischler, I., & Bradley, M. (2006). Event-related potential studies of language and emotion: Words, phrases, and task effects. *Progress in Brain Research*, *156,* 185–203. http://dx.doi.org/10.1016/S0079-6123(06)56009-1

Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. *Psychophysiology*, *46,* 521–530. http://dx.doi.org/10.1111/j.1469-8986.2009.00796.x

Frank, E., Anderson, B., Reynolds, C. F., III, Ritenour, A., & Kupfer, D. J. (1994). Life events and the research diagnostic criteria endogenous subtype: A confirmation of the distinction using the Bedford College methods. *Archives of General Psychiatry*, *51,* 519–524. http://dx.doi.org/10.1001/archpsyc.1994.03950070011005

Fuligni, A. J., Telzer, E. H., Bower, J., Cole, S. W., Kiang, L., & Irwin, M. R. (2009). A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. *Psychosomatic Medicine*, *71,* 329–333. http://dx.doi.org/10.1097/PSY.0b013e3181921b1f

Gershon, A., Hayward, C., Schraedley-Desmond, P., Rudolph, K. D., Booster, G. D., & Gotlib, I. H. (2011). Life stress and first onset of psychiatric disorders in daughters of depressed mothers. *Journal of Psychiatric Research*, *45,* 855–862. http://dx.doi.org/10.1016/j.jpsychires.2011.03.016

Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology*, *5,* 243–251. http://dx.doi.org/10.1038/nri1571

Goddard, G. V., McIntyre, D. C., & Leech, C. K. (1969). A permanent change in brain function resulting from daily electrical stimulation. *Experimental Neurology*, *25,* 295–330. http://dx.doi.org/10.1016/0014-4886(69)90128-9

Goldstein, B. L., Hayden, E. P., & Klein, D. N. (2015). Stability of self-referent encoding task performance and associations with change in depressive symptoms from early to middle childhood. *Cognition and Emotion*, *29,* 1445–1455. http://dx.doi.org/10.1080/02699931.2014.990358

Goodwin, R. D., Fergusson, D. M., & Horwood, L. J. (2004). Asthma and depressive and anxiety disorders among young persons in the community. *Psychological Medicine*, *34,* 1465–1474. http://dx.doi.org/10.1017/S0033291704002739

Goodyer, I. M., Herbert, J., Tamplin, A., & Altham, P. M. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *British Journal of Psychiatry*, *177,* 499–504. http://dx.doi.org/10.1192/bjp.177.6.499

Gorman, D. M. (1993). A review of studies comparing checklist and interview methods of data collection in life event research. *Behavioral Medicine*, *19,* 66–73. http://dx.doi.org/10.1080/08964289.1993.9937567

Graff, L. A., Walker, J. R., & Bernstein, C. N. (2009). Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. *Inflammatory Bowel Diseases*, *15,* 1105–1118. http://dx.doi.org/10.1002/ibd.20873

Graham, J. E., Christian, L. M., & Kiecolt-Glaser, J. K. (2006). Stress, age, and immune function: Toward a lifespan approach. *Journal of Behavioral Medicine*, *29,* 389–400. http://dx.doi.org/10.1007/s10865-006-9057-4

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child and Adolescent Psychology*, *33,* 412–425. http://dx.doi.org/10.1207/s15374424jccp3302_23

Grisanti, L. A., Woster, A. P., Dahlman, J., Sauter, E. R., Combs, C. K., & Porter, J. E. (2011). α1-adrenergic receptors positively regulate Toll-like receptor cytokine production from human monocytes and macrophages. *Journal of Pharmacology and Experimental Therapeutics*, *338,* 648–657. http://dx.doi.org/10.1124/jpet.110.178012

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology*, *100,* 555–561. http://dx.doi.org/10.1037/0021-843X.100.4.555

Hammen, C. (1992). Life events and depression: The plot thickens. *American Journal of Community Psychology*, *20,* 179–193. http://dx.doi.org/10.1007/BF00940835

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1,* 293–319. http://dx.doi.org/10.1146/annurev.clinpsy.1.102803.143938

Hammen, C. (2006). Stress generation in depression: Reflections on origins, research, and future directions. *Journal of Clinical Psychology*, *62*, 1065–1082. http://dx.doi.org/10.1002/jclp.20293

Hammen, C. (2009). Stress exposure and stress generation in adolescent depression. In S. Nolen-Hoeksema, L. M. Hilt, S. Nolen-Hoeksema, & L. M. Hilt (Eds.), *Handbook of depression in adolescents* (pp. 305–333). New York, NY: Routledge.

Hammen, C. (2016). Depression and stressful environments: Identifying gaps in conceptualization and measurement. *Anxiety, Stress, and Coping: An International Journal*, *29*, 335–351. http://dx.doi.org/10.1080/10615806.2015.1134788

Hammen, C., & Brennan, P. A. (2001). Depressed adolescents of depressed and nondepressed mothers: Tests of an interpersonal impairment hypothesis. *Journal of Consulting and Clinical Psychology*, *69*, 284–294. http://dx.doi.org/10.1037/0022-006X.69.2.284

Hammen, C., & Brennan, P. A. (2002). Interpersonal dysfunction in depressed women: Impairments independent of depressive symptoms. *Journal of Affective Disorders*, *72*, 145–156. http://dx.doi.org/10.1016/S0165-0327(01)00455-4

Hankin, B. L., Kassel, J. D., & Abela, J. R. (2005). Adult attachment dimensions and specificity of emotional distress symptoms: Prospective investigations of cognitive risk and interpersonal stress generation as mediating mechanisms. *Personality and Social Psychology Bulletin*, *31*, 136–151. http://dx.doi.org/10.1177/0146167204271324

Harkness, K. L. (2008). Life events and hassles. In K. S. Dobson, D. J. A. Dozois, K. S. Dobson, & D. J. A. Dozois (Eds.), *Risk factors in depression* (pp. 317–341). http://dx.doi.org/10.1016/B978-0-08-045078-0.00014-9

Harkness, K. L., Lumley, M. N., & Truss, A. E. (2008). Stress generation in adolescent depression: The moderating role of child abuse and neglect. *Journal of Abnormal Child Psychology*, *36*, 421–432. http://dx.doi.org/10.1007/s10802-007-9188-2

Harkness, K. L., & Luther, J. (2001). Clinical risk factors for the generation of life events in major depression. *Journal of Abnormal Psychology*, *110*, 564–572. http://dx.doi.org/10.1037/0021-843X.110.4.564

Harkness, K. L., & Monroe, S. M. (2006). Severe melancholic depression is more vulnerable than non-melancholic depression to minor precipitating life events. *Journal of Affective Disorders, 91*, 257–263. http://dx.doi.org/10.1016/j.jad.2005.12.009

Harkness, K. L., & Monroe, S. M. (2016). The assessment and measurement of adult life stress: Basic premises, operational principles, and design requirements. *Journal of Abnormal Psychology*, *125*, 727–745. http://dx.doi.org/10.1037/abn0000178

Harkness, K. L., & Stewart, J. G. (2009). Symptom specificity and the prospective generation of life events in adolescence. *Journal of Abnormal Psychology*, *118*, 278–287. http://dx.doi.org/10.1037/a0015749

Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews*, *12*, 123–137. http://dx.doi.org/10.1016/S0149-7634(88)80004-6

Hawton, K., Saunders, K. E., & O'Connor, R. C. (2012). Self-harm and suicide in adolescents. *Lancet*, *379*, 2373–2382. http://dx.doi.org/10.1016/S0140-673660322-5

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*, *284*, 592–597. http://dx.doi.org/10.1001/jama.284.5.592

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*, *71*, 171–186. http://dx.doi.org/10.1097/PSY.0b013e3181907c1b

Irwin, M. R., & Cole, S. W. (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*, *11*, 625–632. http://dx.doi.org/10.1038/nri3042

Irwin, M. R., & Slavich, G. M. (2017). Psychoneuro-immunology. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (4th ed., pp. 354–376). http://dx.doi.org/10.1017/9781107415782.017

Jarcho, M. R., Slavich, G. M., Tylova-Stein, H., Wolkowitz, O. M., & Burke, H. M. (2013). Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. *Biological Psychology*, *93*, 150–158. http://dx.doi.org/10.1016/j.biopsycho.2013.01.018

Joiner, T. (2005). *Why people die by suicide*. Cambridge, MA: Harvard University Press.

Joiner, T. E., Jr., & Rudd, M. D. (1995). Negative attributional style for interpersonal events and the occurrence of severe interpersonal disruptions as predictors of self-reported suicidal ideation. *Suicide and Life-Threatening Behavior*, *25*, 297–304.

Karin, M. (2006). Nuclear factor-kappaB in cancer development and progression. *Nature*, *441*, 431–436. http://dx.doi.org/10.1038/nature04870

Kaslow, N. J., Thompson, M. P., Okun, A., Price, A., Young, S., Bender, M., . . . Parker, R. (2002). Risk and protective factors for suicidal behavior in abused African American women. *Journal of Consulting and Clinical Psychology*, *70*, 311–319. http://dx.doi.org/10.1037/0022-006X.70.2.311

Katz, P. P., & Yelin, E. H. (1993). Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis. *Journal of Rheumatology*, *20,* 790–796.

Kendler, K. S., Gardner, C. O., & Prescott, C. A. (2002). Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry*, *159,* 1133–1145. http://dx.doi.org/10.1176/appi.ajp.159.7.1133

Kendler, K. S., Gardner, C. O., & Prescott, C. A. (2003). Personality and the experience of environmental adversity. *Psychological Medicine*, *33,* 1193–1202. http://dx.doi.org/10.1017/S0033291703008298

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., & Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Archives of General Psychiatry*, *60,* 789–796. http://dx.doi.org/10.1001/archpsyc.60.8.789

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1998). Stressful life events and major depression: Risk period, long-term contextual threat, and diagnostic specificity. *Journal of Nervous and Mental Disease*, *186,* 661–669. http://dx.doi.org/10.1097/00005053-199811000-00001

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry*, *156,* 837–841. http://dx.doi.org/10.1176/ajp.156.6.837

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry*, *152,* 833–842. http://dx.doi.org/10.1176/ajp.152.6.833

Kendler, K. S., Thornton, L. M., & Gardner, C. O. (2000). Stressful life events and previous episodes in the etiology of major depression in women: An evaluation of the "kindling" hypothesis. *American Journal of Psychiatry*, *157,* 1243–1251. http://dx.doi.org/10.1176/appi.ajp.157.8.1243

Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R., Demyttenaere, K., Gasquet, I., . . . Ustün, T. B. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *6,* 168–176.

Kessler, R. C., Berglund, P., Borges, G., Nock, M., & Wang, P. S. (2005). Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990–1992 to 2001–2003. *JAMA*, *293,* 2487–2495. http://dx.doi.org/10.1001/jama.293.20.2487

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of *DSM–IV* disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62,* 593–602. http://dx.doi.org/10.1001/archpsyc.62.6.593

Khan, M. M., Mahmud, S., Karim, M. S., Zaman, M., & Prince, M. (2008). Case-control study of suicide in Karachi, Pakistan. *British Journal of Psychiatry*, *193,* 402–405. http://dx.doi.org/10.1192/bjp.bp.107.042069

Kirmayer, L. J., Boothroyd, L. J., & Hodgins, S. (1998). Attempted suicide among Inuit youth: Psychosocial correlates and implications for prevention. *Canadian Journal of Psychiatry*, *43,* 816–822. http://dx.doi.org/10.1177/070674379804300806

Kivimäki, M., Virtanen, M., Elovainio, M., Kouvonen, A., Väänänen, A., & Vahtera, J. (2006). Work stress in the etiology of coronary heart disease—a meta-analysis. *Scandinavian Journal of Work, Environment, and Health*, *32,* 431–442. http://dx.doi.org/10.5271/sjweh.1049

Klein, D. N., Lewinsohn, P. M., & Seeley, J. R. (1997). Psychosocial characteristics of adolescents with a past history of dysthymic disorder: Comparison with adolescents with past histories of major depressive and non-affective disorders, and never mentally ill controls. *Journal of Affective Disorders*, *42,* 127–135. http://dx.doi.org/10.1016/S0165-0327(96)01403-6

Köhler, O., Benros, M., Nordentoft, M., Mors, P., & Krogh, J. (2015). Effect of anti-inflammatory treatment on depression, depressive symptoms and side effects: A systematic review and meta-analysis of randomized clinical trials. *European Psychiatry*, *30,* 342. http://dx.doi.org/10.1016/S0924-9338(15)30268-6

Kohn, Y., Zislin, J., Agid, O., Hanin, B., Troudart, T., Shapira, B., . . . Lerer, B. (2001). Increased prevalence of negative life events in subtypes of major depressive disorder. *Comprehensive Psychiatry*, *42,* 57–63. http://dx.doi.org/10.1053/comp.2001.19753

Kuiper, N. A., & Derry, P. A. (1982). Depressed and nondepressed content self-reference in mild depressives. *Journal of Personality*, *50,* 67–80. http://dx.doi.org/10.1111/j.1467-6494.1982.tb00746.x

Leff, M. J., Roatch, J. F., & Bunney, W. E., Jr. (1970). Environmental factors preceding the onset of severe depressions. *Psychiatry: Interpersonal and Biological Processes*, *33,* 293–311. http://dx.doi.org/10.1080/00332747.1970.11023630

Leserman, J. (2003). HIV disease progression: Depression, stress, and possible mechanisms. *Biological Psychiatry*, *54,* 295–306. http://dx.doi.org/10.1016/S0006-3223(03)00323-8

Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression:

Differential processes of psychosocial risk. *Journal of Abnormal Psychology*, *108,* 483–489. http://dx.doi.org/10.1037/0021-843X.108.3.483

Lewinsohn, P. M., Rohde, P., & Gau, J. M. (2003). Comparability of self-report checklist and interview data in the assessment of stressful life events in young adults. *Psychological Reports*, *93,* 459–471. http://dx.doi.org/10.2466/pr0.2003.93.2.459

Liu, R. T. (2013). Stress generation: Future directions and clinical implications. *Clinical Psychology Review*, *33,* 406–416. http://dx.doi.org/10.1016/j.cpr.2013.01.005

Liu, R. T., & Alloy, L. B. (2010). Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clinical Psychology Review*, *30,* 582–593. http://dx.doi.org/10.1016/j.cpr.2010.04.010

Liu, R. T., Choi, J. Y., Boland, E. M., Mastin, B. M., & Alloy, L. B. (2013). Childhood abuse and stress generation: The mediational effect of depressogenic cognitive styles. *Psychiatry Research*, *206,* 217–222. http://dx.doi.org/10.1016/j.psychres.2012.12.001

Liu, R. T., & Miller, I. (2014). Life events and suicidal ideation and behavior: A systematic review. *Clinical Psychology Review*, *34,* 181–192. http://dx.doi.org/10.1016/j.cpr.2014.01.006

Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., . . . Kipnis, J. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, *523,* 337–341. http://dx.doi.org/10.1038/nature14432

Lovejoy, M. C., & Steuerwald, B. L. (1997). Subsyndromal unipolar and bipolar disorders II: Comparisons on daily stress levels. *Cognitive Therapy and Research*, *21,* 607–618. http://dx.doi.org/10.1023/A:1021800106223

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10,* 434–445. http://dx.doi.org/10.1038/nrn2639

Mann, J. J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., . . . Hendin, H. (2005). Suicide prevention strategies: A systematic review. *JAMA*, *294,* 2064–2074. http://dx.doi.org/10.1001/jama.294.16.2064

Marin, T. J., Chen, E., Munch, J. A., & Miller, G. E. (2009). Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. *Psychosomatic Medicine*, *71,* 378–384. http://dx.doi.org/10.1097/PSY.0b013e318199dbc3

Mazure, C. M. (1998). Life stressors as risk factors in depression. *Clinical Psychology: Science and Practice*, *5,* 291–313. http://dx.doi.org/10.1111/j.1468-2850.1998.tb00151.x

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840,* 33–44. http://dx.doi.org/10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S., & Kalia, M. (2010). The role of corticosteroids and stress in chronic pain conditions. *Metabolism: Clinical and Experimental, 59*(Suppl. 1), S9–S15. http://dx.doi.org/10.1016/j.metabol.2010.07.012

McKeown, R. E., Garrison, C. Z., Cuffe, S. P., Waller, J. L., Jackson, K. L., & Addy, C. L. (1998). Incidence and predictors of suicidal behaviors in a longitudinal sample of young adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37,* 612–619. http://dx.doi.org/10.1097/00004583-199806000-00011

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47,* 578–591. http://dx.doi.org/10.1016/j.neubiorev.2014.10.012

McQuaid, J. R., Monroe, S. M., Roberts, J. E., Johnson, S. L., Garamoni, G. L., Kupfer, D. J., & Frank, E. (1992). Toward the standardization of life stress assessment: Definitional discrepancies and inconsistencies in methods. *Stress Medicine*, *8,* 47–56. http://dx.doi.org/10.1002/smi.2460080107

Medzhitov, R. (2001). Toll-like receptors and innate immunity. *Nature Reviews Immunology*, *1,* 135–145. http://dx.doi.org/10.1038/35100529

Medzhitov, R. (2007). Recognition of microorganisms and activation of the immune response. *Nature*, *449,* 819–826. http://dx.doi.org/10.1038/nature06246

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature, 454,* 428–435. http://dx.doi.org/10.1038/nature07201

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16,* 22–34. http://dx.doi.org/10.1038/nri.2015.5

Miller, G., Chen, E., & Cole, S. W. (2009). Health psychology: Developing biologically plausible models linking the social world and physical health. *Annual Review of Psychology*, *60,* 501–524. http://dx.doi.org/10.1146/annurev.psych.60.110707.163551

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology*, *21,* 531–541. http://dx.doi.org/10.1037/0278-6133.21.6.531

Monroe, S. M. (2008). Modern approaches to conceptualizing and measuring human life stress. *Annual Review of Clinical Psychology*, *4,* 33–52. http://dx.doi.org/10.1146/annurev.clinpsy.4.022007.141207

Monroe, S. M., Harkness, K., Simons, A. D., & Thase, M. E. (2001). Life stress and the symptoms of major depression. *Journal of Nervous and Mental Disease*, *189,* 168–175. http://dx.doi.org/10.1097/00005053-200103000-00005

Monroe, S. M., & Harkness, K. L. (2005). Life stress, the "kindling" hypothesis, and the recurrence of depression: Considerations from a life stress perspective. *Psychological Review*, *112,* 417–445. http://dx.doi.org/10.1037/0033-295X.112.2.417

Monroe, S. M., Rohde, P., Seeley, J. R., & Lewinsohn, P. M. (1999). Life events and depression in adolescence: Relationship loss as a prospective risk factor for first onset of major depressive disorder. *Journal of Abnormal Psychology*, *108,* 606–614. http://dx.doi.org/10.1037/0021-843X.108.4.606

Monroe, S. M., & Slavich, G. M. (2016). Psychological stressors: Overview. In G. Fink (Ed.), *Stress: Concepts, cognition, emotion, and behavior* (pp. 109–115). Cambridge, MA: Academic Press.

Monroe, S. M., Slavich, G. M., & Georgiades, K. (2014). The social environment and depression: The roles of life stress. In I. H. Gotlib & C. L. Hammen (Eds.), *Handbook of depression* (3rd ed., pp. 296–314). New York, NY: Guilford Press.

Monroe, S. M., Slavich, G. M., & Gotlib, I. H. (2014). Life stress and family history for depression: The moderating role of past depressive episodes. *Journal of Psychiatric Research*, *49,* 90–95. http://dx.doi.org/10.1016/j.jpsychires.2013.11.005

Monroe, S. M., Thase, M. E., Hersen, M., Himmelhoch, J. M., & Bellack, A. S. (1985). Life events and the endogenous-nonendogenous distinction in the treatment and posttreatment course of depression. *Comprehensive Psychiatry*, *26,* 175–186. http://dx.doi.org/10.1016/0010-440X(85)90038-0

Murphy, M. L. M., Slavich, G. M., Chen, E., & Miller, G. E. (2015). Targeted rejection predicts decreased anti-inflammatory gene expression and increased symptom severity in youth with asthma. *Psychological Science*, *26,* 111–121. http://dx.doi.org/10.1177/0956797614556320

Murphy, M. L. M., Slavich, G. M., Rohleder, N., & Miller, G. E. (2013). Targeted rejection triggers differential pro- and anti-inflammatory gene expression in adolescents as a function of social status. *Clinical Psychological Science*, *1,* 30–40. http://dx.doi.org/10.1177/2167702612455743

Muscatell, K. A., Slavich, G. M., Monroe, S. M., & Gotlib, I. H. (2009). Stressful life events, chronic difficulties, and the symptoms of clinical depression. *Journal of Nervous and Mental Disease*, *197,* 154–160. http://dx.doi.org/10.1097/NMD.0b013e318199f77b

Newman, S. C., & Bland, R. C. (1994). Life events and the 1-year prevalence of major depressive episode, generalized anxiety disorder, and panic disorder in a community sample. *Comprehensive Psychiatry*, *35,* 76–82. http://dx.doi.org/10.1016/0010-440X(94)90173-2

Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and suicidal behavior. *Epidemiological Review*, *30,* 133–154. http://dx.doi.org/10.1093/epirev/mxn002

Nock, M. K., Green, J. G., Hwang, I., McLaughlin, K. A., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2013). Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: Results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*, *70,* 300–310. http://dx.doi.org/10.1001/2013.jamapsychiatry.55

Nusslock, R., & Miller, G. E. (2016). Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biological Psychiatry*, *80,* 23–32. http://dx.doi.org/10.1016/j.biopsych.2015.05.017

O'Donovan, A., Slavich, G. M., Epel, E. S., & Neylan, T. C. (2013). Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging. *Neuroscience and Biobehavioral Reviews*, *37,* 96–108. http://dx.doi.org/10.1016/j.neubiorev.2012.10.013

Pan, A., Keum, N., Okereke, O. I., Sun, Q., Kivimaki, M., Rubin, R. R., & Hu, F. B. (2012). Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. *Diabetes Care*, *35,* 1171–1180. http://dx.doi.org/10.2337/dc11-2055

Patton, G. C., Coffey, C., Posterino, M., Carlin, J. B., & Bowes, G. (2003). Life events and early onset depression: Cause or consequence? *Psychological Medicine*, *33,* 1203–1210. http://dx.doi.org/10.1017/S0033291703008626

Paykel, E. S. (1983). Methodological aspects of life events research. *Journal of Psychosomatic Research*, *27,* 341–352. http://dx.doi.org/10.1016/0022-3999(83)90065-X

Paykel, E. S. (1997). The Interview for Recent Life Events. *Psychological Medicine*, *27,* 301–310. http://dx.doi.org/10.1017/S0033291796004424

Paykel, E. S. (2003). Life events and affective disorders. *Acta Psychiatrica Scandinavica*, *108*(Suppl. 418), 61–66. http://dx.doi.org/10.1034/j.1600-0447.108.s418.13.x

Paykel, E. S., Rao, B. M., & Taylor, C. N. (1984). Life stress and symptom pattern in out-patient depression. *Psychological Medicine*, *14,* 559–568. http://dx.doi.org/10.1017/S0033291700015166

Poole, H., White, S., Blake, C., Murphy, P., & Bramwell, R. (2009). Depression in chronic pain patients: Prevalence

and measurement. *Pain Practice*, *9,* 173–180. http://dx.doi.org/10.1111/j.1533-2500.2009.00274.x

Poon, D. C., Ho, Y. S., Chiu, K., & Chang, R. C. (2013). Cytokines: How important are they in mediating sickness? *Neuroscience and Biobehavioral Reviews*, *37,* 1–10. http://dx.doi.org/10.1016/j.neubiorev.2012.11.001

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, *149,* 999–1010. http://dx.doi.org/10.1176/ajp.149.8.999

Post, R. M. (2007). Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neuroscience and Biobehavioral Reviews*, *31,* 858–873. http://dx.doi.org/10.1016/j.neubiorev.2007.04.003

Post, R. M., Rubinow, D. R., & Ballenger, J. C. (1986). Conditioning and sensitisation in the longitudinal course of affective illness. *British Journal of Psychiatry*, *149,* 191–201. http://dx.doi.org/10.1192/bjp.149.2.191

Poulton, R. G., & Andrews, G. (1992). Personality as a cause of adverse life events. *Acta Psychiatrica Scandinavica*, *85,* 35–38. http://dx.doi.org/10.1111/j.1600-0447.1992.tb01439.x

Rahe, R. H. (1978). Life change measurement clarification. *Psychosomatic Medicine*, *40,* 95–98. http://dx.doi.org/10.1097/00006842-197803000-00001

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27,* 24–31. http://dx.doi.org/10.1016/j.it.2005.11.006

Ravindran, A. V., Matheson, K., Griffiths, J., Merali, Z., & Anisman, H. (2002). Stress, coping, uplifts, and quality of life in subtypes of depression: A conceptual frame and emerging data. *Journal of Affective Disorders*, *71,* 121–130. http://dx.doi.org/10.1016/S0165-0327(01)00389-5

Regier, D. A., Boyd, J. H., Burke, J. D., Jr., Rae, D. S., Myers, J. K., Kramer, M., . . . Locke, B. Z. (1988). One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Archives of General Psychiatry*, *45,* 977–986. http://dx.doi.org/10.1001/archpsyc.1988.01800350011002

Ricciotti, E., & FitzGerald, G. A. (2011). Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *31,* 986–1000. http://dx.doi.org/10.1161/ATVBAHA.110.207449

Robins, C. J., Block, P., & Peselow, E. D. (1990). Endogenous and non-endogenous depressions: Relations to life events, dysfunctional attitudes and event perceptions. *British Journal of Clinical Psychology, 29,* 201–207. http://dx.doi.org/10.1111/j.2044-8260.1990.tb00870.x

Roy, A., Breier, A., Doran, A. R., & Pickar, D. (1985). Life events in depression. Relationship to subtypes. *Journal of Affective Disorders*, *9,* 143–148. http://dx.doi.org/10.1016/0165-0327(85)90093-X

Safford, S. M., Alloy, L. B., Abramson, L. Y., & Crossfield, A. G. (2007). Negative cognitive style as a predictor of negative life events in depression-prone individuals: A test of the stress generation hypothesis. *Journal of Affective Disorders*, *99,* 147–154. http://dx.doi.org/10.1016/j.jad.2006.09.003

Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P., & Vale, W. (1987). Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science*, *238,* 522–524. http://dx.doi.org/10.1126/science.2821621

Sarason, I. G., & Johnson, J. H. (1976). *The Life Experiences Survey: Preliminary findings*. Seattle: University of Washington.

Segal, Z. V., Williams, J. M., Teasdale, J. D., & Gemar, M. (1996). A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine*, *26,* 371–380. http://dx.doi.org/10.1017/S0033291700034760

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130,* 601–630. http://dx.doi.org/10.1037/0033-2909.130.4.601

Seo, D., Tsou, K. A., Ansell, E. B., Potenza, M. N., & Sinha, R. (2014). Cumulative adversity sensitizes neural response to acute stress: Association with health symptoms. *Neuropsychopharmacology*, *39,* 670–680. http://dx.doi.org/10.1038/npp.2013.250

Shah, P. J., Ebmeier, K. P., Glabus, M. F., & Goodwin, G. M. (1998). Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *British Journal of Psychiatry*, *172,* 527–532. http://dx.doi.org/10.1192/bjp.172.6.527

Sheline, Y. I., Gado, M. H., & Price, J. L. (1998). Amygdala core nuclei volumes are decreased in recurrent major depression. *NeuroReport*, *9,* 2023–2028. http://dx.doi.org/10.1097/00001756-199806220-00021

Sheline, Y. I., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience*, *19,* 5034–5043.

Shestyuk, A. Y., & Deldin, P. J. (2010). Automatic and strategic representation of the self in major depression: Trait and state abnormalities. *American Journal of Psychiatry*, *167,* 536–544. http://dx.doi.org/10.1176/appi.ajp.2009.06091444

Shields, G. S., Moons, W. G., & Slavich, G. M. (2017). Better executive function under stress mitigates the effects of recent life stress exposure on health in young adults. *Stress*, *20,* 75–85. http://dx.doi.org/10.1080/1-253890.2017.1286322

Shields, G. S., Moons, W. G., & Slavich, G. M. (in press). Inflammation, self-regulation, and health: An immunologic model of self-regulatory failure. *Perspectives on Psychological Science.*

Shih, J. H. (2006). Sex differences in stress generation: An examination of sociotropy/autonomy, stress, and depressive symptoms. *Personality and Social Psychology Bulletin*, *32,* 434–446. http://dx.doi.org/10.1177/0146167205282739

Shih, J. H., Abela, J. R., & Starrs, C. (2009). Cognitive and interpersonal predictors of stress generation in children of affectively ill parents. *Journal of Abnormal Child Psychology*, *37,* 195–208. http://dx.doi.org/10.1007/s10802-008-9267-z

Shrout, P. E., Link, B. G., Dohrenwend, B. P., Skodol, A. E., Stueve, A., & Mirotznik, J. (1989). Characterizing life events as risk factors for depression: The role of fateful loss events. *Journal of Abnormal Psychology*, *98,* 460–467. http://dx.doi.org/10.1037/0021-843X.98.4.460

Simons, A. D., Angell, K. L., Monroe, S. M., & Thase, M. E. (1993). Cognition and life stress in depression: Cognitive factors and the definition, rating, and generation of negative life events. *Journal of Abnormal Psychology*, *102,* 584–591. http://dx.doi.org/10.1037/0021-843X.102.4.584

Slavich, G. M. (2015). Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority. *Brain, Behavior, and Immunity*, *45,* 13–14. http://dx.doi.org/10.1016/j.bbi.2014.10.012

Slavich, G. M. (2016a). Life stress and health: A review of conceptual issues and recent findings. *Teaching of Psychology*, *43,* 346–355. http://dx.doi.org/10.1177/0098628316662768

Slavich, G. M. (2016b). Psychopathology and stress. In H. L. Miller (Ed.), *The Sage encyclopedia of theory in psychology* (pp. 762–764). Thousand Oaks, CA: Sage.

Slavich, G. M., & Cole, S. W. (2013). The emerging field of human social genomics. *Clinical Psychological Science*, *1,* 331–348. http://dx.doi.org/10.1177/2167702613478594

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, *140,* 774–815. http://dx.doi.org/10.1037/a0035302

Slavich, G. M., Monroe, S. M., & Gotlib, I. H. (2011). Early parental loss and depression history: Associations with recent life stress in major depressive disorder. *Journal of Psychiatric Research*, *45,* 1146–1152. http://dx.doi.org/10.1016/j.jpsychires.2011.03.004

Slavich, G. M., O'Donovan, A., Epel, E. S., & Kemeny, M. E. (2010). Black sheep get the blues: A psychobiological model of social rejection and depression. *Neuroscience and Biobehavioral Reviews*, *35,* 39–45. http://dx.doi.org/10.1016/j.neubiorev.2010.01.003

Slavich, G. M., & Shields, G. S. (in press). Assessing lifetime stress exposure using the Stress and Adversity Inventory for Adults (Adult STRAIN): An overview and initial validation. *Psychosomatic Medicine.*

Slavich, G. M., Tartter, M. A., Brennan, P. A., & Hammen, C. (2014). Endogenous opioid system influences depressive reactions to socially painful targeted rejection life events. *Psychoneuroendocrinology*, *49,* 141–149. http://dx.doi.org/10.1016/j.psyneuen.2014.07.009

Slavich, G. M., Thornton, T., Torres, L. D., Monroe, S. M., & Gotlib, I. H. (2009). Targeted rejection predicts hastened onset of major depression. *Journal of Social and Clinical Psychology*, *28,* 223–243. http://dx.doi.org/10.1521/jscp.2009.28.2.223

Slavich, G. M., Way, B. M., Eisenberger, N. I., & Taylor, S. E. (2010). Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proceedings of the National Academy of Sciences, USA, 107,* 14817–14822. http://dx.doi.org/10.1073/pnas.1009164107

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: A prospective study. *Psychoneuroendocrinology*, *38,* 188–200. http://dx.doi.org/10.1016/j.psyneuen.2012.05.013

Speed, B. C., Nelson, B. D., Auerbach, R. P., Klein, D. N., & Hajcak, G. (2016). Depression risk and electrocortical reactivity during self-referential emotional processing in 8 to 14 year-old girls. *Journal of Abnormal Psychology*, *125,* 607–619. http://dx.doi.org/10.1037/abn0000173

Starr, L. R., Hammen, C., Brennan, P. A., & Najman, J. M. (2013). Relational security moderates the effect of serotonin transporter gene polymorphism (5-HTTLPR) on stress generation and depression among adolescents. *Journal of Abnormal Child Psychology*, *41,* 379–388. http://dx.doi.org/10.1007/s10802-012-9682-z

Stein, D. J., Chiu, W. T., Hwang, I., Kessler, R. C., Sampson, N., Alonso, J., . . . Nock, M. K. (2010). Cross-national analysis of the associations between traumatic events and suicidal behavior: Findings from the WHO World Mental Health Surveys. *PLOS ONE*, *5,* e10574. http://dx.doi.org/10.1371/journal.pone.0010574

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, *21,* 901–912. http://dx.doi.org/10.1016/j.bbi.2007.03.011

Stewart, J. G., Esposito, E. C., Glenn, C. R., Gilman, S. E., Pridgen, B., Gold, J., & Auerbach, R. P. (2017). Adolescent self-injurers: Comparing non-ideators, suicide ideators, and suicide attempters. *Journal of Psychiatric Research*, *84,* 105–112. http://dx.doi.org/10.1016/j.jpsychires.2016.09.031

Tennant, C. (2002). Life events, stress and depression: A review of recent findings. *Australian and New Zealand Journal of Psychiatry*, *36,* 173–182. http://dx.doi.org/10.1046/j.1440-1614.2002.01007.x

Thomson, K. C., & Hendrie, H. C. (1972). Environmental stress in primary depressive illness. *Archives of General Psychiatry*, *26,* 130–132. http://dx.doi.org/10.1001/archpsyc.1972.01750200034007

Toussaint, L., Shields, G. S., Dorn, G., & Slavich, G. M. (2016). Effects of lifetime stress exposure on mental and physical health in young adulthood: How stress degrades and forgiveness protects health. *Journal of Health Psychology*, *21,* 1004–1014. http://dx.doi.org/10.1177/1359105314544132

Türkçapar, M. H., Akdemir, A., Orsel, S. D., Demirergi, N., Sirin, A., Kiliç, E. Z., & Ozbay, M. H. (1999). The validity of diagnosis of melancholic depression according to different diagnostic systems. *Journal of Affective Disorders, 54,* 101–107.

van Loo, H. M., de Jonge, P., Romeijn, J. W., Kessler, R. C., & Schoevers, R. A. (2012). Data-driven subtypes of major depressive disorder: A systematic review. *BMC Medicine*, *10,* 156. http://dx.doi.org/10.1186/1741-7015-10-156

Waaktaar, T., Borge, A. I. H., Fundingsrud, H. P., Christie, H. J., & Torgersen, S. (2004). The role of stressful life events in the development of depressive symptoms in adolescence—A longitudinal community study. *Journal of Adolescence*, *27,* 153–163. http://dx.doi.org/10.1016/j.adolescence.2003.09.006

Waelde, L. C., Silvern, L., & Hodges, W. F. (1994). Stressful life events: Moderators of the relationships of gender and gender roles to self-reported depression and suicidality among college students. *Sex Roles, 30,* 1–22. http://dx.doi.org/10.1007/BF01420737

Wenzel, A., & Beck, A. T. (2008). A cognitive model of suicidal behavior: Theory and treatment. *Applied and Preventive Psychology*, *12,* 189–201. http://dx.doi.org/10.1016/j.appsy.2008.05.001

Wetherington, E., Kessler, R. C., & Brown, G. W. (1993). *Training manual and tech. rep. no. for the Structured Life Events Inventory*. Ithaca, NY: Cornell University, Life Course Institute.

Whooley, M. A. (2006). Depression and cardiovascular disease: Healing the broken-hearted. *JAMA, 295,* 2874–2881. http://dx.doi.org/10.1001/jama.295.24.2874

Williamson, D. E., Birmaher, B., Anderson, B. P., al-Shabbout, M., & Ryan, N. D. (1995). Stressful life events in depressed adolescents: The role of dependent events during the depressive episode. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34,* 591–598. http://dx.doi.org/10.1097/00004583-199505000-00011

Wong, J. P. S., Stewart, S. M., Ho, S. Y., Rao, U., & Lam, T. H. (2005). Exposure to suicide and suicidal behaviors among Hong Kong adolescents. *Social Science and Medicine*, *61,* 591–599. http://dx.doi.org/10.1016/j.socscimed.2004.12.012

World Health Organization. (2016). *Suicide data.* Retrieved from http://www.who.int/mental_health/prevention/suicide/suicideprevent/en

Wulsin, L. R., & Singal, B. M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosomatic Medicine*, *65,* 201–210. http://dx.doi.org/10.1097/01.PSY.0000058371.50240.E3

Zimmerman, M., Coryell, W., Pfohl, B., & Stangl, D. (1986). The validity of four definitions of endogenous depression. II. Clinical, demographic, familial, and psychosocial correlates. *Archives of General Psychiatry*, *43,* 234–244. http://dx.doi.org/10.1001/archpsyc.1986.01800030052005