Life Stress, the “Kindling” Hypothesis, and the Recurrence of Depression: Considerations From a Life Stress Perspective

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Major depression is frequently characterized by recurrent episodes over the life course. First lifetime episodes of depression, however, are typically more strongly associated with major life stress than are successive recurrences. A key theoretical issue involves how the role of major life stress changes from an initial episode over subsequent recurrences. The primary conceptual framework for research on life stress and recurrence of depression is the “kindling” hypothesis (R. M. Post, 1992). Despite the strengths of the kindling hypothesis, a review of the research literature reveals inconsistencies and confusion about life stress and its implications for the recurrence of depression. Adopting a life stress perspective, the authors introduce 3 major themes that resolve the inconsistencies in the current literature. They integrate these themes and extrapolate the ideas with available data to develop a preliminary framework for evaluating competing explanatory models and to guide research on life stress and the recurrence of depression.

Major advances in the understanding of mood disorders over recent years have come from recognition of the often chronic and persistent course of depression over the life span (Belsher & Costello, 1988; Keller, 2003; Kennedy, Abbott, & Paykel, 2003). In particular, the likelihood of an individual suffering from repeated episodes of depression has been underscored, along with the related personal and public health implications (Kessler, 2002). Current widely publicized estimates suggest that at least 50% of individuals who have had one depressive episode will have another, 70% of individuals who have had two depressive episodes will have a third, and 90% of individuals with three episodes will have a fourth episode (American Psychiatric Association, 2000; Solomon et al., 2000).

For theories attempting to explain the origins of depression, the distinction between first and subsequent episodes could prove critical (Hammen, Mayol, de Mayo, & Marks, 1986; Monroe, 1982). When taking into account account recurrences of depression, the new challenge of understanding dynamic changes in psychobiological systems over time is introduced. Not only are the investigators and theoretician confronted with sorting out the role of different causal factors and their unification in the etiology of a single episode, but the possible changing roles of causal factors and their configurations in producing subsequent episodes need to be thought through and reconciled as well. Simply put, the conditions that bring on a first episode of depression may differ in kind or arrangement from those that bring on subsequent episodes: “It suggests that the neurobiology of affective disorder is a moving target and changes as a function of the longitudinal course of illness” (Post, 1992, p. 1005).

Life stress and biological susceptibility have long been suspected to play important roles in the onset of a depressive episode (Jackson, 1986; Mazure, 1998; Monroe & Depue, 1991). Obtaining a clear understanding of how such factors unite to cause any particular occurrence of depression, however, has remained a significant barrier to progress (Kendler, Gardner, & Prescott, 2002; Monroe & Simons, 1991). With the emerging awareness of the high rate of recurrence of depression, challenges for understanding how life stress and biological susceptibility coalesce in precipitating a depressive episode are magnified and expanded. Yet in this regard, too, there have been long-standing suspicions that the contribution of life stress changes over time with repeated episodes of depression. Such thinking is poignantly captured by Kraepelin’s (1921) classic observation about a patient who became depressed “. . . after the death first of her husband, next of her dog, and then of her dove” (p. 179).

It is in this light that theorizing about stress sensitization and behavioral kindling has been insightful and significant (Post, 1992; Post & Weiss, 1999). On the basis of animal laboratory studies of electrophysiological kindling as well as research on stress and cocaine sensitization, a framework of ideas has been proposed to explain episodic disorders that initially are stress related but eventually appear to emerge independent of stress: “. . . the model presents a clear-cut example of the shift from episodes that are triggered to those that occur autonomously” (Post, 1992, p. 1001). An extensive research literature consistently supports the kindling...
premise that there is a greater role for major life stress “... in association with the first episode of major affective disorder than with subsequent episodes” (Post, 1992, pp. 999–1000).

The kindling and episode sensitization viewpoint is the major conceptual system available to guide thinking and research on depression and its recurrence over time, particularly with regard to life stress. The theory is widely cited and used to explain a variety of outcomes. To our knowledge, there has been little debate about the thinking involved or about the underlying assumptions of the model (see below; Hlastala et al., 2000; Monroe & Hadjiyannakis, 2002; Segal, Williams, Teasdale, & Gemar, 1996). This is perhaps due to the intuitive appeal of the basic premises, the elegance of the ideas, the breadth of the detailed yet multilevel thinking marshaled in support of the model, and the heuristic intent of the theoretical vignettes provided (e.g., Post, Rubinow, & Ballenger, 1984; Post & Weiss, 1999). This lack of critical discussion, though, does not aid in pressing the fertile ideas forward, in testing the possible limits of the approach’s applicability, or in providing guidance for theoretical development and empirical research. It is in the spirit of furthering the utility and impact of the productive ideas that we offer the present analysis.

At the heart of the matter is the need to explain the changing role of life stress with successive recurrences of depression. Yet what precisely to infer about the changing role of life stress from the clinical observations and empirical findings that support the kindling model simply is not clear. As summarized in Table 1, the basic observation that the role of major life events changes with repeated depressive episodes has been characterized in a variety of ways. For convenience, we categorize the quotations by emphases on particular aspects of the respective characterizations (although it is readily apparent that the similarities and differences are often but of degree). Although these assorted characterizations revolve around similar themes, they are broadly consonant with the empirical evidence, and overlap in their meanings, they are not identical. Indeed, subtle differences in wording create interpretations that are not only distinctly different but are mutually incompatible. For example, the interpretation that “progressively less stress can trigger an episode” (Mazure, 1998, p. 297) is distinct from and can be seen to contradict the interpretation that “with recurrent episodes of major depression, the role of environmental stressors will progressively diminish” (Kendler, Thornton, & Gardner, 2000, p. 1243; see Table 1, Section C vs. Section D). These differing interpretations, among others, exist side by side in the research literature and are sometimes even expressed by the same investigator at different times. Obviously, the changing role of life stress with successive recurrences can be viewed in many ways.

Such tolerated imprecision strongly suggests subtle ambiguities in underlying concepts. Our central thesis is that different interpretations reflect inexplicit meanings of the terms used and of the ideas involved. These inexplicit meanings and ideas have been used interchangeably to explain the changing association between life stress and depressive episodes over time. The complex and interrelated problems that have arisen because of this state of affairs can be revealed by adopting and for illustrative purposes emphasizing a life stress perspective on depression and its recurrence. From the vantage point of life stress, we can also outline a preliminary framework for research on the role of life stress in depression recurrence over time.

Overview

We begin the article with a description of the origins of the kindling premise and the implications of the idea for multiple levels of analysis in research on mood disorders. Although the kindling hypothesis is framed originally within a neurobiological perspective, we emphasize that other levels of analysis are important as well. We next critically examine the empirical bases for the kindling hypothesis to determine if the ideas involved have secure scientific underpinnings for unipolar major depression. The basic premise of the kindling hypothesis rests on the legitimacy of the assertion that the first episode of a mood disorder “... is more likely to be associated with major psychosocial stressors than are episodes occurring later in the course of the illness” (Post, 1992, pp. 999–1000). Although we conclude from this section of the article that the existing evidence is broadly convincing and consonant with this idea, we also conclude that the evidence is not sufficiently detailed or precise for understanding the nature of the changing role of life stress over successive recurrences of depression.

We next present the core of our conceptual analysis, focusing on three major themes that largely explain the varied interpretations in the current literature with regard to the changing role of life stress over repeated recurrences of depression. The first of these major themes is autonomy, in which we examine the multiple meanings of the idea that an episode of depression can arise autonomously. We identify two related but distinguishable autonomy ideas that are commonly confused with one another. These ideas underlie two separate models that are similar and overlapping in some respects but, as we illustrate, very different in several other important respects.

The second major theme is the role of life stress. We demonstrate how the role of life stress involves at least two different components: changes over time in the frequency of major life stress prior to depression onset versus changes over time in the impact of major life stress prior to depression onset. The changing role of life stress (as suggested by the decreasing association between major life events and successive recurrences) can come about in two ways: (a) a decrease in the absolute frequency of major life events preceding onset and (b) a decrease in the actual effects of major life events when such events occur. Without explicit attention to these two distinct matters, little headway can be made in clarifying how the association between life stress and successive recurrences may or may not change over time.

Finally, the third core theme is the dimensions of life stress. We examine the multiple meanings of life stress and varied operational approaches to its assessment. Once again, we illustrate how the apparent simplicity of the terminology masks more complex underlying connotations. Life stress, for example, has almost exclusively referred to major or severe negative life events in research on depression’s recurrence. Such events typically involve major upheavals in life, such as primary relationship losses, deaths of significant others, serious illnesses, major problems with children, loss of permanent employment, and so on. Little conceptual or empirical attention has been paid to other forms of life stress, some of which are quite theoretically relevant for the kindling hypothesis. For example, less noxious but still troublesome life events may possess important psychological consequences for initiating recurrence. We systematically examine major and milder forms of
stressful life events and their implications within the kindling framework, revealing a broader research mandate for evaluating the changing role of life stress in the recurrence of depression.

Collectively, the ambiguities related to these three major themes underlying the kindling hypothesis have presented a formidable obstacle to progress. A systematic conceptual analysis of each theme provides a foundation for moving past the present theoretical and methodological impasse. Consequently, in the Conceptual Considerations: Synthesis and Speculation on Mechanisms and Processes section of the article we build on these foundations by

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### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Quote</th>
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<tr>
<td>Post (1992)</td>
<td>&quot;...the model presents a clear-cut example of the shift from episodes that are triggered to those that occur autonomously&quot; (p. 1001).</td>
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<tr>
<td>Kendler et al. (2000)</td>
<td>&quot;Over the course of illness, the onset of depressive episodes may become increasingly autonomous and less related to environmental adversities&quot; (p. 1243).</td>
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<tr>
<td>Daley et al. (2000)</td>
<td>&quot;Data such as these support Post's (1992) sensitization model of depression, wherein mood episodes are thought to be triggered initially by life stress but grow increasingly autonomous over the course of the disorder&quot; (p. 530).</td>
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<tr>
<td>Post &amp; Weiss (1999)</td>
<td>&quot;Kraepelin and many others have noted that mood disorder episodes are often initially precipitated by psychosocial stressors, but after sufficient numbers of recurrences, they begin to emerge autonomously and independently&quot; (p. 365).</td>
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<td>Lewinsohn et al. (1999)</td>
<td>&quot;Considered together with the body of literature reviewed by Post (1992), the present findings suggest that as the number of depressive episodes experienced by an individual increases, the episodes become independent of the experience of life events&quot; (p. 487).</td>
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<td>Post et al. (1984)</td>
<td>&quot;In our model both biological and social components could occur separately, but a framework is also provided for considering how originally stress- or loss-related reactions could evolve over time, and eventually show a pattern of spontaneity&quot; (p. 453).</td>
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<td>Post et al. (1986)</td>
<td>&quot;Moreover, as patients develop increasing rapidity of cycling, the illness appears to evolve with its own rhythmicity and spontaneity, independent of ongoing life events&quot; (p. 191).</td>
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<td>Post (1992)</td>
<td>&quot;...psychological theories must deal with this transition from episodes that are triggered by psychosocial stresses to ones that are less likely to be triggered in this fashion, even though these latter episodes occur in the context of increasing vulnerability to recurrence&quot; (p. 1001).</td>
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<td>Mazure (1998)</td>
<td>&quot;Recent theoretical work speculating on the etiology of depressive episode occurrence has suggested that recurrent episode patients are more vulnerable to stressors, resulting in a greater association of stressful life events with first episode depression compared to recurrent episode depression&quot; (p. 297).</td>
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<td>Mazure (1998)</td>
<td>&quot;Several studies suggest that stressful life events are significantly more likely to occur prior to first or second episode depressions than prior to recurrent depressions&quot; (p. 297).</td>
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<td>Post &amp; Weiss (1999)</td>
<td>&quot;This increasing spontaneity or automaticity does not mean that psychosocial stresses cannot play an important role in precipitation of episodes later in the course; rather, they become less essential as triggering mechanisms&quot; (p. 365).</td>
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<tr>
<td>Post (1992)</td>
<td>&quot;...either more psychosocial stressors were involved in the first episode than in subsequent episodes of major affective disorder or psychosocial stressors appeared to have less impact on episodes occurring later in the course of illness, after many recurrences, than on the initial episode&quot; (p. 1001).</td>
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<td>Kendler et al. (2000)</td>
<td>&quot;...with recurrent episodes of major depression, the role of environmental stressors will progressively diminish&quot; (p. 1243).</td>
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<td>Segal et al. (1996)</td>
<td>&quot;Social adversity, for example, is thought to play less of a role in the return of depressive symptoms because the biological mechanisms underlying the disorder achieve a degree of functional autonomy from psychosocial triggers&quot; (p. 378).</td>
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<td>Kendler et al. (2000)</td>
<td>&quot;Consistent with the kindling hypothesis, previous research had suggested that the strength of the relationship between stressful life events and major depression declined with an increasing number of previous depressive episodes&quot; (p. 1248).</td>
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<td>Teasdale et al. (2000)</td>
<td>&quot;...environmental provoking events appear to play a progressively less important role in onset with increasing number of episodes...&quot; (p. 622).</td>
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<td>Keller (2003)</td>
<td>&quot;Furthermore, there is evidence to suggest that with multiple episodes, the brain becomes more sensitized to the depressive state and the onset of future episodes is less related to stressful life events&quot; (p. 3156).</td>
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<tr>
<td>Mazure (1998)</td>
<td>&quot;Thus, progressively less stress can trigger an episode, with a concomitant shift toward more biological processes playing a causal role in the manifestation of depression&quot; (p. 297).</td>
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<td>Hammen et al. (2000)</td>
<td>&quot;Post (1992) proposed that stressors and episodes of mood disorder cause neurobiological changes such that less stress is required to precipitate subsequent episodes&quot; (p. 783).</td>
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<tr>
<td>Teasdale et al. (2000)</td>
<td>&quot;Accounts at both biological and cognitive levels are consistent with the finding that, with repeated experiences of episodes of major depression, less environmental stress is required to provoke relapse/recurrence&quot; (p. 616).</td>
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<tr>
<td>Post &amp; Weiss (1999)</td>
<td>&quot;The sensitization models would appear particularly pertinent to the extent that stress or sensitization to stress is apparent in many patients with unipolar and bipolar illness whose episodes are initially triggered by psychosocial stresses but later may be brought on by more symbolic events&quot; (p. 369).</td>
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A: Recurrences become more autonomous, spontaneous, or independent.

B: Major life events less frequently trigger successive recurrences.

C: Major life events have less impact, play less of a role, or are less associated with onset over successive recurrences.

D: Less stress is required to trigger successive recurrences.
synthesizing the three themes and portraying their integrated implications for understanding the changing role of life stress with depression recurrence. In the Empirical Considerations: Implications for Longitudinal Predictions section we evaluate these integrated ideas in light of existing data to determine the utility of competing theoretical models and to provide a beginning framework for inquiry on the longitudinal relations between life stress and depression recurrence. We conclude the article with a discussion of several implications for theory and research.

Basic Premises and Boundaries of the Kindling Hypothesis

The origins of the kindling and stress sensitization ideas can be traced initially to clinical observations, then to animal laboratory studies, and finally to more systematic empirical research comparing life stress for people with first onset of a mood disorder with those suffering a recurrence. The animal model of kindling refers to the sensitization of brain tissue, particularly limbic areas, to seizure-inducing electrical current such that after sufficient applications, current that was previously below the threshold for seizure induction begins to elicit seizures (Goddard, McIntyre, & Leech, 1969). Electrical kindling leads to a functional and structural alteration of brain structures and a resultant sensitization to future stimulation. Structural changes include the induction of gene transcription factors, most notably c-fos messenger RNA, in subcortical brain structures (M. Clark, Post, Weiss, & Nakajima, 1991; Dragunow & Robertson, 1987). Gene transcription factors are primarily responsible for the sprouting and retraction of nerve terminals as well as for cell death, all of which are crucial for learning (Kaczmarek, 1993). The induction of c-fos consequently leads to alterations in neuromodulator and peptide functioning, including short-term increases in transmission of excitatory neuromodulators (e.g., norepinephrine, dopamine, and corticotrophin-releasing factor), followed by long-term down-regulation of excitatory neuromodulatory autoreceptors and up-regulation of inhibitory neuromodulatory activity (e.g., gamma-aminobutyric acid). The effect of autoreceptor down-regulation is a decrease in the effectiveness of the neuromodulator substance at the synapse, resulting eventually in enhanced neuromodulator synthesis. This latter process is believed to be the primary mechanism of sensitization (Corcoran & Weiss, 1989; Goddard, Dragunow, Maru, & MacLeod, 1986).

Kindling has been proposed as an analogy for the stress sensitization seen in human mood disorders. However, it is important to note that exposure to chronic, intermittent environmental stressors, such as foot shock, in animals has also been found to induce a process of sensitization to the behavioral and hormonal responses to milder environmental stressors, such as a loud noise (e.g., Van Dijken, Mos, Tulp, & Tilders, 1992). Furthermore, similar to electrical kindling, the stress of environmental events (e.g., foot shock) is associated with c-fos induction in limbic and other subcortical areas (Melia, Ryabinin, Schroeder, Bloom, & Wilson, 1994; Smith, Banerjee, Gold, & Glowa, 1992) as well as similar changes in norepinephrine, dopamine, corticotrophin-releasing factor, and gamma-aminobutyric acid.

Even more compelling, two lines of evidence from imaging studies support a neurobiological basis of stress sensitization in humans. First, several studies have documented reduced hippocampal volume in chronic and recurrent depressed patients versus nondepressed individuals, assumed to result from the toxic effects of stress hormones (e.g., glucocorticoids; Bremner et al., 2000; Shah, Ebmeyer, Glabus, & Goodwin, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996). More important for stress sensitization, Sheline, Gado, and Price (1998) found significant reductions in amygdala volume in depressed patients versus nondepressed participants and a significant negative correlation between hippocampal and amygdala volume and total time depressed in the patient group that was independent of age. Second, recent neuroendocrine studies have found that participants who experienced traumatic stress as children and were currently suffering from major depression exhibited more than 6 times the adrenocorticotrophic hormone response to mild stress in adulthood than those with no history of abuse (Heim et al., 2000). These results suggest that those with a history of traumatic stress experience dysregulation of the hypothalamic–pituitary–adrenal axis response to stress such that they become sensitized to future life events. This evidence in humans suggests that electrical kindling and behavioral stress sensitization may be more than simply analogous mechanisms. On the basis of such information and in keeping with the recent work on life events and depression, we refer to the kindling and sensitization models generically as the kindling model.

Given these origins, the kindling model is typically anchored within a neurobiological framework. For the research on humans, however, the idea is rooted in the consistent empirical finding that the association between major life stress and episode onset weakens from a first episode over successive recurrences. Thus, it is important to consider that complementary or alternative mechanisms from psychological and social levels of analysis may be useful for explaining the changing association between life stress and depression onset with recurrences. Although a detailed exposition of all possible alternative mechanisms by which kindling may exert its effects is beyond the focus of this article, we nonetheless briefly discuss below two psychological mechanisms that have received the most empirical and theoretical attention: cognitive schema consolidation and personality scarring.

Segal and colleagues (1996) proposed that a cognitive analysis of kindling theory, “positioned between the environment and the cell” can “dovetail” (p. 372) with the neurobiological emphasis of Post’s (1992) thinking. In their model, they suggested that repeated stressors and depressive episodes contribute to progressive changes in information processing that reduce the threshold for triggering recurrence. Specifically, according to cognitive theory, depression is associated with particularly negative belief structures, called schemas (see D. A. Clark & Beck, 1999). Negative schemas represent a complex of associations among interrelated emotions (e.g., sadness), beliefs (e.g., worthlessness), and recollections (e.g., neglect) that are strengthened over time as a result of repeated experiences that confirm the belief structure of the schema. According to Segal et al., the stronger the interconnections between the elements of the schema network become over time, the more easily the entire network is activated in the presence of increasingly more minor stressors and milder dysphoric states. This has the effect of reducing the threshold for the downward spiral into a recurrent depressive episode. Segal and colleagues considered their model as operating in parallel with Post’s neurobiological account of stress sensitization, but at a different level of
analysis. Therefore, a compelling question for future investigation is whether the neurobiological changes proposed to underlie kindling also mediate cognitive schema consolidation over time.

In a similar way, changes in personality (e.g., neuroticism; Klein, Durbin, Shankman, & Santiago, 2002; Ormel, Oldehinkel, & Brilman, 2001) across repeated depressive episodes could lower the threshold of life stress required to precipitate depression recurrence. In particular, theorists have suggested that episodes of depression may leave scars (Zeiss & Lewinsohn, 1988) that, for example, alter personality in ways that increase susceptibility to future depression (e.g., Hirschfeld & Klerman, 1979). Strong evidence for the scar hypothesis comes from Kendler, Neale, Kessler, Heath, and Eaves’s (1993) prospective longitudinal study showing that elevated neuroticism scores prospectively predicted the 1-year prevalence of a first episode of major depression. More important, even when levels of neuroticism prior to their first onset are controlled for, levels of neuroticism on remission were elevated in those who had had an episode of major depression compared with those who had not (the scar effect). Elevated neuroticism scores that persist following remission of depressive episodes can then facilitate further depression recurrences by increasing reactivity to stress (see Bolger & Zuckerman, 1995). As a result, and consistent with the kindling model, minor stressors that would not have triggered a first onset can come, through heightened reactivity, to trigger a depression recurrence. We note that these psychological levels of explanation complement neurobiological accounts of how repeated depressive episodes render the individual more vulnerable and increase the chances of future depressive episodes. However, for parsimony in presentation and fidelity to the original kindling premises, we typically resort in our discussion to the neurobiological mechanisms implied by the initial theory. Yet we urge readers to bear in mind the broader possibilities and encourage investigators to examine the links among neurobiology, stress sensitization, and additional psychological processes.

Empirical Foundations of the Kindling Hypothesis

In Post’s (1992) seminal article outlining the kindling hypothesis, he reviewed the evidence from 16 studies of major mood disorders and concluded that there was a remarkable consistency in the demonstration that either more psychosocial stressors were involved in the first episode than in subsequent episodes of major affective disorder or psychosocial stressors appeared to have less impact on episodes occurring later in the course of illness, after many recurrences, than on the initial episode. (p. 1001)

He indicated that these sources of information “overwhelmingly document a greater role for psychosocial stressors in association with the first episode of major affective disorder than with subsequent episodes” (p. 999).

Although the basic finding for stress and recurrence was consistent for the majority of the research reported in Post’s (1992) review, individual studies varied in terms of important methodological features. On the one hand, consistency of results might be viewed as all the more remarkable given such diversity of approaches (as Post, 1992, emphasized). On the other hand, variability in procedures might be cause for some caution and careful follow-up research. For example, a wide range of assessment procedures was used to measure life stress, and only a minority of the studies used psychometrically sound stress measures. Furthermore, four of the studies reviewed by Post (1992) focused on patients with bipolar disorder, whereas the rest involved patients with unipolar major depression. (Bipolar disorder involves cycling episodes of mania and major depression, whereas unipolar major depression involves episodes of depression only; Depue & Monroe, 1978.) Although Post viewed kindling as relevant to both unipolar and bipolar mood disorders, we focus in the present article on kindling and unipolar disorder. Given these methodological inconsistencies, further attention to the empirical basis for the kindling hypothesis and unipolar depression is warranted.

It is with such concerns in mind that Mazure (1998), as part of a broader review of life stress and depression, also reviewed the role of life stress in regard to first onset and recurrence of depression for mood disorders. This more recent review addressed methodological concerns about life stress measurement, severity of stress prior to onset, and the unipolar–bipolar distinction. This later review overlapped to some degree with the research reported in Post’s (1992) review, yet three of the eight studies were not previously covered, and studies focusing only on mania were omitted. Although Mazure’s (1998) analysis was more cautious overall about the differential role of life stressors in first versus recurrent episodes of major depression, she concluded that “. . . the data derived from unipolar depressed subjects using a structured instrument to assess occurrence of independent severe events suggest that life events are more common prior to first versus recurrent depression” (p. 298).

Since publication of Mazure’s (1998) review, nine additional articles have been published from six different data sets that address the differential role of life stress with regard to a first versus recurrent episode of unipolar depression.2 On the whole, these studies are characterized by increased methodological rigor with regard to defining life stress, diagnosing depression, and sampling sophistication. The findings from each study are consistent with the general premise that major life stress has a greater association with the first onset of a depressive episode relative to a recurrence. Nonetheless, differences in procedures and specific

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1 Although there are 12 studies reported in Table 1 of Post’s (1992) article, he provided evidence in the text from 2 additional published articles that supports the kindling hypothesis and addressed problems with 2 other studies that did not support the hypothesis.

2 Two additional studies bearing on the kindling hypothesis were located. One study examined the differential association of severe life events for first-time hospitalizations for depressive and/or anxiety disorders versus subsequent hospitalizations (Amiel-Lebigre, Lacalmontie, & Menard, 2002). This study used state-of-the-art methods for assessing life stress, and the results were congruent with the premise that more stress preceded first hospitalizations than later ones. However, the lack of clarity concerning actual episodes versus hospitalizations as well as the merging of depression and anxiety disorders mitigated against including the work as supportive of the hypothesis of the differential role of life stress for first onsets versus recurrences. The second study was an empirical report on life stress and bipolar disorder by Hlastala et al. (2000). Although this latter report did not find support for the kindling premise, we did not include the findings in our review because we focus on life stress and the recurrence of unipolar major depression. However, some of the ideas put forth by Hlastala et al. are quite pertinent to the present article, and we address these matters in a subsequent section.
findings across these investigations provide important insights into several issues and foreshadow the three conceptual themes we subsequently develop. Consequently, we review the major features and findings of each study individually.

In a prospective study predicting first onset versus recurrence of depression in adolescence, Lewinsohn, Allen, Seeley, and Gotlib (1999) reported findings consistent with the premise that life stress was significant only for predicting first onset cases, not recurrences. The sample consisted of 1,470 currently nondepressed adolescents; the second assessment took place approximately 1 year later (mean interval = 13.8 months). During the time between the two assessments, 70 adolescents experienced a first lifetime episode of depression, and 43 experienced a recurrence (i.e., these latter adolescents had a prior episode of depression before the initial assessment but were not depressed at the initial assessment).

Depression was assessed with a structured diagnostic interview that derived diagnoses of past and current psychiatric disorders as outlined in the third edition, revised, of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–III–R; American Psychiatric Association, 1987). Life events were measured with a self-report inventory at the first assessment “to examine the occurrence of 10 negative life events that have been experienced by the adolescent during the past year, all of which are likely to be severe and salient” (Lewinsohn et al., 1999, p. 485). The authors found a significant interaction between history of depression (first onset vs. recurrence) and the total number of life events, $LR(1, N = 1470) = 9.37, p < .01$, such that life events prospectively predicted onset for adolescents experiencing a first episode of depression but did not significantly predict depression recurrence.

In a second prospective study based on the same sample of adolescents from Lewinsohn et al.’s (1999) investigation, the specific major life event of a recent loss of a romantic relationship was tested with regard to first onset versus recurrence of depression. Monroe, Rohde, Seeley, and Lewinsohn (1999) found that the loss of relationship significantly interacted with depression history, $\Delta \chi^2(1, N = 1470) = 3.85, p < .05$, such that the loss of a romantic relationship in the past year predicted first onsets of depression but did not predict recurrences. Again, it is noteworthy that these findings along with those of Lewinsohn et al. (1999) were based on a prospective design clearly establishing temporal precedence of the life events prior to episode onset.

In a third prospective investigation examining predictors of first onset cases and recurrences for adolescents and young women initially between age 16 and age 19, Daley, Hammen, and Rao (2000) followed 128 women over a 5-year follow-up period. Sixty-five of the women experienced an episode of major depression during the study period; 39 were first onsets, and 26 were recurrences. Again, diagnoses were based on a structured clinical interview, and life stress was assessed using well-validated interview-based methods and consensus rating procedures (Hammen et al., 1987). Both acute event and chronic stressor totals in the 3 months prior to onset, or a comparable time period for control participants, significantly predicted the emergence of a new depressive episode. However, only chronic stressors evidenced a significant interaction with depressive history, $\Delta \chi^2(1, N = 128) = 5.31, p < .001$. For women without a history of depression, those who incurred a first episode had higher chronic stress scores than those who did not. For those with a history of depression, young women developing a recurrence did not differ from those who did not develop a recurrence with regard to chronic stress.

Using a sib-pair design to evaluate the familial factors involving depressive disorder and major life events, Farmer et al. (2000) also compared the degree of association between severe life events and depression onset for first lifetime episodes ($n = 36$) versus recurrences ($n = 72$). The 108 depressed individuals, aged 18–65, were recruited from a variety of treatment facilities, were interviewed with the Schedule for the Clinical Assessment of Neuropsychiatry (Version 2; SCAN; Wing et al., 1990), and were diagnosed with moderate to severe unipolar depression according to the *International Classification of Diseases* (10th rev.; World Health Organization, 1993). This study is also noteworthy in the use of the Life Events and Disabilities Schedule (LEDS; Brown & Harris, 1978, 1989) to assess life stress, a well-validated investigator-based measure of life events and difficulties (Mazure, 1998; Monroe & McQuaid, 1994). Although specific percentages are not provided in the report, Farmer et al. (2000) documented that individuals with a first episode of depression had significantly more severe events prior to onset compared with individuals with a recurrence ($Mann–Whitney U$ test: $z = –3.40, p < .001$, and $z = –3.05, p = .001$, for the 3- and 12-month time periods before onset, respectively).

In a recent prospective case-control study, Ormel et al. (2001) investigated life stress and the onset of subsyndromal and full syndromal depression in older adults, and they also examined the differential prediction of onset for first depressive episodes versus recurrences (see also Brilman & Ormel, 2001). Participants were 83 individuals aged 57 or older who developed a subsyndromal ($n = 58$) or full syndromal ($n = 25$) depressive episode beginning in the 9 months preceding the interview (diagnosed according to the Present State Examination module from the SCAN; World Health Organization, 1992). These depressed individuals were selected from a larger community survey of 3,700 noninstitutionalized older persons, with 83 comparison participants selected from the same pool (Ormel et al., 1998). History of depression was defined as positive for participants for whom “there had been at least one previous episode that would have met the criteria for at least a subsyndromal depressive episode” (Ormel et al., 2001, p. 886). This study is noteworthy, too, in the use of the LEDS (Brown & Harris, 1978, 1989) to assess life stress. Ormel et al. (2001) reported a differential role of life stress in the 3-month period prior to depression onset: The effects of severe life events were considerably stronger for first episodes of depression compared with recurrences (odds ratios of 41.00 vs. 9.11, respectively) $\chi^2(1, N = 83) = 5.75, p = .02$. Additionally, mild stressful life events predicted recurrence of depression but not onset of a first episode (odds ratio of 2.94, $p = .01$, vs. odds ratio 1.09, $p = .89$, respectively): difference between mild stressful life events for a first onset versus a recurrence, $\chi^2(1, N = 83) = 3.29, p < .07$. Chronic difficulties did not predict differentially for first onset versus recurrent episodes. Overall, these findings again provide support for the differential role of major life events for a first episode of depression but not for a recurrence. They also add to the literature the finding that milder forms of stress may be capable of triggering a recurrence.

Maciejewski, Prieger, and Mazure (2001) reported on the changing role of life stress and depression for a community sample of 1,024 men and 1,800 women. The study drew from the Amer-
icans’ Changing Lives data set (House, 1994), a multistage stratified area probability sample of individuals over age 25 in the United States, with an oversampling of African Americans and individuals 60 years of age and older. Participants were interviewed in two waves, separated by 3 years. Past depression was assessed by inquiring about whether participants had “experienced a period in their life lasting at least 1 week when they felt sad or depressed most of the time or when they lost all interest and pleasure in things about which they usually cared” (Maciejewski et al., 2001, p. 596). If they responded affirmatively to this question and it was determined that at least one of these periods preceded the date of the entry into the study, participants were considered to have “a history of severely depressed mood” (n = 508; Maciejewski et al., 2001, p. 596). Diagnosis of major depression was based on meeting Diagnostic and Statistical Manual of Mental Disorders (4th. ed., txt. rev.; American Psychological Association, 2000) symptom criteria during the interval between Wave 1 and Wave 2. Eleven specific life events occurring during the 12-month period preceding the calendar month of the respondent’s interview (n = 237) were assessed “using a simple inventory approach” (Maciejewski et al., 2001, p. 602). Using Cox regression models, Maciejewski et al. tested risk ratios for events as a group as well as individually occurring during the month of depression onset. These investigators reported that the risk ratio for life events considered collectively was significantly lower for participants reporting a prior history of severely depressed mood (95% confidence interval = 0.13, 0.61, p < .001). It is interesting to note that risk ratios for individual events suggested that prior depression modified the relationship for only particular events and not others. Overall, though, the authors concluded there was a diminishing association between life events and episode onset over successive recurrences.

The two remaining studies represent some of the most sophisticated research to date bearing directly on the kindling hypothesis. These reports come from the same research group but address different facets of the kindling hypothesis. First, Kendler et al. (2000) assessed 2,395 Caucasian female–female twin pairs from the population-based Virginia Twin Registry. Most participants (88%) were interviewed in person first, followed by telephone interviews in three subsequent assessment waves (all assessments separated by at least 13 months); the remainder received an initial personal interview and a Wave 4 assessment. In an interview section prior to the assessment of major depression, major life events were assessed (e.g., 11 personal life events, 4 network events). For Waves 3 and 4, life events also were rated by the interviewer on long-term contextual threat and independence (using LEDS principles; Brown & Harris, 1978, 1989). Depression and history of depression were assessed by structured interview based on the Structured Clinical Interview for DSM–III–R (Spitzer & Williams, 1985).

To test changes in the association between a stressful life event and depression onset as a function of previous depressive episodes, Kendler et al. (2000) used an event history analysis with a discrete-time approach. The unit of analysis was the “person-month,” focusing on life events and depressive onsets within the past year and examining the presence or absence of a major life event within the same month of depression onset. Depending on the particular analysis, person-months varied between 100,956 (with 1,419 onsets) and 97,515 (with 1,380 onsets). These authors also took care to initially specify the relationship between previous depressive episodes and risk for major depression, providing a useful platform for evaluating the interaction of stressful life events and prior episodes in predicting new onsets of depression. They found that this relationship was nonlinear and best captured with a piecewise, discrete-time survival logistic regression with an inflection point at nine previous episodes. Because relatively few participants had nine or more prior episodes (5.2% of the total), the first linear component for individuals with zero to nine prior episodes was used for testing the strength of association between major life events and episode onset as a function of prior depression history.

Kendler et al. (2000) specifically predicted “that with an increasing number of previous depressive episodes, the strength of the association between stressful life events and depressive onsets would diminish” (p. 1246). For the person-months of individuals with zero to nine prior depressive episodes, there was a highly significant interaction with life stress, \( \chi^2(1, N = 97515 \text{ person-months}) = 35.80, p < .0001 \). The odds ratio associated with this effect (odds ratio = 0.87) indicated that for each additional prior depressive episode from zero to nine, “the strength of the association between stressful life events and depressive onsets declined approximately 13%” (Kendler et al., 2000, p. 1247). Illustrating these findings further, Kendler et al. (2000) indicated that for individuals without a history of depression, the odds ratio for major depression and a life event was highly significant (odds ratio = 9.38), yet as the number of prior episodes increased, the odds ratio for depression onset and a prior major life event consistently decreased (e.g., odds ratio = 6.74 for one prior episode, 5.22 for two prior episodes, and 3.63 for three prior episodes; yet all odds ratios were statistically significant). In another set of follow-up analyses limiting the life event variable to independent events ascertained in accord with LEDS procedures (i.e., events beyond the person’s influence or control), Kendler et al. (2000) found an overall similar pattern of findings, although “the main effect of stressful life events declined due to the reduced number of events” (p. 1247).

It is important to point out that because the study reported by Kendler et al. (2000) was longitudinal, the investigators could examine both within-individual and between-individuals changes in association between stressful life events and major depression as the number of prior depressive episodes increases. In particular, the follow-up analyses that focused on within-person changes in this association replicated the main analyses, suggesting that the observed decline in the association between stressful life events and depressive onsets with increasing numbers of previous depressive episodes is a true within-individual phenomenon and cannot be explained by systematic differences between the kind of individuals who have a low versus high number of previous depressive episodes. (Kendler et al., 2000, p. 1248)

These findings provide a very important addition to the literature, clearly supporting the idea that the association between life stress and recurrence weakens over time for the person with repeated episodes (rather than different types of people or subtypes of depression are more or less likely to have stress prior to an initial vs. subsequent episode onset).

In a follow-up report working with the same sample and methods, Kendler, Thornton, and Gardner (2001) refined the research question to examine how the changing role of stress in depressive
episodes might be moderated by genetic factors. The female twins sample was divided into four groups for genetic risk: lowest risk (monozygotic twin whose cotwin had no lifetime history of major depression; \( n = 927 \)), low risk ( dizygotic twin whose cotwin had no lifetime history of major depression; \( n = 582 \)), high risk ( dizygotic twin whose cotwin had a lifetime history of major depression; \( n = 325 \)), and highest risk ( monozygotic twin whose cotwin had a lifetime history of major depression; \( n = 401 \)). Using a discrete-time survival analysis based on 92,521 person-months of exposure, they tested the interactions among genetic risk, number of previous depressive episodes, and life event exposure in relation to the onset of a new depressive episode. The results indicated that the changes in the odds ratio for depression after a stressful life event over repeated recurrences held most strongly for women at the lower levels of genetic risk. For example, for women at lowest genetic risk, the strength of association between a stressful life event and onset of major depression declined 23% with each prior depressive episode; for the middle genetic risk groups, the corresponding figure was approximately 12%. For the highest risk group, the association between major stress and episode onset declined only 8% with each additional prior episode. Furthermore, the weakening of the association between a major life event and episode onset for the low genetic risk group occurred primarily by the third episode. It is interesting to note that Kendler et al. (2001) inferred that the decline in the strength of association between stress and onset as the number of prior episodes increased was due to “an increasing propensity either for spontaneous depressive episodes or for episodes precipitated by stressors too minor or too idiosyncratic in our extensive inventory of stressful life events” (p. 586).

Considered collectively, these nine recent studies possess important strengths with regard to establishing the empirical basis for the kindling hypothesis. At the broadest level, they build on and supplement the studies reviewed previously by Post (1992) and Mazure (1998) supporting the general premise that life stress plays a differential role for first onset depressions compared with recurrences. These recent studies provide further support using different samples of depressed individuals (e.g., adolescents, young women, older adults) and different measures of life stress (e.g., self-report vs. interview-based instruments), and all incorporated prospective research designs. One study, too, presents valuable evidence of within-person changes in the association between life events and recurrence as a function of prior episodes, an important complement to the predominately between-persons findings (Kendler et al., 2000). There are limitations as well with most of the investigations. For example, some studies possess shortcomings in the assessment of life stress (e.g., Lewinsohn et al., 1999; Maciejewski et al., 2001; Monroe et al., 1999), potential problems with definitions of the depressed sample (e.g., both subsyndromal and full syndromal depressives; Ormel et al., 2001), questionable timing of life events and the onset of depression (Kendler et al., 2000; Maciejewski et al., 2001), crude measures of depression history (Maciejewski et al., 2001), or differences in the type of life stress found to be of relevance (e.g., acute events vs. chronic difficulties; Daley et al., 2000; different types of events providing different types of effects; Maciejewski et al., 2001). None of these previous studies addressed the themes we next develop concerning different interpretations of autonomy and sensitization, different roles of life stress with regard to frequency and impact, or major versus minor life events (cf. Ormel et al., 2001). Overall, though, it is consistently found across these studies that major life stress plays a different role in first onset depressions versus recurrences, with life stress uniformly found to be more important for the first onset of depression. It is worth mentioning, too, that there has not been a single report of the converse effect (i.e., major life stress is more strongly related to recurrence than to a first episode of depression).

There is a critical issue, though, that comes to light with closer scrutiny of these more recent reports. In particular, there has been a subtle shift in emphasis with regard to the nature of the association between life stress and first onsets versus recurrences. This shift reflects the interpretative elasticity introduced in Table 1 and calls attention to the confusion in the current literature. Specifically, the earlier reviews of Post (1992) and Mazure (1998) focused solely on differences in the proportion of first onset depressive episodes versus recurrent depressive episodes with prior major life stress. Major life stress was consistently found to be more prevalent in the lives of people with a first onset compared with people with a recurrence. In contrast, the more recent studies generally focus on the differential prediction by life stress of a first onset versus a recurrence of depression. Major life stress consistently and strongly predicted onset of a first lifetime depressive episode but less consistently or strongly predicted onset of a recurrence of depression. (In turn, these recent studies did not systematically address the question of proportional differences between the first onset and recurrence groups. Indeed, the data from several of these recent studies suggest that major life stress is also elevated for the recurrent group but is statistically unrelated to recurrence onset; Daley et al., 2000; Lewinsohn et al., 1999; Monroe et al., 1999.) Overall, two related but importantly different questions are being addressed by the earlier and recent sets of studies, which suggests significant underlying differences in conceptualizing the processes linking life stress to episode onset over successive recurrences.

We conclude that the available evidence is consistent and reasonably strong for the general premise that major life events more commonly precede and predict a first onset of major depression relative to a recurrence and that the association of major life events with depression onset changes with successive episodes. There are important gaps, however, in understanding of the underlying processes accounting for these associations. These gaps stem from the ambiguities introduced earlier with regard to the major themes of autonomy, role of life stress, and dimensions of life stress. We now turn to a systematic analysis of these themes and demonstrate how clarification of these matters provides useful guidelines for future research.

On the Independent Meanings of Autonomous

The basic premise of autonomous is that depressive episodes can arise unrelated to psychosocial stressors. We identify two distinguishable meanings of autonomous that are prevalent in the literature but are consistently confused with one another. Both meanings suggest that with repeated stress and successive depressive episodes, recurrences can begin to arise in the absence of major life stress. Where they critically diverge, however, is whether major life stress remains capable of triggering a recurrence or whether major life stress actually loses potency for
precipitating recurrences over time. These alternative meanings are illustrated in Figure 1.

The first meaning of autonomous is that episodes of depression can eventually emerge autonomously, without prior severe life stress (i.e., Episode 4, top row, Figure 1). Note, though, that major life events are still capable of provoking an episode (see Episode n, top row, Figure 1). From this perspective, two complementary pathways evolve over time via which recurrence eventually can be initiated: major life events and mechanisms other than major life events. The second related, but clearly distinguishable, meaning of autonomous implies that depression becomes less likely to be triggered when major life stress actually happens (i.e., in the bottom row of Figure 1, there is no episode following the fourth major life event). For this meaning of autonomous, major life stress progressively decreases in etiologic importance, with an increasing disassociation between major life stress and episode onset. Over repeated episodes, the individual becomes less sensitive to the depressogenic impact of major life events, while other nonstress mechanisms emerge to dominate in the explanatory scheme.

The same confusion about the dual meanings of autonomous extends to similar terms commonly used in the literature on depression. For example, depressive recurrences may be taken to be independent of life stress or appear to be spontaneous with respect to the absence of life stress. In all of these instances, there is ambiguity between (a) recurrences that are not triggered by major life stress, but which can complement recurrences that are triggered by major stress, and (b) recurrences that progressively become less likely to happen in the face of major life stress. In the former case, life stress maintains or increases potency for triggering depression; in the latter case, life stress decreases or eventually loses potency over time for triggering depression. These different views can be consolidated into two distinct models that provide alternative accounts of the developmental processes and changing pathways via which life stress may lead to recurrence. We formally label and describe each model next.

**Stress Sensitization Model**

The first model is the stress sensitization model. From this viewpoint, major stress is essential for the initial and early episodes but decreases in unique importance for episode initiation with successive recurrences. However, major stress is still fully capable of triggering recurrence when it is experienced (see Figure 1, top row). An important additional component of the stress sensitization model holds that if one is sensitized to stress, then one can succumb to lower and lower severity levels of stress after

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3 The idea of autonomy can be traced far back into the history of medicine, wherein early observers and physicians reported people with severe depressions that apparently came from out of the blue—that is, without any obvious or apparent psychosocial precipitants (Jackson, 1986; Monroe & Depue, 1991). These autonomous depressions have been viewed as more endogenous and neurobiologically driven, whereas the reactive depressions have been viewed as more environmentally related (Monroe & Depue, 1991). In purest form this sense of autonomous or endogenous means that life stress—even the most severe negative life event—is unrelated to onset of a depressive episode. Although the literature on the endogenous–reactive distinction has been the subject of considerable debate over the years, the basic ideas involving autonomous neurobiologic mechanisms still permeate current thinking about depression and its origins (Brown et al., 1994; Harkness, Thase, & Monroe, 2005; Monroe & Hadijyannakis, 2002). Most pertinent for present purposes, kindling theory attempts to bring together these social and biological domains into a common developmental framework to explain the changing association of life stress with episode onset over time. As stated by Post et al. (1984), "In our model both biological and social components could occur separately, but a framework is also provided for considering how originally stress- or loss-related reactions could evolve over time, and eventually show a pattern of spontaneity" (p. 453). Much confusion in the literature can be traced to the incompletely articulated consequences of this admirable theoretical effort. As we address throughout the present article, a major challenge is to explain how mechanisms that are initially triggered by major life events change over time in relation to repeated recurrences. It is this developmental progression—the changing relation between life stress and recurrence—that requires greater specification and clarity and that is unique to, and a result of, the within-person feature of the kindling perspective. (These matters are irrelevant to traditional endogenous and reactive depression subtypes, which are based on between-subjects distinctions and disorders.) We suspect that the vestigial connotations of the traditional endogenous–reactive distinction provide a conceptual background that colors and contributes yet another layer of confusion for interpretations of autonomy in kindling theory.
repeated recurrences. This implies that life events that initially were incapable of triggering a first depressive episode later acquire the capacity to trigger a recurrence. Ultimately and most extremely stated, with numerous repeated episodes and at the far end of the recurrence distribution, increasingly minor vagaries and vicissitudes of day-to-day social life may become sufficient to initiate a recurrence.

The stress sensitization model is fully congruent with the studies of major life stress and recurrence of depression and implies that major life events become progressively less associated with recurrence onset over time. Major life stress, though, is still capable of initiating a recurrence; such stress is just no longer essential nor typical. Much as the animal laboratory literature suggests a kindled or sensitized animal still responds to the initial stimulus conditions, so would a sensitized person with recurrent depression still become depressed in response to a severe stressor (e.g., Goddard et al., 1986). It is simply that the conditions required for an initial onset become a less common pathway for the particular outcome. As a result of sensitization of neural pathways to the effects of stress, the threshold for episode recurrence in response to stress decreases and lower degrees of stress begin to dominate in the etiologic scheme. Eventually recurrences typically take place in response to relatively minor perturbations—stressors that are below the current conceptual and operational radar—giving the appearance that the recurrences are spontaneous or independent of environmental circumstances (e.g., Episode 4, top row, Figure 1).

Within this stress sensitization model, automaticity or spontaneity is more apparent than real. The findings of Ormel et al. (2001) cited previously fit well with this viewpoint: Major life events were stronger predictors of first onsets of depression relative to recurrence, whereas less severe events were stronger predictors of recurrences relative to first onsets.

**Stress Autonomy Model**

The stress autonomy model (bottom row in Figure 1) captures the essence and completeness of the idea of independence. Although major stressors are important for initiating the first episode of depression, later episodes become less dependent on socio-environmental input, to the point at which recurrences may eventually emerge entirely and only autonomously (i.e., uncorrelated with psychosocial factors). Note that it must also be assumed within this model that major life stressors and depressive episodes contribute to the development of another process that with successive episodes, begins to take over for initiating later recurrences.

The stress autonomy model, too, is broadly in accord with the studies of life stress and recurrence of depression and also implies that major life events will become progressively less correlated with recurrence onsets over time. However, this model appears to be less readily reconciled with the animal laboratory literature. In kindling and sensitization studies, the original stimulus still possesses the capability of eliciting the original response; the original stimulus simply becomes less necessary in the face of emerging alternative mechanisms. With the stress autonomy model, though, major life stress loses the capacity to trigger recurrences. Thus, the stress autonomy model provides a less parsimonious explanatory scheme (given that the transition from sensitization to episode to stress insensitivity and eventually autonomy is required). For example, animal laboratory studies indicate “that the anatomical and biochemical substrates underlying the expression of sensitization change progressively over time with repeated intermittent exposures” (Post & Weiss, 1999, p. 370). Although acquisition of the potential for new mechanisms to initiate recurrences is relatively easy to envision, it is less readily apparent how the potential of previously effective mechanisms fades (i.e., stress).

We do not mean to suggest that the processes implied by the stress autonomy model are impossible or even implausible. For example, adjustments by the organism over time in response to major stress or depressive episodes could foster adaptations that eventually extinguish prior sensitivities and that recruit other initiating mechanisms. But, at least as currently conceived, such a model comes with added theoretical costs. Most generally, one has to explain not only how the transition from stress to spontaneity takes place but also how stress initially capable of bringing about an episode becomes less capable of bringing about a subsequent episode. At what point—and how in the developmental progression—does stress become progressively less consequential?

Although the stress autonomy model presents some conceptual challenges, it is important to recognize that recent research most often has been interpreted in line with this perspective. The majority of studies documenting a decrease in the association between major stress and episode onset with successive recurrences imply that it is the progressive loss of stress impact that accounts for the findings (see Kendler et al., 2000; Lewinsohn et al., 1999; Maciejewski et al., 2001; Monroe et al., 1999; see also Table 1, Sections A, B, and C). Indeed, we found only one instance in which processes implicated by the stress sensitization model had been mentioned in these empirical studies (Kendler et al., 2000, stated, “We have inferred that this change reflects an increasing propensity either for spontaneous depressive episodes or for episodes precipitated by stressors too minor or idiosyncratic to be contained in our extensive inventory of stressful life events,” p. 586). Furthermore, it is important to note that the results of the recent studies reviewed previously support the stress autonomy model: Major life events significantly predicted first onsets but did not significantly predict recurrences, even though major life events were experienced by those with prior depression. These results suggest that some other etiological process is associated with the precipitation of recurrent episodes in these individuals. Thus, although the stress autonomy model possesses certain conceptual limitations, it is important to appreciate that the general premises are active and probably dominant in the current research.

**General Considerations and Model Comparisons**

Somewhat surprisingly, these definitional problems with kindling theory have gone largely unrecognized. Few have raised concerns about the two contradictory meanings within the general concept. An important exception is a recent article by Hlastala et al. (2000). In an empirical report examining premises of the kindling model for bipolar disorder (see Footnote 2), these investigators raised the problem of testing the kindling model, given the “two distinct phenomena that are tied together: kindling and sensitization” (Hlastala et al., 2000, p. 778). They also pointed out that research drawing on the “two distinct although conceptually linked models” (p. 778) is difficult to interpret with consistency. They noted that the emphasis within one model (which they term kindling) on progressive autonomy of the disorder and a diminishing
role for stress inherently conflicts with the emphasis within the other model (which they term sensitization) on progressive vulnerability to stress and the enlarging role of stress for triggering onset. These observations by Hlastala et al. reinforce the present analysis and help set the stage for a more extensive and broad-based critical evaluation of the kindling hypothesis (see also Monroe & Hadjijannakis, 2002).

As we have outlined, there are noteworthy parallels and differences between the stress sensitization and the stress autonomy models. Each features major life events as prominent in the etiological arrangement for early episodes and major life events as less prominent for later recurrences. Each model suggests that the general role of major life stress progressively diminishes over time. Each model also implies—although rather indirectly and vaguely—that different processes develop over time that eventually complement or replace the original etiologic circumstances responsible for the first onset (i.e., major life events). Where the two models begin to most meaningfully diverge is in the features of these implied secondary, and incompletely articulated, developmental processes. In particular, the two models differ in their depiction of the role for life stress in relation to recurrence over time.

For the stress sensitization model, neurobiological sensitization is a progressive process that allows episodes to be triggered by increasingly less severe levels of stress. Changes occurring in the underlying mechanisms over time alter the conditions responsible for recurrent episodes, but these recurrent episodes still require life stress triggers; it is simply that the severity of stress required becomes increasingly more minor. For the stress autonomy model, sensitization becomes an apparently quasi-independent process: At some point, as a result of prior stressors and depressive episodes, sensitization initially increases. But responsibility for episode initiation is transferred to other mechanisms, and the capacity for life stress to initiate an episode progressively weakens. Changes in the underlying substrate become the necessary and sufficient conditions for triggering recurrence, entirely unrelated to life stress. Overall, each model provides an alternative account of how the role of major life stress changes with successive recurrences.

However, the role of life stress, too, has been incompletely considered conceptually and empirically, which has compounded the ambiguity and confusion arising from conflating the stress sensitization and stress autonomy models. Although we know that a major life event is in general more prominent for early episodes occurring later in the course of illness. . ." (p. 1001). Obviously these issues were considered in the original formulation by Post, but the richness of the presentation and lack of systematic differentiation of these two matters has contributed to the present state of confusing these separate considerations.

The Role of Life Stress: Frequency and Impact Matters

Another hindrance for understanding the role of stress is the particular sense in which major life stress is viewed as more or less important. Is it that major life stress loses its impact, or is it that major life stress becomes less frequent in triggering recurrence? That is, does major life stress lose its potential to trigger depression, or does it lose its opportunity to do so? This represents a crucial distinction that has been completely overlooked in the recent literature on recurrence (cf. Kessler, 1979). Because this issue follows from the particular model of life stress adopted, we portray the considerations for the stress sensitization and stress autonomy models separately.

Stress Sensitization Model

Although we know that a major life event is in general more strongly associated with a first episode than a recurrence, it does not necessarily follow that a major life event loses causal significance for a recurrence (i.e., loses impact when it occurs). Major life events may simply become less routine triggers of onset (i.e., lower frequency) as recurrences progress and as the more prevalent, less severe, life events become a more common trigger of recurrence onset. So, in one sense, major life events may play a greater role, play a differential role, or play a role that will progressively diminish. But this may be accurate only in a very limited sense. Indeed, if repeated depressive episodes result in neurobiological sensitization, then major stressors should become all the more capable of precipitating a recurrence. Overall, in terms of frequency, the role of major life events may diminish, but in terms of impact, the role of major life events should increase.

It is useful to portray the different roles of major life stress in terms of separate conditional probabilities for impact and frequency with regard to depression history and episode initiation. On the one hand, we wish to know how the relative probability of a current depressive episode given the presence of a preonset major stressful life event changes as a function of prior depression history. On the other hand, we want to know how the relative probability of the presence of a preonset major stressful life event changes as a function of a current depressive episode and prior depression history. These distinctions nicely capture and make explicit the two different roles of impact and frequency for life stress that have not been previously distinguished and set the stage for systematically evaluating their respective implications by the two stress models. In the relative conditional probability statements below, the three variables (SLE for stressful life event, DEP for current depressive episode, and DHX for prior depression history) are dichotomized, and we denote absence of a variable with a line above (see also Figure 2).

For impact differences between a first depressive episode and recurrences we have

\[ P(\overline{\text{DEP}|\text{SLE}}, \overline{\text{DHX}}) \text{ versus } P(\overline{\text{DEP|SLE}}, \overline{\text{DHX}}). \]  

(1)

For frequency differences between a first episode and a recurrence we have

\[ P(\overline{\text{SLE|DEP}}, \overline{\text{DHX}}) \text{ versus } P(\overline{\text{SLE|DEP}}, \overline{\text{DHX}}). \]  

(2)

Most generally with regard to Statement 1, the probability of a current depressive episode given a stressful life event increases in

\[ P(\overline{\text{DEP|SLE}}, \overline{\text{DHX}}) \text{ versus } P(\overline{\text{DEP|SLE}}, \overline{\text{DHX}}). \]  

(1)

4 In this regard, it is interesting to reconsider the quote by Post (1992) on the consistency “in the demonstration that either more psychosocial stressors were involved in the first episode than in subsequent episodes of major affective disorder or psychosocial stressors appeared to have less impact on episodes occurring later in the course of illness . . .” (p. 1001). Obviously these issues were considered in the original formulation by Post, but the richness of the presentation and lack of systematic differentiation of these two matters has contributed to the present state of confusing these separate considerations.
accord with the stress sensitization model. As a person becomes more sensitized over time, the probability of a current depressive episode given an antecedent stressful life event should be high; indeed, the probability should increase with repeated episodes because individuals are sensitized to stress. Thus, for the stress sensitization model and indicators of impact,

\[ P(\text{DEP} | \text{SLE}, \text{DHX}) < P(\text{DEP} | \text{SLE}, \text{DHX}) \]  \hspace{1cm} (3)\]

The opposite is predicted for the conditional probability within the stress sensitization model for frequency: The probability of a stressful life event given a current depressive episode should decrease as a function of increasing prior depression history. This is because the particular pathway of becoming depressed via a stressful life event becomes less necessary and less prominent and thus less practically consequential. This is due to the more frequent but less severe stressors acquiring the capacity to trigger episodes for the increasingly sensitized individual. Thus, from this perspective we expect for Statement 2 above and the frequency of major life events,

\[ P(\text{SLE} | \text{DEP}, \overline{\text{DHX}}) > P(\text{SLE} | \text{DEP}, \text{DHX}) \]  \hspace{1cm} (4)\]

**Stress Autonomy Model**

According to the stress autonomy model, the effects of major life stress diminish over time and episodes as quasi-independent factors become responsible for triggering recurrence. Examining the dual roles (impact and frequency) of major life stress from this stress autonomy perspective points to some parallels and to some important differences compared with the stress sensitization perspective. In particular, from the stress autonomy perspective, as depression history increases, the impact of a stressful life event will decrease over time. Recurrences are less likely to be triggered by a major life event because stress loses its consequences, and other autonomous processes take over for initiating the episode. When a major life event does occur, it progressively loses the capacity to trigger a recurrence. Thus for impact we have

\[ P(\text{DEP} | \text{SLE}, \overline{\text{DHX}}) > P(\text{DEP} | \text{SLE}, \text{DHX}) \]  \hspace{1cm} (5)\]

In terms of the probability of a stressful life event given that one is depressed in relation to depression history (i.e., frequency), the predictions afforded by the two models converge. Given a depressive episode, the likelihood of a precipitating stressful life event will decrease as a function of prior depression history. (Obviously, as impact diminishes, frequency becomes less relevant.) Expressly, the frequency of major life events prior to onset decreases with successive recurrences is

\[ P(\text{SLE} | \text{DEP}, \overline{\text{DHX}}) > P(\text{SLE} | \text{DEP}, \text{DHX}) \]  \hspace{1cm} (6)\]

Although the general form of this prediction is similar for the stress sensitization and stress autonomy models, the underlying processes are quite different. As we address subsequently, this prediction is achieved via differentiable developmental mechanisms implied within the respective models.

**Summary and Conclusions**

In this section the distinction between the impact and frequency roles of life stress was introduced, and the general implications were formalized for major life events in relation to the stress sensitization and stress autonomy models (see Figure 2). Specifically, for the stress sensitization model over time, the impact of major life events increases, and their frequency decreases, with regard to onset of recurrences. By contrast, for the stress autonomy model the impact of major life events decreases over time and recurrences, whereas their frequency prior to onset necessarily also decreases. Fortunately, the competing predictions afforded by the two models readily lend themselves to empirical testing (an issue we later expand on).
With respect to the research literature on major life events and recurrence, frequency versus impact considerations are of immediate and obvious significance. As reviewed previously, several studies have reported that the association between major life events and episode onset weakens from a first lifetime episode through repeated recurrences (e.g., Kendler et al., 2000, 2001; Maciejewski et al., 2001). These results have been interpreted to suggest that life events lose their impact in predicting recurrences, presumably as other neurobiological mechanisms take over in the etiological scheme. However, it is indeterminate from these reports whether the weakening association is indeed due to a diminished potency of major life events (as predicted uniquely by the stress autonomy model) or to a lower frequency of major life events with successive episodes (as predicted by both the stress sensitization and stress autonomy models). Without attention to these separate issues, research on life stress and recurrence will remain uninformative about the underlying mechanisms involved in the changing relation of life stress to onset across recurrences.

The final major theme that contributes to the confusion in the current literature on kindling involves what is meant by life stress. According to the stress sensitization model, severe stressors are required to bring on a first episode of depression, but milder stressors are subsequently able to trigger a recurrence within the sensitized neurobiological system. This suggests an increasing role of life stress with regard to subsequent episodes (at least for the stress sensitization model; see also Hlastala et al., 2000). However, most research examining life stress and recurrence has restricted the conceptualization and measurement of life stress to major life events (cf. Ormel et al., 2001). Without systematically considering information on lower severity levels of life stress, there is another sense in which existing research represents an incomplete portrayal of the role of life stress in recurrence.

Dimensions of Life Stress: More or Less Important?

In most of the research investigating life stress and the recurrence of depression, the dimensions of life stress essentially have been compressed into a single dichotomous variable: the presence or absence of a major (or severe) stressful life event. As is now well established, major life stress is more relevant for a first onset of depression relative to a recurrence. By viewing life stress in such truncated terms, however, investigators have been confined to a blunt conceptual and operational tool for studying effects that, by theory, may be more differentiated and nuanced yet practically still quite pronounced. Enlarging the conceptual scope to incorporate lower severities of stressors uncovers additional strengths and weaknesses of the stress sensitization and stress autonomy models. The predictions are summarized in Figure 3. To again simplify the presentation, we dichotomize lower-level life events and examine the relative conditional probabilities with regard to current depression and history of recurrences by the respective stress models.

Stress Sensitization Model

Most generally, the probability of a current depressive episode given a lower-level life event parallels the effects predicted for the major stressful life events for the stress sensitization model (Statement 3 above): The probability increases. As a person becomes more sensitized to stress over time, the probability of a current depressive episode given an antecedent lower-level life event rises. With repeated recurrence episodes, progressively more minor events become ever more capable of precipitating recurrence. From this perspective even lower levels of stress will progressively acquire relevance for triggering onset. (So in a sense, this may be even more influential than would first appear given our simple dichotomization of life stress at this level of analysis.) For the stress sensitization model and indicators of impact (where LLE stands for lower-level life event),

\[ P(D|LLE, HX) < P(D|LLE, DHX). \]  

In contrast to the predictions related to frequency for the stress sensitization model and major stressful life events, the frequency of lower-level life events will increase over time with recurrences.

\[ \text{Figure 3. Stress sensitization model and stress autonomy model: Summary of impact versus frequency differences for major and minor life events.} \]
This is because, with sensitization, the more common and frequent lower-level stressors will acquire the capacity to trigger onset and thereby will become eventually the major mechanisms triggering recurrence. Thus, from this perspective we would expect to find for the frequency of minor life events,

\[ P(\text{LLE|DEP, DHX}) < P(\text{LLE|DEP, DHX}) \]. (8)

Note that because lower-level life events are expected to increase in their contributions with regard to both impact and frequency, the net effect of the combined processes should be considerable over time and recurrences for the stress sensitization model. Intriguingly, the dual roles of life stress are of exponential relevance as one descends the dimension of stress severity. That is, not only will more minor forms of stress gain in impact and frequency, but increasingly more minor forms of increasingly more common stress will eventually gain in impact and in frequency.\(^5\) This escalation of stress effects can explain why recurrences eventually appear to be autonomous in origin.

**Stress Autonomy Model**

Estimating the conditional probabilities for the stress autonomy model again points to the current conceptual limitations of this perspective. On the one hand, the sensitization feature of the model suggests that more minor degrees of stress can acquire the capability of bringing about recurrent depressive episodes. With this situation, both impact and frequency estimates would initially rise for lower-level life events with successive episodes. On the other hand, it is challenging to reconcile this progressive sensitization for lower degrees of stress while positing an alternative mechanism of progressive insensitization (or resilience) to major forms of life stress. The latter suggests an eventual lowering of impact and frequency for lower-level life events over time. Overall, it is unclear within this model when the sensitization is maximized and when it starts to give way to automaticity.

Nonetheless, it is of use to make certain assumptions and to work through the implications for the stress autonomy model. The empirical foundation for the kindling premise is that major life stress is related more to first onset depressions relative to recurrences. Consequently, from a stress autonomy perspective the stress sensitization processes peak early in the lifetime course. The insensitivity processes to major stressors therefore likely begin with the first episode or with early recurrences. This view is reinforced by the research that suggests that the association between major life stress and episode onset weakens following the first lifetime episode (e.g., Kendler et al., 2000, 2001; Maciejewski et al., 2001; Ormel et al., 2001). (Yet, we also note the ambiguity of these data with regard to frequency and impact considerations as addressed previously and with regard to additional issues we raise in a later section.) Further, we have no theory or evidence to target a different turning point in the developmental progression at which (a) stress and automaticity mechanisms crossover in their consequences or (b) stress sensitivity reverses into stress insensitivity. Therefore, we examine this issue with the view that sensitization has peaked at the first episode and declines thereafter. (Note that this particular assumption is not essential for the overall utility of the argument; i.e., if the crossover occurs later in the developmental progression, the general principles and conditional probabilities are applicable but simply become relevant further down in the recurrence chain.)

Thus for impact of lower severity life events,

\[ P(\text{DEP|LLE, DHX}) > P(\text{DEP|LLE, DHX}) \]. (9)

Given that the impact of lower-level life events decreases over time for the stress autonomy model, the representation of lower-level life events as effective triggers must also decrease in terms of their frequency. Thus, for the frequency of lower-level life events with successive recurrences,

\[ P(\text{LLE|DEP, DHX}) > P(\text{LLE|DEP, DHX}) \]. (10)

**Summary**

The stress sensitization and stress autonomy models provide competing and testable predictions regarding the associations between different roles (i.e., impact vs. frequency) and severity levels (i.e., major vs. minor events) of life stress and the recurrence of depression over time. In the sections that follow we further build on these basic themes by first extending the ideas conceptually and then by adapting and elaborating the ideas in accord with the available empirical information in the current literature.

**Conceptual Considerations: Synthesis and Speculation on Mechanisms and Processes**

We have developed three major analytic themes involving (a) the stress sensitization and stress autonomy models, (b) the different roles of major life stress (i.e., impact and frequency), and (c) the different levels of stress severity (e.g., major vs. minor life events). We have outlined at a very general level the implications of these three interrelated themes for life stress and the recurrence of depression. The ambiguities and inconsistencies revealed in Table 1 can now be systematically deconstructed, paving the way to reassemble the underlying ideas into a more coherent framework for testing between competing hypotheses. The observations that recurrences become more autonomous given an increasing number of prior episodes or that the association between stressful life events and episode onset declines with successive recurrences must be reexamined in light of (a) the different meanings of autonomous and the respective stress models implied, (b) frequency versus impact considerations for major life events, and (c) frequency versus impact considerations for less severe life events.

One direction to pursue is conceptual, taking a closer look at the hypothetical mechanisms and processes as structured by the foregoing analysis. For example, how might the different mechanisms...

\(^5\) We are aware that if taken too literally, our projection here could be somewhat misleading; we could become victims of our own argument within this example. That is, because we have dichotomized life stress into the presence or absence of more minor life events, with increasing recurrences and susceptibility, progressively lower levels of stress could eclipse the relatively more severe stressors, resulting in a decreasing frequency of such events as depicted for major life events. Again, though, the general argument is secure: With increasing recurrences, there is increasing susceptibility to trigger depression in relation to progressively more minor degrees of stress.
implied in the respective models play out over time and recurrences? How can the apparent shifting of importance of major life events over repeated episodes of depression best be explained within each model? By addressing these matters from a life stress perspective, several interesting ideas and novel implications readily become evident.

**Stress Sensitization Model**

If one adopts the stress sensitization viewpoint, both major and eventually minor life events can trigger recurrences. How can this stance be reconciled with the data consistently demonstrating that recurrences are less likely to be preceded by a major stressful event than first onset? To answer this question, we must first consider the base rates of life events that differ in terms of severity. Obviously (and fortunately), less severe life events typically are more common in the population than are severe life events (Brown & Harris, 1978, 1989; Monroe & Simons, 1991). As a result of a differential frequency distribution between severe and nonsevere life events, recurrences over time will be preceded most commonly by stressors that have a higher base rate yet still meet minimal severity criteria to trigger a recurrence. The frequency distribution for life events at threshold for initiating recurrence may be such that these types of events determine in a practical sense the modal mechanism for triggering recurrence, the effects detected, and the inferences drawn. Eventually with many recurrences, progressively more minor life events will appear to be more important in the predictive scheme (see also Footnote 5). There are some subtle implications of this thinking that further influence the picture with regard to the prevalence of major and minor forms of stress and recurrence. As less severe life events become capable of producing a recurrence, people with recurrent depression will become depressed in response to the more frequent less severe events and thereby be rather quickly and systematically “removed” from the available pool of nondepressed persons (see Ormel et al., 2001, for similar ideas). Therefore, not only do these more minor stressors precipitate recurrences in an absolute sense (owing to the higher base rate in the population), but also by virtue of their greater frequency per unit time, they hasten the time to recurrence. Effectively, less severe stressors twice eclipse the potential of more severe stressors to have a consequence.

Put differently, the highly stress-sensitive individuals are removed relatively quickly from the available pool for recurrence because they succumb in response to the more frequent, less severe life events. As a result, there is less opportunity over time for the already relatively infrequent, but severe, events to occur prior to onset. Consequently, the demonstration of causal potential for severe events is compromised in most conventional approaches to statistical analysis (owing to diminished statistical power). This process, too, nicely explains another well-documented clinical course characteristic of recurrent depression: the acceleration of episode onset with repeated recurrences (Post & Weiss, 1999). Overall, the two factors involving (a) a higher prevalence of minor forms of stress that become capable of triggering depression and (b) the consequent acceleration of onset timing make it progressively less likely that major events will feature as a common mechanism via which recurrence is triggered.

This line of reasoning can be stretched further (although these ideas admittedly may be more creative than credible). Many if not most major life events can be anticipated, and many types of adversity may appear possible but are not certain to come about. Relatively few of life’s major setbacks are without any forewarning, and other potential calamities mercifully never materialize. For example, one might guess that serious troubles lie ahead at work or that a core interpersonal relationship is imperiled. The highly stress-sensitive and depression-prone person may need but a modicum of evidence to quickly conclude that what is at present only a possibility is in the future a felt certainty. This could result in anticipatory psychological foreclosure on the life event and triggering of recurrence. Most noteworthy with this conjecture, major life events would not be evident prior to recurrence onset (i.e., the event never happens or the event happens after onset). This suggests that the effects of major events would be even further underestimated owing to their relative absence in the period of time prior to onset. Once again, this would make it very difficult to detect potential effects of preonset severe events. The net consequence would lead to further lowering of the likelihood that major events precede recurrence onset, perhaps leading to a reduced frequency of major events in the time period before onset that is even lower than population base rates.

In the most extreme case, the sensitization process could explain the apparent effects of symbolic events for triggering depression recurrence (see Post & Weiss, 1999). On the basis of a history of depression and severe stress, highly sensitized individuals may not simply overanticipate negative events but may overreact to increasingly more remote possibilities or even to vestigial reminders of past adversity. Given a heightened sensitivity and/or lowered threshold for activating depressogenic cognitive schema, processes may be initiated by life situations that are only distantly related to the original environmental circumstances or that are only remotely likely to happen. Viewed from another perspective, conditioned responses to past traumas may be elicited by apparently minor life events and thereby acquire the ability to trigger depressive episodes. Most generally, these cognitive processes or conditioned responses become functionally equivalent in consequence to the actual events, in the past or anticipated future, for triggering depression (Segal et al., 1996). These ideas provide alternative perspectives on how symbolic events may acquire the capability for initiating pathological outcomes.

Taken together, all of these considerations strongly suggest that according to the stress sensitization model the detection of major life event effects as recurrences accumulate will be difficult given typical research designs and modes of analysis. This does not mean

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6 It is worth noting that this is a population-specific effect. That is, different populations will have different rates of major versus minor life events (e.g., political–cultural differences between countries; socioeconomic differences within countries; see Brown, 1996). The more common severe events might be relative to more minor stressors, the less likely the eclipsing process depicted for lower severity stressors will be operative.

7 Depression often presents with considerable anxiety comorbidity (Monroe, 1990). One might speculate about these ideas with regard to the degree of uncertainty about the future life crises and the cognitive processes involved to explain variation and mixture of depressive and anxiety symptoms (Brown, 1993; Kendler, 1996).
that major events cannot provide one mechanism via which recurrence is triggered or that major life events have lost their impact. It simply means that the mechanisms involving major events will become increasingly difficult to detect given the increasing preponderance of other stress-related processes and with conventional data analytic procedures.

**Stress Autonomy Model**

The stress autonomy perspective is less clearly specified with regard to the processes that evolve over the course of repeated depressive episodes. Nonetheless, some projections can be made with respect to general matters. First, there is the requirement to explain the changing role of major life stress for an initial episode compared with a later recurrence. On the basis of theory, we would anticipate some degree of progressive sensitization early on. However, given the endpoint of stress autonomy, one might also expect some progressive insensitivity to stress over time. This represents the core conceptual conundrum for this model: When such shifts between the vaguely implicated mechanisms occur and why remain obscure. Clearly it is difficult to account for the “shift from episodes that are triggered to those that occur autonomously” with a unitary process (Post, 1992, p. 1001). It is most likely that at least two hypothetical but related mechanisms need to be entertained together: one pertaining to stress sensitization and one pertaining to stress resilience.

What is most theoretically burdensome, though, is the progressive decoupling of stress from the likelihood of recurrence with the stress autonomy model. Thus, a process similar to the one proposed for the stress sensitization model can be envisioned, wherein the major life events are eclipsed in frequency by alternative processes of increasingly dominant influence. Instead of more minor forms of stress being the eclipsing mechanism and eventually assuming the dominant triggering role, however, we would expect for the stress autonomy model an independent secondary mechanism (e.g., endogenous neurobiologic processes; see Footnote 3). This secondary mechanism would be initially associated with stress and recurrence but would progressively extinguish or “saturate” (Kendler et al., 2000) in relation to stress.

**Summary and Conclusions**

Clarifying the underlying mechanism(s) linking life stress to successive recurrences represents a critical starting point for research on life stress and depression. The stress sensitization and stress autonomy models provide very different accounts of the relationships by successive recurrences of depression in relation to major

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**Empirical Considerations: Implications for Longitudinal Predictions**

At this point it is useful to examine the theoretical picture in light of the current research literature. How do the ideas we have developed fit with the available data? How might findings from recent research provide additional structure for modeling these matters? We derive below more fine-grained estimates for the probability statements derived in the preceding sections for stress impact and frequency in relation to recurrence (see Statements 3–10, above). This important exercise readily brings to light competing hypotheses that are testable and unveils several novel considerations for future research. This activity, too, underscores the need for a framework to systematically organize the many complex considerations involved. It must be borne in mind, though, we are providing general direction not specific detail. Fortunately, the points established are likely to be robust to limitations imposed by the coarseness of the existing data or by flaws in the reasoning based on these tentative numerical estimates.

One complication is that the number of estimates is large and the available data are limited. For example, for 10 episodes of depression there are 80 estimates (2 stress models × 2 stress roles × 2 stress severities × 10 episodes). Even when we dichotomize depression history in terms of first onset versus overall recurrence, 16 separate estimates are required. Owing to the lack of recognition in the literature of the issues we have raised, existing studies have not provided specific information on impact and frequency stratified by first onsets or recurrences. Therefore, we use information from the literature that most closely approximates present needs. Such information often requires further refinement given other factors that likely influence the approximation. By making well-reasoned and explicit estimates, we provide an initial platform of information. After establishing these preliminary estimates, we forecast in a general manner the subsequent relationships by successive recurrences of depression in relation to major
and minor life stress (i.e., the remaining 64 estimates). These are depicted separately for frequency and impact in Figures 4 and 5, respectively. The final longitudinal framework yields an integrated picture of the specific and competing predictions afforded by the stress sensitization and stress autonomy models for the consequences of stress over time in relation to depression onset and recurrence.

**Frequency of Life Stress Prior to Episode Onset**

We begin with the estimates for which information is most readily available from the empirical literature: the frequency of major life events and minor life events prior to depression onset (see Figure 4). The reviews of Post (1992) and Mazure (1998) respectively suggest that between 59% and 67% of people with a first onset have recent major life stress. These are direct estimates from 15 independent studies in the literature for a first lifetime mood disorder episode. These figures are applicable for both the stress sensitization and stress autonomy models. (It should be noted that there were five studies common to both reviews and that the review by Post, 1992, included all mood disorders [unipolar and bipolar] in the analysis.)

There are a few issues to consider for refining this estimate. Mazure (1998) also reported on community samples of depressed people with recent stressful life events. Although these data were not differentiated into first episodes versus recurrences, all of these community studies used state-of-the-art assessment methods for measuring life stress (the LEDS; Brown & Harris, 1978, 1989). (Other study estimates for life stress prior to first episodes included a variety of stress measures, several of which possess limited psychometric qualities; Brown, 1989.) The estimates for community cases were significantly higher, indicating approximately 82% of depressed persons in the community report a major life event prior to onset. Because most people do not seek treatment for depression, community-based samples provide a more representative approximation of the proportion of first onset depressed persons with prior severe stress. (This would be especially true if major stress impeded access to treatment; see Ginsberg & Brown, 1982; cf. Monroe, Simons, & Thase, 1991.) In light of these

![Figure 4](image-url)

*Figure 4.* Frequency of major and minor life events for the stress sensitization and stress autonomy models by successive episodes of depression. SLE = stressful life event; DEP = current depressive episode; LLE = lower-level life event.
considerations, we estimate conservatively that about 70% of people with a first onset depression have a recent major life event. Again, this figure applies equally for the stress sensitization and stress autonomy models.

Assuming 70% of people with a first onset of depression have a recent major life event, we can extrapolate to the proportion of first onset cases with recent lower levels of life stress. This is straightforward for the stress sensitization model, which directly dictates that the remaining 30% have a recent nonsevere life event (i.e., cases that do not have recent major stress must be sufficiently sensitized to succumb to lower levels of life stress). For the stress autonomy model the comparable estimate is not as straightforward, given the openness of the model to processes unrelated to life stress for initiating a first episode (e.g., some individuals may be already highly sensitized or "prekindled" by prior life experiences or genetic liability such that their onset is already unrelated to life stress; Kendler et al., 2001). For first onset cases of depression, however, this estimate is likely similar to that afforded by the stress sensitization model. Yet to establish the difference between the models and to provide a reasonable approximation, we estimate as a starting point for the stress autonomy model that 20% of first onset cases have a lower-level life event.

For major event frequency and overall recurrence of depression (i.e., collapsed across all recurrences), Post’s (1992) and Mazure’s (1998) reviews also provide useful starting points. Respectively, these reviews indicate that between 32% and 43% of people with recurrences have recently experienced a major life event. If we consider the quality of the stress measures in the studies included in the two reviews as well as the reference populations (patient vs. community sample), there is a tendency again to favor the information provided by Mazure (1998). Given these considerations, a reasonable overall estimate is that approximately 40% of people with recurrences have a recent major life event. Because this again is a direct estimate based on the combined literature reviews for the frequency of stressful life events collapsed across recurrences, it is equally applicable to the stress sensitization and stress autonomy models. However, because relatively more people have fewer lifetime episodes, the 40% estimate for all recurrences should be weighted more heavily by the people with relatively few lifetime

Figure 5. Impact of major and minor life events for the stress sensitization and stress autonomy models by successive episodes of depression. DEP = current depressive episode; SLE = stressful life event; LLE = lower-level life event.
recurrences. On the basis of this information, we modify the percentage estimates accordingly over first recurrences and subsequent recurrent episodes. For a first recurrence overall (i.e., not specified by stress model), this suggests somewhat more than 40% would have recent major stress, with the proportion tailing off over successive recurrences.

Most crucially, the stress sensitization and stress autonomy models yield very different predictions for specific recurrence episodes (i.e., a first vs. second or third recurrence). The distinctive predictions between the two models emerge with the first recurrence of depression and follow in a consistent pattern over time and recurrences. Consequently, deriving estimates for the frequency of a major life event before the onset of the first recurrence represents a critically important reference point.

For the stress sensitization model, the proportion of episodes precipitated by a major life event declines over successive recurrences because major events are eclipsed by progressively more minor life events. For the stress autonomy model, there is also a decline in the proportion of episodes precipitated by major life events, but this is due to the developing alternative etiological mechanism and the progressive insensitivity to stress. The stress sensitization model therefore projects a greater ultimate decrease in frequency of major life events prior to recurrence onset over time than does the stress autonomy model. Specifically, for the stress sensitization model the frequency of major events theoretically could fall below the expected population base rate, whereas for the stress autonomy model the frequency of major events eventually would approximate the expected population base rate. Consequently, there should be a relatively larger “compensatory” increase in percentage of first recurrence cases over the 40% general recurrence estimate for the stress sensitization compared with the stress autonomy model. Given these considerations, we estimate that for the stress sensitization model 50% of people with first recurrences experience a recent major life event. For the stress autonomy model, a comparable estimate is 45%. For the remaining recurrences, we provide a systematic decline in frequency of major life events per model from these initial recurrence points, with the eventual respective endpoints dictated by theory (i.e., below base rate frequency of major events for the stress sensitization model and base rate frequency of major events for the stress autonomy model). These projections are portrayed by the lines with diamonds and the lines with squares in Figure 4.

Estimates for the frequency of lower severity life events and first recurrence also diverge for the stress sensitization and stress autonomy models. (Because these estimates are not directly available from recent reviews, the extrapolations again require adjustments according to the particular assumptions of the two models.) For stress sensitization, the task is again straightforward: Fifty percent of first recurrences should have a recent life event of lower magnitude (i.e., all individuals who did not have a major life event). For stress autonomy, the task is again less clear and more speculative. Taking into consideration the operation of an autonomous mechanism for a portion of the remaining 55% of individuals on their first recurrence, we suggest that 30% of recurrences from this perspective have an event of a lower severity level. (The remaining 25% would be attributable to the autonomous secondary mechanism responsible for onset.) Again, we provide estimates for minor stress frequency over later recurrences as follows from these initial estimates and the assumptions of the respective stress models: In Figure 4, the line with triangles indicates increasing frequency of lower-level events preceding onset for the stress sensitization model, and the line with Xs reaches a plateau for the base rate for lower-level events for the stress autonomy model (owing to the decreasing correlation with onset). Note that the frequency of lower severity life events for the stress sensitization model increases with a decreasing frequency of major life events, whereas for the stress autonomy model both lower-level and major life events decrease over recurrences.

At the broadest level, there are two important competing predictions afforded by each stress model that hold irrespective of any inaccuracies in the specific estimates. First is the emerging and dramatic importance of minor forms of life stress as triggers of recurrence within the stress sensitization model. This represents a very testable prediction but one that has not been seriously considered in the literature to date (see below). A second major prediction pertains to the lowered frequency of major life events given a history of many recurrences for the stress sensitization model. This prediction follows directly from our discussion about the manner in which increasingly lower levels of stress eclipse the opportunities for severe events to occur prior to onset and thereby for the frequently occurring lower levels of life stress to accelerate successive recurrences. Because the person is highly stress sensitive (owing to a history of repeated stress and recurrences), he or she will be very unlikely to incur a major life event when in a nondepressed state (e.g., minor events will preempt the less common severe events, or anticipatory processes may trigger onset before the event occurs). Far from representing the ineffectiveness of major life stress to bring about recurrence, however, such a result represents the “double-eclipsing” of major life events by more minor life events and progressively quicker depressive episodes (i.e., shorter well intervals between episodes). If major life events eventually become less frequent than anticipated by base rates alone, it could also signify important psychological processes that are only loosely linked in time or content to environmental events or possibilities. Such findings would suggest changes in thinking about timing issues for life stress and depression onset, to accommodate psychosocial stressors that may “occur” psychologically earlier than they actually occur in real time. Indeed, such findings could help place clinician’s hunches about the importance of symbolic events for recurrence within an operational framework that could be more readily investigated.

Impact of Life Stress Prior to Episode Onset

We turn now to estimates for stress impact: the likelihood of developing depression given prior life stress. There are fewer sources of information available to structure these approximations. Yet this is a matter so central for distinguishing between the stress sensitization and stress autonomy models that preliminary empir-
ical guidelines must be drawn from a life stress perspective. Concerns about the precision of the estimates are far outweighed by the importance of the issues that are brought to light. Indeed, this exercise provides the basis for several interesting avenues of research and exposes a central contradiction between our conceptual analysis and recent empirical research. The estimates for stress impact are provided in Figure 5.

A pivotal piece of information for estimating stress impact is that approximately one in five women exposed to a recent severe life event develop depression (Brown & Harris, 1978, 1989). The 20% impact estimate is based on studies of predominately younger, lower-class women undifferentiated with regard to first onset versus recurrence. As such, the 20% figure is likely an overestimate for the population at large. (These women have fewer resources for buffering the adverse effects of stress; so they will evidence a higher degree of impact for major life events; Kessler, 1997). Therefore, for first onset cases in the general population given a recent severe event, an estimate of 10% breakdown for both the stress sensitization and stress autonomy models is reasonable. This impact figure must now be apportioned according to first onset versus recurrences, major and minor stressors, and the stress sensitization and stress autonomy models.

Impact comparisons for overall recurrence estimates and life stress begin to diverge immediately by stress model. As articulated above, the stress sensitization model dictates an overall increase in impact over time for major life events, whereas the stress autonomy model dictates an overall decrease in impact over time. The most interesting prediction is the dramatic spike for stress impact estimates projected to occur between the first lifetime episode and the first recurrence for both the stress sensitization (the line with diamonds) and the stress autonomy (the line with squares) models in Figure 5. This spike indicates a greatly enhanced sensitivity to stress for samples depressed once previously compared with samples never previously depressed. To our knowledge, this apparent theoretical necessity has not been recognized previously.

The predicted spike increase in impact for the first recurrence derives from the shift in target population for the two depression conditions (i.e., first vs. second episode). Estimates for recurrence are by definition based on a very different population than are estimates for first lifetime episodes (i.e., people who have been depressed previously vs. people who have never been depressed previously). When calculating the likelihood of a first depressive episode given a major life event, the sample should be representative of the never depressed general population. However, not all individuals in the never depressed general population will become depressed or perhaps even depression capable (Monroe & Simons, 1991). Further, people previously exposed to severe stressors in the never depressed general population are likely to be stress vulnerable and thereby less likely to incur a depression in relation to life stress. Overall, the presence of people in the never depressed population who are at low risk for ever developing depression will dilute estimates of depression following major life stress (i.e., impact) for the subset of people who actually are at risk for the disorder.

In contrast, when one is estimating a first recurrence of depression, the target population is by definition proven to be depression capable and thereby represents a relatively small subset of the general population. Risk for depression accordingly is considerably elevated for this subgroup, and sensitivity to the depressogenic effects of stress similarly should be enhanced. Because we have estimated that approximately 70% of the first episode people have a major life event prior to onset, it follows that a large proportion of the population defined by a single prior episode is likely to be stress sensitive (by either stress model, although the exact proportions will vary per model, as we discuss below). Consequently, people who have already experienced one episode of depression should have a greatly heightened likelihood of depression onset following major life stress compared with people who have never been depressed. In short, stress impact will be much more pronounced for people with a first recurrence relative to people with a first episode. (We would expect a relatively less pronounced increase for the impact of stress between the first recurrence and later recurrences, given less dramatic shifts in reference population with increasing recurrences.9)

Although the general form of the predicted spike in impact holds for both the stress sensitization and the stress autonomy models (as well as for both major and minor life events), there is an additional factor to consider. If first onset depressed people with and without prior major life stress differ in their current sensitivity to stress, then the projected spike will be more or less pronounced. There are two points to weigh: (a) the degree to which people with first onset depression without prior major stress are sensitized and (b) how sensitization changes following a first onset.

For the stress sensitization model, people without a major life event prior to a first depression onset are necessarily highly sensitized. It follows, then, that these highly sensitized individuals are more likely to incur another episode, owing to their heightened vulnerability to become depressed in response to the more common lower severity life events. The people with a major life event prior to their first depressive episode, too, will be sensitized initially and will become more so subsequently. Consequently, the anticipated spike in sensitivity for major and minor stress (i.e., impact) should be especially pronounced for the stress sensitization model: All first onset people are initially sensitized and become more sensitized as a result of their episode. On the basis of these considerations, we estimate 70% of once-depressed persons become depressed again given a major life event.

In contrast, for the stress autonomy model individuals who first become depressed without prior major life stress are to some extent already less sensitive to stress (i.e., they become depressed via nonstress mechanisms). Also, of those who first become depressed with prior major life stress, a proportion subsequently become less vulnerable to stress and more autonomous (i.e., vulnerable to nonstress mechanisms for triggering onset). The net effect is to lower representation of the stress sensitive in the pool available for a first recurrence and consequently to lower the estimate for the impact spike (for both major and minor events as previously discussed). However, there still should be an impact spike, given the likely profound implications of the change in reference population (i.e., never depressed general population vs. the once depressed). On the basis of these considerations, we

9 We note that this predicted spike is in conflict with recent reports in the literature, reviewed previously, indicating a weakening association between life stress and episode onset following a first depression. We address this issue in considerable detail in the next sections.
suggest 45% of once-depressed persons become depressed again given a major life event.

For lower levels of life stress there should be relatively little impact for first episodes of depression according to either the stress sensitization or stress autonomy models. However, in theory there would be some individuals who are already highly sensitized and who succumb to minor stressors. We estimate that 2% of persons exposed to low-level stress conditions develop a first episode of depression within both the stress sensitization and stress autonomy models.

Where the differences should become most apparent for less severe stress levels again is in the predictions by stress model over successive recurrences. For the stress sensitization model, people with prior episodes will be vulnerable to progressively more minor events. There will also be the projected spike for impact estimate from the first depressive episode to the first recurrence. Given such matters, a preliminary impact estimate for less severe stressors and a first recurrence is 25%. For the stress autonomy model, people with recurrences will have episodes triggered progressively with less stress. However, it is likely that there also will be some impact enhancement from the first lifetime episode to the first recurrence for more minor stressors (owing to the change in reference sample and consequent increased sensitivity). Given such matters, a preliminary impact estimate for less severe stress and a first recurrence within the stress autonomy model is 20%. As before, we provide subsequent estimates for minor stress impact over later recurrences as follow from these initial estimates and the assumptions of the respective stress models (see Figure 5). Note that for the stress sensitization model, minor stressors become just as capable of provoking depression as major life events when sensitization (i.e., number of recurrences) increases. By contrast, for the stress autonomy model minor stress becomes just as consequential in provoking depression as major life events while putative autonomous mechanisms take over.

Summary and Conclusions

A number of intriguing and novel issues come to light when systematically working through estimates for the impact of life stress over the lifetime course of recurrent depression. The predictions afforded by the stress sensitization and stress autonomy models diverge dramatically over time and offer many opportunities for testing different facets of the respective models. An especially key issue also emerges with this analysis that points to the pivotal importance of life stress and recurrence in the very early stages of the lifetime course of depression. In particular, we predict distinct changes in impact for major and minor life events as one progresses from a first lifetime episode to the first recurrence. It is interesting to note that these theoretical predictions from a life stress perspective clash with empirical findings from several studies reviewed previously (e.g., Kendler et al., 2000; Maciejewski et al., 2001; Ormel et al., 2001). We address and reconcile this situation next, as we present some of the most pressing implications for future research.

Implications for Future Research

Our goal has been to clarify the ambiguities involving three aspects of current theory on life stress and the recurrence of depression and to demonstrate how a systematic portrayal and integration of these themes provides the beginnings of a framework to guide research and theory. We hope our arguments and examples are sufficiently persuasive—or at least provocative—so that they stimulate more sophisticated and revealing ideas and research on life stress and depression. In the remainder of the article, we present the implications for future theory and research, targeting what we consider to be some of the most critical mandates. These include (a) evaluating stress in relation to first onsets versus first recurrences, (b) targeting promising transition periods for stress and recurrence, (c) conceptualizing and measuring non-severe life stress, (d) considering stress generation, and (e) developing alternative conceptual models.

Evaluating Changes in Stress–Onset Relations Over Time

A central topic for future research is to determine precisely how the association between major life events and recurrence changes over time as informed by a life stress perspective. As can be seen in Figures 4 and 5, there are clear differences predicted for impact and frequency by the stress sensitization and stress autonomy models. These are readily testable issues, provided researchers pay attention to the three considerations we have detailed for evaluating the degree of association between life stress and episode onset. The full importance of this matter is forcefully illustrated by the most recent research bearing on this topic.

Recent research has emphasized that the strength of the association between major life stress and episode onset declines from the first lifetime episode over successive recurrences. The investigations by Kendler et al. (2000, 2001), Ormel et al. (2001), and Maciejewski et al. (2001) all report that the odds ratio (or risk ratio; Maciejewski et al., 2001) for major events and episode onset is considerably higher for a first onset depression compared with the first or subsequent recurrence (e.g., 9.38 vs. 6.74, respectively; Kendler et al., 2000; 41.00 vs. 9.11, respectively; Ormel et al., 2001). These studies represent the most sophisticated work on this central precept of the kindling hypothesis and are very influential in guiding present-day thinking and research. Yet these findings directly contradict our prediction that there should be a spike in impact between a first onset and a first recurrence (see Figure 5). How can we reconcile this well-replicated empirical result with what seems to be a theoretical necessity?

First and most simply, the findings from these studies are ambiguous with respect to the frequency versus impact issue. It is quite plausible that the decline in strength of association is primarily attributable to a progressive decline in frequency of major events precipitating subsequent recurrences, not to a progressive decline in the impact of major events for subsequent recurrences. The decrease in frequency of major life events with successive recurrences, of course, is a direct prediction from both the stress sensitization and stress autonomy models. Consequently, there may still be a spike in impact, but it is masked by the overarching decrease in the frequency of major life events occurring prior to successive recurrences.

Second and less simply, there are subtle methodological concerns that constrain what may be inferred from these recent studies. These methodological matters simultaneously involve (a) the use of the odds ratio as the index of statistical association between life stress and episode onset and (b) the sampling confound be-
Turning to the association between a major life event and the first recurrence of depression, the situation is quite different and more complex. This odds ratio is a function of (a) the change in reference samples (never depressed vs. once depressed) and (b) the strength of the association between a major life event and a first recurrence (which involves both the frequency and impact of major life events). It is important to first fully appreciate the implications of the reference sample shift (introduced previously) between the first onset and recurrence analyses. Note that only cells \(a\) and \(b\) (see Table 2) from a first depression onset table provide the entire sample for a subsequent \(2 \times 2\) table recurrence table. In other words, the previous nondepressed individuals in \(c\) and \(d\) (see Table 2) are by definition dropped from the first recurrence analysis (because they never became depressed). However, the vast majority of people for the first onset analysis populated cells \(c\) and \(d\). (Incidence of depression is relatively low, and especially low for people who have never been depressed previously.) First recurrence analyses therefore draw from a very small portion of the sample represented for first onset analyses. This is a substantial shift in population numbers and characteristics, the consequences of which need to be recognized and evaluated.

For a first recurrence, the numerator of the odds ratio, \(\frac{ab}{cd}\), inevitably will be smaller than for a first lifetime episode. The existing research directly supports this statement (and both the stress sensitization and stress autonomy models also dictate this outcome; i.e., there is a diminished frequency of depressed individuals with a recurrence who have prior major stress—\(a\)—as more individuals with a recurrence succumb either to lower levels of stress or to alternative initiating mechanisms—\(b\). Consequently, the numerator for the first recurrence odds ratio must decrease relative to the odds ratio for a first onset. The denominator, \(c\) and \(d\), however, must almost certainly increase for recurrence cases relative to first onsets. This follows from the necessary exclusion from a first recurrence analysis of individuals who have never been depressed previously—individuals who were by far the most common in the first onset sample (i.e., the extreme loss of representation of nondepressed people, the vast majority of whom populated the prior \(d\) cell). Overall, if the numerator, \(\frac{ab}{cd}\), inevitably becomes relatively smaller for a first recurrence compared with a first onset and if the denominator, \(c\) and \(d\), in all likelihood becomes relatively larger for a first recurrence compared with a first onset, the resulting odds ratio inexorably decreases. This can occur irrespective of the actual changes in impact and frequency between major stress and episode onset or of the changes in overall strength of association between major stress and episode onset.\(^{10}\)

\(^{10}\) The \(c\) cell represents the only source of possible contention in the above line of reasoning. That is, if the proportionate changes in \(c\) relative to \(d\) for a first recurrence are such that the overall odds ratio denominator \((c/d)\) becomes smaller rather than larger, the net effect could conceivably offset the inevitable decrease in the numerator of the odds ratio and thereby increase the overall odds ratio for a first recurrence somewhat (conceivably approximating or possibly surpassing that for a first onset). This, though, is an extremely weighty and doubtful requirement for loss of representation in the \(c\) cell, given the dramatic loss of representation in the \(d\) cell. The \(c\) cell is especially interesting, though, in that it is the most relevant component within the odds ratio calculation that reflects the idea of stress.
Any true increase in impact of a major life event from a first lifetime episode to a first recurrence could easily be masked by the consequences of the shift in reference sample on the computed odds ratio. Nonetheless, we acknowledge that the changes in sample composition between a first lifetime onset and a first recurrence present a major problem and that the consequences of this problem prevent firm conclusions at present about how associations between life stress and depression onset change over time. Future research needs to recognize and address this issue and to do so in the context of the three themes we have discussed for first onsets and first recurrence of depression.\footnote{The analytic procedures used by the research groups documenting the decreasing association between major life events and recurrence over time were more complex than simple odds ratio calculations. For example, the odds ratio was calculated from the logistic regression coefficient after a variety of other covariates were controlled for (Kendler et al., 2000). Nonetheless, the basic logic of the odds ratio along with the shift in sample representation between a first onset and a first recurrence exposes the underlying methodological problem and its likely influence on any measure of strength of association between the variables involved.}

Most generally with regard to this matter, the relationship of stress to recurrence is especially interesting and informative between a first lifetime episode and a first recurrence. For example, the once depressed represent a highly interesting and important risk group. Targeting interventions for such persons could be most informative. Randomized trials could help to determine what interventions might be effective in the short and the long run. Theoretically, by arresting the development of stress sensitization (for the stress sensitization model) or of the autonomous initiating mechanism (for the stress autonomy model), one could alter the long-term course of the disorder for the better (Post, 1992; Post & Weiss, 1999; Segal, Pearson, & Thase, 2003). Understanding how less severe stressors feature in regard to first onsets and first recurrences, too, would represent an extremely important element of such work. Overall, investigators should be alerted to this pivotal juncture in the course of recurrent depression and plan accordingly to depict the nature of the associations between life stress and recurrence in the early stages of the disorder.

Targeting Promising Transition Periods for Stress and Recurrence

The question of how stress sensitivity changes between a first and second episode of depression points to the utility of studying stress processes early in the developmental course of depression and its recurrence. Most work to date has covered the full range of people with recurrences, with studies reporting lifetime episodes often of considerable magnitude (e.g., greater than 34; Kendler et al., 2000). In light of the present analysis, it might be prudent to target individuals with lifetime episodes in a range that could be more informative for studying stress processes and exclude individuals with extreme histories. The value of including individuals with extreme histories of prior depression is doubtful on several counts. Empirically, it is likely that the stress processes for people with numerous prior episodes will be hard to detect. For example, the stress sensitization model predicts that after many recurrences, only more minor or even symbolic events could trigger an episode. Although in

impact (i.e., the number of individuals who do not become depressed after major life stress). For the odds ratio to increase from a first onset to a first recurrence there would have to be a very large and proportionate decrease in c to offset the tremendous loss of participants in d, with the net denominator proportion then offsetting the required increase in the numerator proportion. This seems an unlikely scenario, but the major point is that the confound must be recognized and reconciled before substantive interpretations can be offered with confidence.
is quite clear in theory but less pronounced in empirical backing. To be certain, there are data documenting the potential triggering effects of nonsevere forms of life stress (e.g., Hammen, Henry, & Daley, 2000; Kendler, Karkowski, & Prescott, 1998; Monroe et al., 2005; Monroe, Roberts, Kupfer, & Frank, 1996; Ormel et al., 2001). Several of these studies, too, have used strong life stress assessment procedures and have studied especially vulnerable groups. For example, both the Monroe et al. (1996) and the Ormel et al. (2001) reports demonstrated that nonsevere, undesirable life events predicted recurrences of depression. If most depressive onsets, though, are recurrences (Kessler, 1997) and if recurrences are capable of being initiated by lower degrees of life stress, why is there not a stronger empirical record for more minor life event effects (Monroe & Hadijyannakis, 2002)?

We suggest much of the problem lies in the tremendous heterogeneity of experiences that are captured within more moderate and minor classes of life event severities (Monroe & Simons, 1991). In a sense, severe life events are powerful and convenient for probing stress effects. But they might also be rather crude tools. Severe events are so impactful and of such relatively clear psychological importance for an individual that they form a potent class of depression initiators. Moderate and minor life events do not possess such uniform, psychologically meaningful characteristics. Proportionately there are many more events that are moderate or minor compared with severe events, indicating there is likely to be a great deal more noise in these lower severity classes of events with respect to depressogenic potential. All of this suggests that more care needs to be taken to define and target specific types of moderate and minor life events that could precipitate a recurrence of depression. Assessing these forms of stress will therefore be more methodologically demanding and may require more sophisticated theory to delineate the types of experiences that are most meaningful for possibly triggering a recurrence of depression.

In terms of methodology, steps can be taken to better specify the types of events that are most likely to have meaning for the participant. For example, in the LEDS system many of the events that are rated as moderate or minor actually occur to, and primarily affect, others in the person’s social network (e.g., sister’s divorce, friend’s loss of job). That is, they are not directly focused on the participant. It is not readily apparent to what extent such events impact the participant. Another example of this methodological theme is reports of deaths. More often than not, such events tend to involve the deaths of people who are rather remote from the participant; again, it is not clear from such instances how impactful the loss may be for the particular participant involved. As a result, a considerable number of events falling within the moderate to minor severity classes of events will involve experiences that may not be very psychologically compelling or meaningful for the participant. In the early course of recurrent depression, it might require moderately stressful events that are more person centered to be of threshold potential to trigger a recurrence.

By way of comparison, severe life events within the LEDS system require that the participant must be a central player in the consequences of the event, which is codified through the determination of event focus (and this is ensured through detailed information and interview, along with operational guidelines for making such determinations). Thus, not only are severe events likely to be very stressful, but they also have a major impact on the participant. Many of the investigator-based methods for assessing life stress, too, incorporate other procedures to help enhance the likelihood of better capturing the personal meaning of life events for the particular individual involved. For example, the LEDS system draws heavily on a contextual rating procedure (Brown & Harris, 1978, 1989). Detailed information about the person’s recent and current circumstances is sought to provide background and biographical context for evaluating the likely emotional significance of life events. Particular events might be more or less psychologically important given individual differences in past history and current circumstances; using the contextual procedures provides greater sensitivity to such issues. In general, the value of interview-based procedures has been recommended for assessing major life events in the literature (e.g., McQuaid, Monroe, Roberts, Kupfer, & Frank, 2000), and the importance of such approaches is likely to be all the more critical for the assessment of moderate and minor types of life events. Fortunately, several available investigator-based approaches to the assessment of life stress provide a broad range of event severities to test the premises we are outlining (Brown & Harris, 1989; Dohrenwend, Raphael, Schwartz, Stueve, & Skodol, 1993; Hammen et al., 2000).

A caveat to be borne in mind, though, is that there are probably limits on how far one might be able to reliably pursue the operationalization of progressively more minor life events. As one proceeds to the level of the truly minor psychosocial perturbations, it becomes progressively more difficult to apply operational criteria and to determine if an experience meets threshold criteria for definition of an event (Brown & Harris, 1978; Dohrenwend & Shrout, 1985). This, however, would represent a problem only for testing the stress autonomy or stress sensitization models at the extreme end of the recurrence distribution, where the truly minor and mundane hassles of daily life in theory could trigger onset. As we have emphasized, future research targeting the early episodes of depression (e.g., zero to three or four prior episodes) will be critical to distinguish between the stress autonomy and stress sensitization models. The resolution capabilities of interview-based procedures is more than adequate to provide reliable assessment of the moderate and more minor forms of stress that may or may not be operative in recurrence within this range (and likely even higher; e.g., nine episodes; Kendler et al., 2000). There still will be many more types of events captured than are likely to be informative for recurrence, however; so, we turn to the importance of theory to further guide research and to target classes of nonsevere events with the most likely depressogenic capabilities.

Prominent theories for depression can provide guidance as to what types of nonsevere life events may be especially pertinent for triggering recurrence in the highly vulnerable. For example, cognitive theories of depression emphasize the potential depressogenic attributional or inferential response to life stress (Abramson et al., 2002; Beck, 1987). According to these models people differ in overall cognitive vulnerability and also may differ with respect to specific domains of vulnerability. For example, Beck (1987) hypothesized that people place different value on certain types of experiences; some individuals are more invested in social relationships (sociotropy), and others in achievement and independence (autonomy). It is at lower levels of life stress, beneath the threshold of severe events, where such individual differences in vulnerability may most convincingly come into play with respect to specific types of life events potentially triggering depression (Abramson et
al., 2002). For instance, individuals who are cognitively vulnerable to one domain or the other may become depressed when a specific lower-level life event occurs that matches the particular vulnerability. Although research bearing on this topic has produced inconsistent findings to date, there are many considerations that could clarify the empirical picture (Coyne & Whiffen, 1995). By tightening life stress assessment procedures, clarifying the lower-level events of general psychological importance, and further linking such experiences to specific cognitive vulnerabilities, researchers may be able to make the role of moderate forms of life stress evident in relation to recurrence.

Investigator-based procedures for assessing life stress become especially crucial for testing the role of theoretically driven nonsevere events in a methodologically sound manner. Without clear separation of the measure of environmental adversity from the hypothetical vulnerability factor, little headway can be made in understanding what may account for the potential effects found. In other words, the investigator must be exceedingly mindful of the possibility that the diathesis influences participant ratings of events, thereby confounding the measure of stress with the measure of the diathesis (see Monroe & Simons, 1991). For example, a cognitively vulnerable individual might rate very minor experiences differently than such experiences would be rated in the LEDS system (e.g., experiences that might not qualify as events with LEDS criteria might qualify by participant’s criteria). Under such conditions, the investigator would not be deriving a consensually defined environmental reference for indexing stress but rather an individually contaminated measure (which cannot exclude the possibility of confounding with the diathesis, or possibly with depression; Simons, Angell, Monroe, & Thase, 1993). Thus, it becomes all the more important to separate the objective characteristics of life stress from the subjective perception of stress in such research designs. Relations between life events and vulnerability factors can be systematically investigated best when the measurement of each is independently derived (Brown & Harris, 1978; Monroe & Simons, 1991; Shrout et al., 1989). It stands to reason that individual differences in subjective appraisal will be more pronounced once the circumstances that lend themselves to the appraisal process are better defined, categorized, and rated in a methodologically sound manner. Well-considered measurement and operationalization of life stress should result in enhanced predictive capability of other vulnerability indices (Monroe & Kelley, 1995).

Finally, our approach has been driven by the underlying notion that changes in social and psychological circumstances trigger an episode of depression and that changes in vulnerability with repeated episodes may alter the potency of the trigger needed. This emphasis on acute stressful life events is not meant to preclude the potential importance of chronic stressors or ongoing difficulties. We consider it likely that these forms of adversity, too, may help to explain the puzzle of findings in the literature. Yet the existing evidence for chronic stress in regard to depression onset in general, and especially in regard to recurrences, is sparse and mixed compared with the information on acute life stress (Brown, Harris, & Hepworth, 1994; Daley et al., 2000; Ormel et al., 2001). Conceptually, too, chronic difficulties provide a less parsimonious explanation for onset: One must account for timing in a way that is unnecessary with acute events (i.e., if the problem is chronic, why does breakdown occur at any one particular point in time as opposed to another? Monroe & Simons, 1991).

The foregoing suggests that chronic stressors may well be of importance and be useful to fill in gaps in our current understanding (e.g., apparent absence of stress as measured by acute events might be explained by the presence of chronic difficulties). However, it is also likely to be a more complex process documenting such influences, most likely requiring studies systematically linking ongoing difficulties with life events that match the difficulty or with exacerbations of difficulties (e.g., Brown & Harris, 1989). It is perhaps owing to a lack of such sophistication that the importance of nonsevere forms of stress has not yet been more convincingly documented. We hope that the central themes and extrapolated ideas from our analysis of acute events will inform and provide a platform for theory and research attempting to establish the role of such chronic forms of stress in depression onset and recurrence.

**Stress Generation and Recurrence**

The stress generation hypothesis, introduced by Hammen (1991), proposes that formerly depressed persons “generate stressful conditions and events, which in turn cause additional symptomatology” (p. 555). There is mounting evidence for the premise that formerly depressed people are at higher risk for experiencing new stress over time (Hammen, 1991; Harkness, Monroe, Simons, & Thase, 1999; Rudolph et al., 2000) and that recurrences and severity of stress are correlated (e.g., Kendler et al., 2000).

Given the logic of our current analysis, stress generation would have differential implications for recurrence depending on the particular model adopted. For instance, the stress sensitization model would predict that life events meeting minimal criteria for triggering recurrence are even more common given stress generation. This would result in additional eclipsing of more severe life event frequencies, would amplify the frequency of depressogenic stressors, and would accelerate the rate of recurrences over time. Stress generation, too, could conceivably offset the eclipsing of severe events by more minor events, if stress generation disproportionately generated severe types of events relative to more minor ones (Harkness et al., 1999; Kendler et al., 2001). In contrast, for the stress autonomy model, stress generation would have less powerful implications over time, given the proposed uncorrelated eventual relationship between life stress and recurrence. These are admittedly early speculations about an issue that when considered more deeply and informed by data, could become quite involved. Nevertheless, the general point again underscores the importance of separating the different models and ideas currently conflated within the general kindling hypothesis and investigating more precisely the roles (i.e., impact and frequency) and forms (i.e., severe and less severe) of life stress in relation to recurrence over time.

**Alternative Conceptual Perspectives and Models**

The stress sensitization and stress autonomy models represent convenient ways of organizing current information and of formalizing competing hypotheses that can point future research in more revealing directions. In all likelihood, though, these models eventually will yield to more complex and sophisticated representa-
tions. For instance, a hybrid model combining sensitization and autonomy mechanisms could provide another viable explanation. Within such a model, progressive sensitization processes could coexist with progressive automaticity processes; episodes could become more sensitive to stress and also could become more capable of spontaneous onset. 

Although more elaborate models such as the hybrid noted are plausible and attractive, they may not provide the most parsimonious account of the current data and phenomenon we are attempting to explain. For example, the hybrid model would require development of two separate mechanisms to account for the changing association of stress with recurrence over time. More pointedly, increasingly elaborate models will be informed by and evolve out of research on the competing predictions afforded by the stress sensitization and stress autonomy models. For instance, the hybrid model represents more of an extension of the stress sensitization model, and not the stress autonomy model; it would in general be supported by the kinds of tests we propose for the former, but not for the latter. Thus, we consider the most pressing research mandate is to first distinguish between the utility of the stress sensitization and stress autonomy models within the preliminary framework we have provided. Much will be gained by keeping research focused first on these issues, with empirical findings guiding further model development.

We have purposefully examined the kindling hypothesis from a life stress perspective level of analysis. Although major life stress is one of the strongest indicators of the likelihood of an episode of major depression, not all people incurring major life stress become clinically depressed (Monroe & Hadjiyannakis, 2002). Other factors obviously are required to more fully explain and model depression. Yet clarification of the two stress models we distinguish along the research lines we propose provides direction for broader theories attempting to integrate life stress with psychological or biological mechanisms in explaining depression’s onset. In particular, different cognitive or biological mechanisms are likely to be implicated by the stress sensitization and stress autonomy models. Depending on the outcome of research evaluating these two models, very distinctive conceptualizations of the cognitive or biological constructs and the respective diathesis–stress models will emerge. For example, the cognitive schema consolidation and personality scarring models discussed briefly at the outset of the article fit best within a stress sensitization framework. That is, the strengthening of schema networks and/or the development of a stress reactive, neurotic personality pattern as a result of previous experiences with stress and depression reduce the threshold required to precipitate recurrence of depression following more minor stress (Bolger & Zuckerman, 1995; Segal et al., 1996). In contrast, the development of stress autonomy may require the operation of different starting conditions (e.g., genetic diathesis; Kendler, 1997) or pathological processes (e.g., neuroendocrine dysregulation that eventually eclipses the ability of stress to precipitate depression onsets). Put slightly differently, the individual difference characteristics proposed by prominent theories of depression may become most pronounced and meaningful when framed within an informed and appropriate model of life stress. Most generally, then, the ideas inherent in our analysis have broad implications for helping to direct development of more comprehensive, multifactorial theories of depression’s origins.

Finally, our analysis has treated major depression as a homogeneous disorder in terms of etiology and with respect to the importance of life stress for initiating a first lifetime episode of depression. This has provided a useful position for addressing the ambiguities in the current literature regarding life stress and the kindling hypothesis and is in keeping with the stance adopted by recent research on life stress and recurrence of depression. This position, however, likely oversimplifies the nature of depression by excluding from consideration depressive conditions that can arise initially entirely unrelated to life stress (e.g., endogenous depression; see also Brown et al., 1994; Monroe & Depue, 1991; and Footnote 3). Eventually, more encompassing conceptual perspectives that systematically incorporate the suspected etiologic heterogeneity of major depression most likely will prove of value. Nonetheless, the themes developed in the present analysis and the ideas arising from their synthesis remain essential to consider within such a broadened and more differentiated perspective for understanding the role of life stress in the life course of major depression.

Concluding Remarks

The kindling hypothesis provides a powerful framework within which to investigate the evolution of depressive episodes over time. However, inconsistencies and confusion regarding the fundamental assumptions of the theoretical model and interpretations of the research have limited its explanatory potential. In particular, do recurrent episodes become autonomous of stress, such that stress is no longer an etiological mechanism in the precipitation of recurrence? Or, do individuals become sensitized to stress, such that ever more minor forms of adversity are capable of precipitating recurrence? Most generally, if minor events increase in their frequency and impact in precipitating onsets of depression across recurrence, then this would support sensitization. By contrast, if all forms of stress (major and minor) decrease in their frequency and impact in precipitating recurrences, then this would support autonomy and suggest that some other, potentially neurobiological, process takes over in the etiology of depression recurrence. We believe that longitudinal studies that follow individuals across several recurrences are best suited to testing the validity of these two models, as they will allow the charting of within-person changes in the frequency and impact of stress over time. We have presented very specific and testable hypotheses detailing the course that the longitudinal relations between stress and recurrence will take on the basis of the stress sensitization and stress autonomy models. Determining which interpretation best fits the data will hinge on studies that pay attention to the frequency and impact of stress over time and that utilize life stress methodology permitting measurement of a range of severities of life stress.

One of the most promising features of the kindling hypothesis is that interventions targeting the initial unfolding may be more effective than interventions at later stages (Post & Weiss, 1999). Indeed, the problems with cycle acceleration and possible eventual

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refractoriness to treatment with successive recurrences bring concerns for prevention squarely into the foreground (Post & Weiss, 1999). Tackling the kindling hypothesis and recurrence questions from a life stress perspective can help inform how much of the developmental process may be in reaction to life circumstances and how much may be part of an independent psychobiological process. Such information, in turn, may be quite beneficial for considering various treatment and prevention strategies. With a systematic progression of research along the lines we propose, we hope to facilitate realization of the ultimate goal of preventing the too-often lifelong suffering associated with recurrent major depression.

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