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Life Stress and Kindling in Bipolar Disorder: Review of the Evidence and Integration with Emerging Biopsychosocial Theories

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Abstract

Most life stress literature in bipolar disorder (BD) fails to account for the possibility of a changing relationship between psychosocial context and episode initiation across the course of the disorder. According to Post's (1992) influential kindling hypothesis, major life stress is required to trigger initial onsets and recurrences of affective episodes, but successive episodes become progressively less tied to stressors and may eventually occur autonomously. Subsequent research on kindling has largely focused on unipolar depression (UD), and the model has been tested in imprecise and inconsistent ways. The aim of the present paper is to evaluate evidence for the kindling model as it applies to BD. We first outline the origins of the hypothesis, the evidence for the model in UD, and the issues needing further clarification. Next, we review the extant literature on the changing relationship between life stress and bipolar illness over time, and find that evidence from the methodologically strongest studies is inconsistent with the kindling hypothesis. We then integrate this existing body of research with two emerging biopsychosocial models of BD: the Behavioral Approach System dysregulation model, and the circadian and social rhythm theory. Finally, we present therapeutic implications and suggestions for future research.

Keywords

Kindling; bipolar disorder; life events; stress sensitization; stress autonomy

1 Introduction

Bipolar disorder (BD) affects an estimated 2–4% of the U.S. population and is the sixth leading cause of disability among physical and psychological disorders worldwide (Miklowitz & Johnson, 2009; Murray & Lopez, 1996). It is associated with heightened risk of financial problems, relationship dysfunction, substance abuse, homelessness, incarceration, and suicide (Copeland et al., 2009; Miklowitz & Johnson, 2009). Prevalence and public health costs of BD necessitate a better understanding of factors affecting its onset and course. Research examining the impact of life events on symptom expression, timing, and severity of affective episodes in BD has been especially promising. Studies suggest that

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negative life events increase likelihood of bipolar depression, and that certain types of negative and positive events increase likelihood of (hypo)manic episodes (Alloy et al., 2005; Johnson, 2005a). However, most of this literature fails to account for the possibility of a changing relationship between psychosocial context and episode initiation across the course of the disorder. Is the longitudinal association between life stress and mood disorders static or variable? This question is especially important given data suggesting that risk of episode recurrence increases as a function of the number of past episodes (Kendler, Thornton, & Gardner, 2000; Kessing, Andersen, Mortensen, & Bolwig, 1998; Post, Leverich, Xing, & Weiss, 2001).

A developmental psychopathology perspective highlights the importance of a changing relationship between genes, neurobiology, stress, and psychological factors in determining illness course (Miklowitz & Johnson, 2009). Consistent with this, Post (1992) formulated the kindling hypothesis of mood disorders. The basic tenet of the hypothesis is that major psychosocial stressors play a greater role in the initial episodes of a mood disorder, as compared to in subsequent episodes. The kindling model offers a developmental psychopathology perspective on the dynamic relationship between stress and affective episodes.

Although Post (1992) initially suggested that his theory was applicable to both unipolar depression (UD) and BD, subsequent research has largely focused on UD samples. The aim of the present review is to evaluate the evidence for, and heuristic value of, the kindling model as it applies to BD. We first outline the origins of Post's (1992) influential hypothesis, the evidence for the model in UD, and the conclusions drawn in a recent review by Monroe and Harkness (2005). Next, we review the literature on the changing relationship between life stress and bipolar illness over time. We then integrate existing theory and research on the kindling model with two emerging biopsychosocial models of BD: the Behavioral Approach System dysregulation model, and the circadian and social rhythm theory. Based on this review, we present therapeutic implications and suggestions for future research.

2. Theoretical Underpinnings of the Kindling Hypothesis

The kindling model (Post, 1992) is a nonhomologous basic science model of the relationship between psychosocial stress and the course of affective disorders. It is based on an integration of clinical observations, preclinical studies, and empirical research. This analog model draws on preclinical research documenting the development of autonomy in amygdala-kindled seizure stimulation ("kindling"), and of behavioral sensitization ("sensitization") to psychomotor stimulant administration in mice.¹ Kindling refers to a progressive decline in the strength of electrical current required to elicit seizure activity in mice. Although a stronger current is needed initially, the electrical threshold diminishes with each successive seizure. In this way, currents that were previously subconvulsant become capable of triggering full-blown seizures. The process continues until electrophysiological input is no longer required, at which point "spontaneous epilepsy" has developed. The kindling process occurs via functional and structural changes in neural activity (e.g., enhanced neuromodulator synthesis) that lead to sensitization of brain tissue. Post (1992) likened the evolution of stimulated to spontaneous seizures to the shift from stress-triggered to autonomous affective episodes in mood disorders.

¹Of note, the term "kindling" as it relates to BD has also been used to describe episode patterning without reference to psychosocial stress (e.g., Goldberg & Harrow, 1994; Kessing, Mortensen, & Bolwig, 1998; Winokur, Coryell, Keller, Endicott, & Akiskal, 1993; see also Ghaemi, Boiman, & Goodwin, 1999). In the present review, we focus on the kindling model as it applies specifically to the relationship between life events and affective episodes over time, rather than on general descriptors of episode course.

Behavioral sensitization refers to progressive increases in the behavioral intensity of psychomotor stimulant response in rodents. As a result of stimulant (e.g., cocaine) administration, the organism undergoes both acute, short-term neuronal adaptations, as well as adaptations with more lasting effects. Animals also demonstrate behavioral and hormonal sensitization in response to chronic and intermittent environmental stressors (e.g., foot shock; Monroe & Harkness, 2005). This progressive sensitization has been referred to as “reverse tolerance” (Johnson & Roberts, 1995).

Both electrical/chemical stimulation and psychosocial stressors can impact gene expression, imparting long-lasting effects on the organism’s reactivity profile (Post, 1992). Thus, in relation to affective episodes, life stressors may play dual roles: 1) an acute pathophysiological role, and 2) a stimulus that leaves long-term vulnerabilities, thereby lowering the threshold of stress required for episode recurrences. Moreover, mood episodes themselves may exert lasting effects. Through a combination of episode-related decreases in neuroprotective factors and increases in neurotoxic influences, individuals may be vulnerable to additional cellular damage with each successive episode (Post, 2007). Thus, as a function of psychosocial stressors and episodes themselves, lasting changes occur in neuronal functioning that mediate future stress responses (Hlastala et al., 2000).

Therefore, according to the kindling hypothesis, major life stress is required to trigger initial onsets and recurrences of affective episodes, but successive episodes become progressively less tied to stressors and may eventually occur autonomously. The intended utility of the kindling model is to help conceptualize general mechanisms involved in illness progression (Post, 2007). Researchers have noted that the kindling model may be relevant to affective disorders on multiple levels, such as neurobiological (e.g., long-term potentiation), cognitive (e.g., strengthening of associative schema networks; see Segal, Williams, Teasdale, & Gemar, 1996), and personality (e.g., personality “scarring;” see Kendler, Neale, Kessler, & Heath, 1993). Changes occurring within each level are likely interactive, so that insight into kindling processes occurring on one level may yield information about mechanisms of kindling development on another level.

3. Unipolar Depression Kindling Research and Conceptual Issues

Considerable research has since evaluated the utility of kindling and sensitization models of affective disorders. The relative dearth of research on kindling in BD, as compared to in UD, may be partially attributable to the long-held assertion that BD is largely driven by biological processes. It also likely reflects the added challenge of investigating the changing relationship between life events and multiple complex clinical states (depression, hypomania/mania, and mixed states).

All eight UD studies reviewed by Post (1992) were cross-sectional and consistent with the premise that life stress is more strongly associated with first onsets than subsequent recurrences of depression. Of the twelve UD studies that specifically have addressed the kindling hypothesis since Post’s (1992) original paper, eight provide support for the model (for reviews, see Mazure, 1998; Monroe & Harkness, 2005; Stroud, Davila, & Moyer, 2008). The kindling effect has been demonstrated in adolescents (Lewinsohn, Allen, Seeley, & Gotlib, 1999; Monroe, Rohde, Seeley, & Lewinsohn, 1999), adults (Maciejewski, Prigerson & Mazure, 2001; Kendler et al., 2000; 2001; Farmer et al., 2000; Corruble, Falissard, & Gorwood, 2006), and older adults (Ormel, Oldehinkel & Brilman, 2001). A recent meta-analysis indicated that across studies, 11% more individuals experienced a severe stressful life event prior to first episode onset than prior to a recurrence (Stroud et al., 2008).

On the other hand, four studies did not support the kindling model in UD (Bidzinska, 1984; Brown, Harris & Hepworth, 1994; Daley, Hammen & Rao, 2000; Slavich et al., 2009). Thus, of seventeen published English-language studies that have examined the kindling hypothesis in UD, thirteen provided support for the general premise that stressful life events are more closely associated with first onsets and/or early recurrences than with later recurrences.

Based on their review of the extant literature, Monroe and Harkness (2005) concluded that the kindling model has been consistently supported and currently represents “the major integrative conceptual system” related to life stress and the recurrence of UD over time. However, they also noted that the model has been conceptualized and tested in inconsistent ways, which compromises interpretability of relevant findings. The core issues raised are also pertinent to BD, and will therefore be discussed here. Specifically, there is a need for clarification regarding: (1) the meaning of episode autonomy; (2) the importance of varying degrees of stress severity, and (3) the role of stress frequency and impact.

The first core issue is the most central. The general premise of the kindling hypothesis is that over the longitudinal course of recurrent depression, there is a weakening relationship between major life stress and episode initiation. However, multiple processes could be capable of producing this effect. Does the relationship between major life stress and episodes diminish because recurrences are triggered by increasingly lower levels of stress? Or, does it diminish because later episodes are increasingly driven by an endogenous process? Monroe and Harkness (2005) identified these two distinct models as stress sensitization and stress autonomy, respectively. In the original formulation of the kindling model, Post (1992) acknowledged both potential mechanisms; however, most subsequent studies failed to systematically differentiate the two models (Monroe & Harkness, 2005). In the present paper, the term “kindling model” will be used to refer to the general premise that major life stress plays a stronger role in early rather than later stages of affective disorder. Sensitization and autonomy will be used to refer to the two potential processes underlying a kindling effect.

Both sensitization and autonomy formulations posit that major life stress plays an important etiological role in the initial depressive episode, and that successive recurrences are increasingly likely to occur in the absence of severe stressors. The two models are distinguished by their view of the mechanisms underlying the apparent dissociation between stress and episodes. In the stress sensitization model, the declining association between major life stress and episodes occurs because of a progressive sensitization to less severe forms of stress. As a result, psychosocial stressors that were insufficiently severe to initiate a first onset acquire the capability to initiate recurrences. Over time, the stressors most likely to potentiate episodes begin to fall below the threshold of severity captured by the majority of life stress measures. Once stress has fallen below the “conceptual and operational radar” (Monroe & Harkness, 2005), episodes may appear to occur in its absence. Although major stress retains the ability to precipitate episodes, its presence is no longer requisite, and minor stress becomes the more probable trigger.

In contrast, in the stress autonomy model, recurrences become successively less dependent on socioenvironmental input in general. Major life stressors decrease in association with successive recurrences not because they are eclipsed by less severe stress, but because of a “progressive decoupling” between stress and depression. Following the initial episode, an alternative nonstress mechanism develops that takes over as the determinant of recurrent episode timing. Presumably, the nonstress mechanism is an endogenous neurobiological process. The autonomy model thus represents progressive stress insensitivity, as opposed to the progressive stress sensitivity postulated in the sensitization model. Monroe and Harkness

(2005) noted that stress autonomy is less consistent with results of preclinical studies, less parsimonious, and requires more complicated theoretical explanation.

Related to the major analytical theme of sensitization versus autonomy, inadequate attention has been paid to issues of stress severity, frequency, and impact (Monroe & Harkness, 2005; Hlastala et al., 2000). As a result, it is difficult to identify precisely what accounts for the declining association between life stress and recurrences. The vast majority of life stress studies have exclusively examined severe or major life stressors. In life stress measurement, as event severity decreases, there is an increase in definitional subjectivity and the range of associated psychological implications. As a result, intra-category variability increases, and more cumbersome assessment methods are required (Dohrenwend, 2006). Thus, little is known about the longitudinal trajectory of the relationship between *minor* stress and episodes.

Also, for both sensitization and autonomy models, there is a need to determine whether major life stress has less ability (impact) or less opportunity (frequency) to initiate depressive episodes (Monroe & Harkness, 2005). Stress impact can be examined by calculating the probability of a subsequent depressive episode, given the occurrence of a stressful event. In contrast, stress frequency can be examined by calculating the probability of an antecedent stressful event, given the occurrence of an episode. From a developmental psychopathology perspective, it is important to know whether both probabilities change over time as a function of episode history.

Another challenging issue is that of event independence. The stress generation model posits that vulnerable individuals actively contribute to stress in their lives, and may thereby precipitate depressive or (hypo)manic relapse (see Hammen, 1991). From an analytical standpoint, it may be important to exclude actively generated stress when examining changes in stress reactivity over time. However, to a greater or lesser degree, individuals contribute to the majority of events in their lives. Given the psychological significance of many of these partially behavior-dependent events (e.g., breakup of a romantic relationship due to excessive reassurance seeking; see Joiner & Metalsky, 2001), eliminating them from analysis renders the life stress picture incomplete.

The sensitization and autonomy models lead to specific testable predictions with respect to the dimensions of stress severity, impact, frequency, and stress generation (Monroe & Harkness, 2005). The stress sensitization model specifies that with each successive episode, major life stress will increase in impact and decrease in frequency, whereas minor life stress will increase in both impact and frequency. These relationships are observed as a function of the decreasing threshold of severity required to trigger episodes, and a differential frequency distribution between major and minor life stress. The sensitization model also predicts that stress generation produces more life stressors that meet minimal criteria for episode initiation, and thus shortens time to recurrence. In contrast, the stress autonomy model specifies that with each successive episode, both major and minor life stress will decrease in impact and frequency. The effects of stress generation lose impact on the course of depression in the stress autonomy model.

Sensitization vs. autonomy, event severity, impact vs. frequency, and stress generation were each addressed in a seminal review of kindling in UD (Monroe & Harkness, 2005). An additional challenge in BD kindling research is whether the relationship between events and episodes is polarity-specific. Studies on acute episodes of BD have found some specificity in the prediction from life events to depressive vs. (hypo)manic episodes (Alloy et al., 2005; Johnson, 2005a; Johnson et al., 2008). A thorough evaluation of kindling in BD requires

attention to whether sensitization or autonomy processes operate differently across episode polarities.

4. General Methodological Issues in Life Stress Measurement

In and of itself, the conceptualization and measurement of life stress is fraught with challenges. Within a developmental psychopathology framework, researchers are faced with the added challenge of quantifying changes in these dynamic stress processes over time. Several excellent reviews have addressed the general difficulties inherent in life stress measurement (Dohrenwend, 2006; Johnson, 2005a; Monroe, 2008). Thus, the present review focuses on the additional challenge introduced by accounting for changes in stress over time. In this section, we address issues related to methodological design and measurement in kindling studies of BD.

4.1. Research Design

Studies on kindling in BD have used a variety of approaches to life stress measurement, including chart reviews, questionnaires or checklists, unstructured interviews, and semistructured interviews. Hospital chart reviews are problematic for testing kindling processes in BD for several reasons. They are vulnerable to unsystematic data collection and subjectivity in reporting. For example, evaluations may be more thorough and detailed at the time of first admission as compared to at readmissions. This distinction could artificially inflate rates of life stress prior to initial onset relative to recurrences. Hospital chart reviews also capture only the most severe episodes, and use dates of hospital admission rather than dates of episode onset. Using the first hospitalization as the initial measurement point is especially problematic for kindling studies, because patients may have experienced prior episodes that did not result in hospitalization. In such cases, analyses would fail to capture life events prior to the true initial onset of the disorder. Each of these limitations could confound results of studies on kindling in BD.

Cross-sectional studies are also limited for examining a general kindling model. The between-subjects design is problematic for examining processes that unfold within individuals over time. Also, retrospective studies require participants to report on temporal relationships between stress and episodes occurring many years ago (e.g., 10 or more years; Dunner, Patrick, & Fieve, 1979; Glassner, Haldipur, & Dessauersmith, 1979). The process of retrospectively constructing such a timeline is vulnerable to autobiographical memory distortion. Research on primacy and recency effects suggest that events occurring prior to the initial and most recent episodes are more likely to be recalled than those occurring in the interim (Johnson & Roberts, 1995), which could skew findings relevant to kindling. Also, episodes occurring at different phases of illness are differentially susceptible to “effort after meaning” biases (Johnson & Roberts, 1995).

Retrospective studies also largely preclude distinctions between sensitization and autonomy models. Over long periods of time, forgetting and recall bias differentially affect memory for major and minor stressors. Raphael and colleagues (1991) found that monthly prospective assessments over 10 months yielded a mean of 16.7 mostly minor checklist events. In contrast, participants retrospectively reported an average of 6.0 events over the same 10-month period. Given the early stages of the BD kindling literature and the limited number of existing prospective longitudinal studies, we describe these foundational chart review, cross-sectional, and retrospective studies below. However, results of these studies must be interpreted with caution.

A final methodological challenge is more specific to BD. As compared to other psychological disorders, the initial onset of BD can be more difficult to pinpoint

chronologically (Ghaemi, Boiman, & Goodwin, 1999). Those with BD often experience depressive episode(s) prior to their first (hypo)manic episode, and in these cases, a BD diagnosis would not be immediately evident. When the initial episode(s) are depressive, there are no universal guidelines for identifying the episode representing the “first onset” of BD. This issue is especially critical for examining differences in the relationship between events and episodes at the initial development vs. the progression of BD. Sample size limitations in BD kindling studies have also precluded comparisons between individuals with a first episode of depression or (hypo)mania.

4.2. Measurement Issues

The problems with questionnaire measures of life stress have been well documented (Alloy et al., 2005; Dohrenwend, 2006; Johnson, 2005a; Monroe, 2008). In one study, less than 50% of events endorsed on a self-report checklist corresponded with events as defined by a standardized interview measure (Monroe, 2008). This finding demonstrates a lack of common understanding between the researcher and participant as to the intended meaning of events. Given the heightened importance of the specific timing, nature, and severity of events in the context of kindling, studies that rely on questionnaire or checklist measures must be also be interpreted cautiously.

The two most commonly used checklist measures in BD kindling studies are derivatives of the Social Readjustment Rating Scale (SRRS; Holmes & Rahe, 1967) and the Recent Life Events checklist (RLE; Paykel, McGuiness, & Gomez, 1976). With respect to stress severity, items contained on either measure can generally be considered moderate to severe, rather than minor. Both scales were intended to assess readjustment or “life-change” events, rather than negative stressful events per se. In general, earlier studies on life events tended to examine a broader range of events requiring readjustment. Many of these earlier studies found that mood episodes were more strongly associated with negative life events than with positive events, especially in UD (Mazure, 1998). Thus, concomitant with an increased emphasis on life events in UD relative to BD, there was a general shift in focus towards measuring negative experiences.

At present, the gold standard of life stress measurement is the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978) procedure. LEDS-based interviews are the most elaborate and sophisticated in capturing a broad range of event types and severities. The LEDS manual specifies detailed, predetermined event definitions. The narrative-rating procedure is administered in interview format, during which detailed contextual information is recorded for each event endorsed. An independent team of raters, who are blind to the participant’s diagnostic status and subjective response, can then assess event severity by considering both the objective nature of the event and the idiographic context. The LEDS has considerably higher test-retest reliability and intra-pair agreement than checklist measures (Dohrenwend, 2006). Interview-based methods are especially superior in the context of measuring more minor forms of stress, which is a critical component in tests of the kindling hypothesis. Thus, studies using LEDS-based interviews should be given more weight when evaluating evidence relevant to kindling in BD.

4.3. Quantification of Life Stress

Life stress researchers have not identified a universally accepted, standardized index of stress quantification. This methodological inconsistency can produce contradictory findings, and has decreased comparability across studies. The various indices used in BD kindling studies have included: the proportion of patients experiencing at least one event; the proportion of patients experiencing at least one severe event; the sum of total life events; the sum of subjectively weighted life events; and the sum of objectively weighted life events.

Events included in these calculations may be any reported event, or may be restricted to negative events, illness-independent events, or some combination. Given that research has yet to converge upon a preferred stress index, it is important to note the assumptions behind stress quantification methods, and to consider the implications for the kindling model.

In BD kindling studies, the most common quantification method has been to compare the proportion of patients experiencing at least one life event prior to episode onset. Studies that examine only the probability of experiencing at least one *major* event may shed light on whether a general kindling effect occurs, but do not allow for a distinction between sensitization and autonomy models. A dichotomous analysis of experiencing an event of any severity is even less informative in this respect.

In other studies, total stress scores are calculated, either by summing the raw number of events or by summing standardized weighted event values. This method may be better suited for detecting between-subjects variability in stress levels. A comparison of continuous mean stress scores represents one approach to examining the minimal threshold of stress required to trigger episodes. However, such an approach rests on the assumption that stress exerts a continuous additive burden, or “dose-response” effect. Validity of this assumption is critical to examining kindling in BD, given the focus on changes in thresholds that determine episode recurrence. The summed stress score approach also does not examine events separately by severity rating. Without an understanding of what specifically occurs at the minor stress level, it is impossible to definitively distinguish between the stress sensitization and autonomy models.

5. Existing Research on Kindling in Bipolar Disorder

With these considerations in mind, we now review research on the kindling effect in bipolar disorder. Where possible, we indicate whether the studies (1) support a sensitization vs. autonomy perspective; (2) address event severity; (3) examine impact, frequency, or both; and (4) address event independence. In light of the growing body of literature suggesting that specific types of positive events (i.e., goal striving or attainment events) may also uniquely impact the course of bipolar disorder, we indicate whether positive events were assessed in addition to negative ones. Because the kindling hypothesis has been tested in a number of different ways, the following section is organized according to the specific research questions addressed. Additional details about each study are presented in Table 1.

5.1. Cross-Sectional Studies of Rates of Life Events Before First vs. Subsequent Episodes

Four cross-sectional studies have compared rates of life events in patients experiencing a first episode versus a recurrence (see Table 1). Of these, two were chart reviews (Ambelas, 1979, 1987). Ambelas (1979) found that manic patients in their initial hospitalization were significantly more likely to have experienced a pre-admission event in the month prior to admission, as compared to manic patients in a repeat hospitalization. A follow-up chart review indicated that mean scaled stress scores were significantly higher before first than subsequent admissions (Ambelas, 1987). Perris (1984b) assessed the frequency of life events in the three- and twelve-month intervals prior to onset of a depressive index episode in an inpatient sample with various affective disorder diagnoses. Patients experiencing their first episode of depression experienced more negative and conflict events in the three months prior to onset, as compared to patients experiencing a recurrence. No differences emerged in analyses examining events in the twelve months prior to episode onsets. Given the mixed diagnostic groups and the small number of patients with BD ($n = 16$), applicability to BD-specific processes cannot be assumed.

Using a more methodologically rigorous combination of the Recent Life Events Interview (Paykel et al., 1980) and contextual threat methods (Brown & Harris, 1978), Kennedy (1983) compared the frequency of life events four months before and after hospitalization for a manic episode. Event severity was partially addressed by summing the number of overall events, as well as conducting separate analyses among independent, moderate-to-severe events. Compared to orthopedic controls and to themselves during a post-discharge period, pre-admission BD patients had the highest likelihood of a life event, the highest number of life events, the highest proportion of negative events, and the highest rate of independent moderate-to-severe events. However, event patterns did not differ according to whether the index admission was a first onset or a recurrence.

Thus, of these four cross-sectional studies, three provided some support for a higher likelihood of major stressors prior to initial than subsequent episodes. Results from the methodologically strongest study, however, were inconsistent with a kindling effect (Kennedy, 1983). Moreover, none of the three supportive studies conducted analyses that allowed for a distinction between sensitization and autonomy models, or between frequency and impact of events. There was no strong evidence that relative rates of negative and positive events differed according to phase of illness, and the effect of episode polarity was not examined in relation to history of previous episodes.

In addition to limitations inherent to a cross-sectional design for examining this research question, three studies (Ambelas, 1979, 1987; Kennedy, 1983) used the date of hospitalization in place of episode onset. However, each study took care to restrict analyses to illness-independent events (Ambelas, 1979, 1987; Kennedy, 1983; Perris, 1984b).

5.2. Retrospective Studies Comparing Rates of Events Before Initial and Most Recent Episodes

Three retrospective studies (see Table 1 for details) examined life events before patients' recent index episode, as compared to their initial episode. Glassner and colleagues (1979) used an unstructured interview to examine the frequency of role loss events in the year prior to hospitalization, among 25 individuals with BD I. Results indicated that a higher proportion of initial episodes were preceded by at least one stressful event, as compared to recent index episodes. Using the same methods, these researchers (Glassner & Haldipur, 1983) found that neither early- nor late-onset BD patients experienced a significant decline in life event frequency prior to their initial vs. most recent episodes. The pattern of results did not support a kindling model, but suggested that late-onset patients experience a higher frequency of life events prior to episodes across the course of their disorder, as compared to those with an earlier onset. Glassner and Haldipur (1983) hypothesized that patients with earlier onsets could be more genetically predisposed to BD, which could account for differences in stress reactivity.

Bidzinska (1984) administered an unpublished life events questionnaire to 50 bipolar I and II patients, 47 unipolar patients, and 100 matched community controls. The questionnaire assessed illness-independent events of unspecified severity for the three-month periods prior to initial and most recent episodes. Chronologically matched periods were examined among the control group. Ninety vs. 82% of BD patients experienced at least one stressor before their initial vs. their most recent episode. In both matched 3-month observation periods, 65% of controls experienced at least one life event; this finding suggests that there is no normative decrement in life event frequency over time.

Thus, among three retrospective studies conducting within-subjects comparisons of first and most recent episodes, one supported the kindling model (Glassner et al., 1979), another failed to support it (Bidzinska, 1984), and a third failed to support it, but identified group

differences in stress reactivity according to age of BD onset (Glassner & Haldipur, 1983). All studies examined event frequency rather than impact, and none allowed for comparison of sensitization vs. autonomy models due to the absence of a systematic assessment of minor forms of stress. However, long-term retrospective studies are not well suited to distinguishing between sensitization and autonomy anyway, due to the questionable utility of assessing minor events occurring many years ago. The only study to explicitly examine positive events (Bidzinska, 1984) failed to compare rates of such events before first and most recent episodes. Finally, only one study (Bidzinska, 1984) explicitly restricted analyses to illness-independent events, and none accounted for episode polarity.

5.3. Retrospective Studies Comparing Life Events Prior To First/Earlier vs. Later Episodes

Four retrospective studies (see Table 1) have compared the frequency of life events occurring prior to participants' earlier vs. later episodes in the course of bipolar illness. Two relied heavily on chart review techniques. In a sample of 190 patients with bipolar I and II diagnoses, as well as 92 patients with UD, Johnson and colleagues (2000a) found that the proportion of BD patients who experienced at least one event within 12 months of onset diminished with each successive recurrence.

Ehnavall and Agren (2002) integrated data from unstructured interviews and chart reviews of 10 bipolar and 20 unipolar patients. Patients were identified as belonging to a sensitization course group (decreasing well intervals over time) and a nonsensitization course group (stable or increasing well intervals over time²). The sensitization group had more life events prior to the first and second episodes, but demonstrated a successive decrease in life events throughout the first nine episodes. In contrast, the nonsensitization group initially had fewer life events preceding episodes, but the frequency of stressors remained more stable across the course of the disorder. The authors posited that the participants with stable or increasing well intervals had an illness course that was more autonomous from onset. Kindling analyses did not differentiate between UD patients and the smaller BD sample, so the extent to which results apply to BD is unclear.

Using an unstructured interview approach, Dunner and colleagues (1979) examined the frequency of life events before first and subsequent episodes in a sample of 79 bipolar I patients. Half of the first-episode patients reported a life event in the three months prior to onset, as compared to 15% of the recurrent patients; this finding was interpreted as generally supportive of a kindling effect.

In a subset of bipolar patients with a history of at least six episodes, Bidzinska (1984; see above) compared the proportion of episodes preceded by illness-independent life events during earlier and later episodes. Results indicated that the three earliest episodes were significantly more likely to have been preceded by a life event, as compared to the fourth through sixth episodes. Interestingly, these differences were not observed among UD patients. Thus, in this study, although the frequency of experiencing at least one life event did not significantly differ between first and most recent episodes, earlier episodes were more likely to be preceded by stress than later episodes among patients with six or more episodes.

Taken together, these four retrospective studies provide support for a general kindling effect, although two studies found the effect in a specific subgroup of patients (those with six or more episodes, Bidzinska, 1984; and those with decreasing well intervals, Ehnavall & Ågren, 2002). Each study failed to systematically assess more minor stressors, thus precluding a

²This use of the term sensitization refers exclusively to the temporal patterning of episodes, irrespective of their relationship to life events.

comparison of sensitization and autonomy models. Stress indices varied, and all four studies examined event frequency, but not impact. One study found that a higher percentage of initial manic episodes were preceded by life events, compared to initial depressive episodes (Dunner et al., 1979). None of the other studies accounted for potential differences in relationships between events and episodes of different polarity, although two studies compared BD and UD patients (Bidzinska, 1984; Johnson et al., 2000a). Whereas Bidzinska (1984) found a general kindling effect among BD but not among UD patients, Johnson and colleagues (2000a) found similar kindling results among the two groups. None of these studies tested for kindling effects in the positive event domain, and only one attempted to exclude illness-dependent events (Bidzinska, 1984).

5.4. Studies Examining Whether Previous Episodes Moderate the Relationship Between Recent Stress and Index Episode

One retrospective study tested the kindling model by examining relationships between episode history, recent stressors, and recent index episodes in 64 patients with BD (Hlastala et al., 2000). This design was less vulnerable to recall bias, because recall intervals were shorter (three months, in contrast with more than ten years in some retrospective studies). Using LEDS interview techniques, the authors assessed events during the three months prior to onset of the index episode, as well as a three-month episode-free control period. In this study, events were required to be definitely or possibly independent of the participant's influence, which is a more stringent criterion than independence from acute illness. For both pre-episode and control observation periods, participants were categorized as high stress (presence of at least one severe life event), moderate stress (presence of at least one nonsevere life event, and no severe life events), and low stress (no life events during the interval). Inconsistent with the kindling hypothesis, the number of lifetime episodes failed to predict stress levels in either three-month observation period. Moreover, the relationship between lifetime episodes and stress did not significantly differ across the pre-onset and episode-free periods. These researchers did find that in the pre-onset periods, the proportions of high and low stress participants were correlated with age (probability of high stress was negatively correlated with age; probability of low stress was positively correlated with age). Thus, findings did not support the kindling hypothesis, but suggested that something specific to the aging process may underlie developmental changes in the stress-episode relationship. If this were the case, age effects may have confounded results in previous kindling studies (Hlastala et al., 2000).

This study improved upon previous work by categorizing stress levels according to the severity of individual stressors, and by utilizing a shorter recall period. Also, in addition to the early study by Kennedy and colleagues (1983), this was the only study to have included a within-subjects episode-free control period. In studies lacking a within-subjects control period, analyses focus exclusively on periods after which the probability of an episode is 100% (Hlastala et al., 2000). Because of this, results do not establish that stress levels are *uniquely* elevated before episodes. Depending on whether stress is uniquely elevated prior to episodes, examining the relationship between lifetime episodes, current stressors, and new onsets would have different implications. Like the studies reviewed above, this study by Hlastala and colleagues (2000) examined stress frequency but not impact.

Hlastala et al.'s results did not support a general kindling effect, because episode history failed to predict stress severity level prior to index episodes. And, no relevant differences were found in the pre-episode vs. control periods. As stress categories were determined by the presence or absence of at least one moderate or severe stressor, dose-response relationships were not investigated. Also, it is possible that the stringent criteria for event independence had a significant impact on study findings. Analyses did not distinguish between manic and depressive episodes, or investigate the role of positive events.

5.5. Prospective Longitudinal Investigations of Kindling in BD

Hammen and her colleagues (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Hammen & Gitlin, 1997; Swendsen, Hammen, Heller, & Gitlin, 1995) have conducted the only three prospective studies that explicitly address kindling in BD (see Table 1). All three studies used LEDS-based (Brown & Harris, 1978) life stress interviews, administered at three- (Hammen & Gitlin, 1997; Swendsen et al., 1995) or six-month (Dienes et al., 2006) intervals. Only negative life events were assessed. Two of the studies were based on data from the same sample (Hammen & Gitlin, 1997; Swendsen et al., 1995). In the first, correlates of stress reactivity were prospectively examined in individuals with BD I ($N = 45$) and BD II ($N = 13$) over a period of one year (Swendsen et al., 1995). Summed objective impact ratings were calculated for the three months before relapse, or a control period in non-relapsing participants. Stress levels during the follow-up predicted relapse status, even among participants in the upper half of the distribution of prior episodes (greater than 12).

In the second study based on this sample, Hammen and Gitlin (1997) prospectively followed 52 outpatients over a period of two years. In analyses relevant to the kindling model, only major-impact events were included. Among patients in the upper half of the distribution of number of lifetime episodes (9 or more), 76% had a major event in the six months preceding onset, compared to 40% of patients in the lower half of the distribution. A backward survival analysis indicated that patients with 9 or more episodes also relapsed more quickly after a major event. Results suggested that major stress has both higher frequency and impact (as measured by time between event occurrence and relapse) in the later phases of BD.

Dienes and colleagues (2006) conducted a 12-month prospective longitudinal study on stress sensitization in 58 individuals with BD I. A total objective stress variable was dichotomized for the three months prior to relapse, or a random 3-month period in patients who did not relapse. Although stress and dichotomized episode history each predicted relapse status, the interaction between the two variables was nonsignificant.

Thus, of the three prospective LEDS-based studies on kindling in BD, none were interpreted as consistent with a kindling effect. Two studies found that the number of prior episodes did not moderate the relationship between stress levels and relapse status (Dienes et al., 2006; Swendsen et al., 1995). Another found that patients with more prior episodes of BD had a *higher* frequency of major stress prior to new episodes, and relapsed more quickly after a major stressor (Hammen & Gitlin, 1997). In itself, the finding that patients relapsed more quickly after a major stressor later in the course of BD is actually consistent with a sensitization model. That is, it indicates an increased impact of major stressors as a function of previous episodes. However, support for a sensitization model would require both an increased impact of major stressors, and a decreased frequency of major stressors in patients with more prior episodes.

These three studies were the only to include a between-subjects episode-free control period in BD patients who did not relapse during the follow-up. They were also the only BD kindling studies to examine a measure of stress impact. Two of the studies did so by predicting relapse/recurrence status from a stress index (Dienes et al., 2006; Swendsen et al., 1995), rather than predicting stress levels prior to an identified index episode. The third examined impact by performing a backward survival analysis to examine the number of days elapsed between episode onset and the most recent major stressor.

Although these three studies are the methodologically strongest to date and represent important contributions to the field, some limitations should be noted. None systematically examined occurrence of minor stressors: one limited analyses to major stressors (Hammen & Gitlin, 1997), one used a continuous measure of weighted impact scores (Swendsen et al.,

1995), and another dichotomized weighted impact scores (Dienes et al., 2006). In all three studies, episode history was dichotomized according to the mean number of episodes (approximately 18 in Dienes et al., 2006; 8 in Hammen & Gitlin, 1997; and 12 in Swendsen et al., 1995). It is possible that kindling effects are most evident earlier in the course of the disorder. For example, among UD participants, Kendler et al. (2000) found support for the kindling hypothesis through only the first nine episodes, and concluded that there may be a “threshold at which the mind/brain is no longer additionally sensitized to the depressive state (p. 1243).” All three studies failed to differentiate between episodes of different polarity, or to include a measure of positive as well as negative events. Finally, only one study explicitly reported exclusion of illness-dependent events (Hammen & Gitlin, 1997).

5.6. Related Studies

Two other life stress studies examined questions with possible implications for the kindling model in BD. Swann (1990) investigated the relationship between the subjectively perceived role of stressful events and disease characteristics in 85 unipolar depressed patients, 47 bipolar depressed patients, and 19 manic patients. The design was distinct from other kindling studies in that it did not measure the occurrence of predefined stressors within a given time frame before episodes. Instead, stress was measured according to two items in the Schedule for Affective Disorders and Schizophrenia Interview (SADS; Endicott & Spitzer, 1978) that assess the interviewer’s and the respondent’s impression of the degree to which life events played a role in initiating the index episode. The perceived stress ratings were used to classify episodes as “autonomous” or “environment-sensitive.” Across diagnoses, patients with environment-sensitive episodes had fewer previous episodes and a longer duration of index episode. Findings were qualitatively similar, but statistically nonsignificant, among BD patients. Specific monoamine abnormalities were found in BD depressed patients with autonomous episodes, as well as in manic patients with environment-sensitive episodes. Moreover, among manic patients, monoamine measures were correlated with the number of previous episodes and index episode duration. The authors hypothesized that the relationship between perceived stress level and previous episodes reflects a course in which early episodes are longer and more likely to be triggered by stress. Alternatively, low- and high-stress patients could represent distinct subgroups. It is important to note that this study was cross-sectional.

Beyer et al. (2008) examined whether life event rates in BD differ as a function of current age or age of onset. Given that they did not evaluate temporal precedence or independence of life events over the retrospective observation interval, the study was not technically a test of the kindling model. Nevertheless, the authors interpreted their findings as inconsistent with the kindling hypothesis. Among acutely manic participants older than age 50 ($N = 11$), checklist-assessed stress levels did not differ according to episode history. However, the analysis most relevant to the kindling hypothesis was based on a small number of participants.

5.7. Methodological Considerations Involving Study Samples

Several sample-related issues should be noted related to generalizability. First, BD is a heterogeneous condition, and inclusion criteria have varied across studies. Some researchers included only participants with a diagnosis of BD I (Ambelas, 1979, 1987; Beyer et al., 2008; Dienes et al., 2006; Dunner et al., 1979; Glassner & Haldipur, 1983; Glassner et al., 1979; Hammen & Gitlin, 1997; Hlastala et al., 2000; Kennedy, 1983), whereas others included BD II participants (Bidzinska, 1984; Ehnvall & Ågren, 2002; Johnson et al., 2000a; Swendsen et al., 1995). In some cases, researchers excluded rapid cyclers (Ambelas, 1979; Hlastala et al., 2000) or those with “too many episodes to count” (Dienes et al., 2006). Other studies excluded individuals with Axis I comorbidity (Hlastala et al., 2000) and/or recent

history of substance use problems (Beyer et al., 2008; Ehnvall & Ågren, 2002). Particularly in light of claims that kindling effects may develop only in certain subgroups of patients (e.g., Bidzinska, 1984; Ehnvall & Ågren, 2002), sample definition should be carefully considered when interpreting study findings.

It is also important to consider the illness characteristics of each sample. In general, the studies reviewed here involved participants with long histories of affective illness. Mean current ages were often much greater than mean ages at initial onset (a difference of 20 years or more; Dienes et al., 2006; Johnson et al., 2000a; Ehnvall & Agren, 2002; Hlastala et al., 2000; Beyer et al., 2008). The number of prior episodes in each sample was also relatively high (6–18; Ehnvall & Agren, 2002; Hlastala et al., 2000; Johnson et al., 2000a; Dienes et al., 2006; Hammen & Gitlin, 1997; Swendsen et al., 1995). Many samples had relatively high rates of psychiatric hospitalizations as well (3.3 – 5.5; Ehnvall & Agren, 2002; Dienes et al., 2006; Hammen & Gitlin, 1997; Kennedy, 1983).

The relevance of such illness characteristics is twofold. First, reporting bias is more likely to affect long recall periods, as in the retrospective studies reviewed above. Second, even if a kindling effect does occur, the rate is unlikely to be linear or constant. For example, in their combined UD and BD sample, Ehnvall and Agren (2002) found that the frequency of life events decreased before each episode during the first 9 episodes only, with the strongest difference detected during the first 3 episodes. Similar results were reported in an exclusively UD sample (Kendler et al., 2000). Thus, results from studies using individuals with long illness histories may inadequately reflect developmental changes that occur earlier on.

All of the studies reviewed above were conducted using treatment-seeking patients. Several samples were wholly (Ambelas, 1979, 1987; Bidzinska, 1984; Kennedy, 1983; Perris, 1984b) or partially (Beyer et al., 2008; Glassner & Haldipur, 1983; Glassner et al., 1979) comprised of current or recently discharged inpatients. Other studies specified that participants were all receiving pharmacotherapy (Dienes et al., 2006; Dunner et al., 1979; Hammen & Gitlin, 1997; Hlastala et al., 2000; Johnson et al., 2000a; Kennedy, 1983; Swann et al., 1990; Swendsen et al., 1995), and/or psychotherapy (Hlastala et al., 2000). In one study, participants were recruited from a specialized treatment-refractory affective disorders program, and had received treatment for 89% of all episodes over their lifetime (Ehnvall & Ågren, 2002). Although some studies controlled for medication or ruled it out as a confound (Dienes et al., 2006; Hlastala et al., 2000; Kennedy, 1983; Swendsen et al., 1995), various treatment modalities are likely to affect stress reactivity in both qualitative and quantitative ways. Thus, empirical data is lacking on putative kindling processes across the naturalistic course of untreated BD.

5.8. The Role of Age, Age at Onset, and Family History

Hlastala (2000) suggested that something specific to the aging process may underlie changes in stress reactivity, and that this phenomenon may have confounded earlier tests of the kindling hypothesis. In line with this, Perris (1984a, 1984b) found that age was negatively associated with pre-episode life events, but did not examine whether this relationship differed according to stage of illness. Ambelas (1987) similarly reported that manic patients who experienced a pre-episode event were significantly younger (28 vs. 48.1 years), which was not explained by overall age differences in life event rates. Some studies tested for age differences in life event rates and found none (Ambelas, 1979; Beyer et al., 2008; Bidzinska, 1984; Dunner et al., 1979; Glassner & Haldipur, 1983; Swann et al., 1990). Dienes et al. (2006) included age as a covariate in tests of the sensitization model, and reported that it was not a significant predictor of pre-episode stress. Thus, there is only limited evidence that current age plays an important role in stress reactivity in BD. Kindling studies could benefit

from a more systematic approach to measuring the effects of current age on the developmental psychopathology of BD.

Age of initial BD onset may have a special significance in the relationship between episodes and stress. For example, results from the study by Glassner and Haldipur (1983) were inconsistent with a pure kindling effect, but suggested that early-onset patients were less likely to have experienced a pre-episode event across the course of their disorder, as compared to late-onset patients. Similarly, Johnson et al. (2000a) found a strong positive correlation between age of onset and stress level prior to index episode, which was not accounted for by lifetime number of affective episodes. In contrast, three studies found no evidence of association between age at onset and stress prior to episodes (Beyer et al., 2008; Dunner et al., 1979; Swann et al., 1990). Ehnvall and Agren (2002) found no differences in age at first episode between “sensitization” and “non-sensitization” course groups, but did not examine age at onset in relation to frequency of life events prior to episodes. Post and Leverich (2006) noted that early age of onset can have neurodevelopmental implications, including effects on emotion regulation and executive functioning. Such effects would likely impact stress reactivity as well.

It is possible that age of bipolar onset is confounded with genetic loading for BD, and/or that genetic predisposition itself has implications for the relationship between stress and episodes across the course of the disorder. Johnson and colleagues (2000a) found that patients with a family history of affective disorder had an earlier age at onset *and* lower levels of stress prior to the initial onset. According to work by Kendler and colleagues (2001), this finding is consistent with a genetic “prekindling” effect, in which those at high risk are more likely to develop even initial mood episodes in the absence of severe life stress. Two kindling studies found no family history differences between patients with or without stress prior to episodes, but did not examine whether this finding was affected by stage of illness (Ambelas, 1987; Dunner et al., 1979). Most studies did not report family history of psychiatric disorder, or reported it but did not examine its relationship with psychosocial stress reactivity.

5.9. Summary of Findings on the Kindling Model in BD

In sum, support for Post’s (1992) kindling model of BD has been inconsistent. Only eight of fifteen studies detected a kindling effect, and two of the eight found kindling within a specific subgroup of patients (those with six or more episodes, Bidzinska, 1984; and those with decreasing well intervals, Ehnvall & Ågren, 2002). None of the four methodologically strongest studies found evidence consistent with kindling, although one found an increase in both stress impact and stress frequency over the course of BD (Hammen & Gitlin, 1997). Findings have been equivocal on the role of current age, age at onset, or family history of psychopathology in the longitudinal trajectory of the stress-episode relationship.

Although existing research has established an important foundation upon which to continue exploring these issues, much of this literature suffers from serious methodological limitations (e.g., checklist measures of life events, long retrospective recall intervals). Two studies collapsed across unipolar and bipolar diagnoses in kindling analyses (Ehnvall & Ågren, 2002; Perris, 1984b), so that applicability to BD-specific processes cannot be assumed. Most study samples were comprised of treatment-seeking participants with long and relatively severe disease histories. As in UD kindling research, BD kindling studies have focused on analyses of life stress frequency, while overlooking the issue of life stress impact. Life stress indices have varied across studies, and only one study (Hlastala et al., 2000) examined the unique role of nonsevere stressors. As a result, even when findings have been consistent with a kindling effect, it has not been possible to distinguish between sensitization and autonomy models. Studies have yet to systematically examine whether

effects are episode polarity-specific or event valence-specific. Some studies focused on illness-independent events, whereas others did not employ this restriction. Thus, despite underwhelming evidence in support of a kindling effect in BD, it is premature to conclude that the model does not apply.

6. Bipolar Disorder and Kindling: Integration of Theoretical Models

As discussed above, basic methodological inconsistencies could underlie discrepant findings in BD kindling research. However, it is also possible that the traditional conceptualization of life stress (i.e., major negative events) does not adequately capture kindling processes in the context of BD. Life stress research in BD has traditionally focused on acute phases of illness rather than developmental trajectories, and is typically modeled after UD studies. In recent years, two promising biopsychosocial theories of bipolar disorder have received substantial empirical support: the Behavioral Approach System dysregulation theory (Alloy & Abramson, 2010; Alloy, Bender, Wagner, Abramson, & Urošević, 2009; Urošević, Abramson, Harmon-Jones, & Alloy, 2008) and the social rhythm disruption theory (Ehlers, Frank & Kupfer, 1988; Grandin, Alloy, & Abramson, 2006). We next describe these theories, their relevance to life stress in BD, and their predictions with respect to the distinction between stress sensitization and autonomy models of BD.

6.1. Behavioral Approach System (BAS) Dysregulation Theory

Researchers have theorized that behavior is regulated by two fundamental psychobiological systems: the Behavioral Approach System (BAS) and the Behavioral Inhibition System (BIS; Davidson, 1999; Gray, 1981, 1982). The BAS functions to drive approach behavior and motivation to attain rewards, whereas the BIS regulates inhibitory behavior in response to threat and punishment. A growing body of research suggests that BAS sensitivity may play a uniquely important role in the onset and course of BD (Alloy & Abramson, 2010; Alloy et al., 2009; Urošević et al., 2008).

The expanded BAS dysregulation model posits that individuals with or at risk for BD have an overly sensitive BAS that is hyper-reactive to relevant cues (Depue & Iacono, 1989; Depue, Krauss, & Spoont, 1987; Johnson, Ruggero, & Carver, 2005; Urošević et al., 2008). BAS-activation relevant events involve goal striving and attainment, as well as some goal frustration or anger-provoking events (Wright, Lam, & Brown, 2008). Vulnerable individuals experience excessive BAS activation when exposed to these BAS-relevant events (Alloy et al., 2009; Urošević et al., 2008). In turn, excessive BAS activation can precipitate (hypo)manic symptoms like euphoria, increased goal-striving, increased energy, decreased need for sleep, excessive self-confidence, optimism, irritability, and distractibility. On the other hand, vulnerable individuals may experience excessive BAS deactivation in response to events involving definite failure or goal non-attainment. BAS deactivation is theorized to produce depressive symptoms such as anhedonia, decreased energy, psychomotor retardation, hopelessness, sadness, and decreased confidence.

In support of this model, several studies have found that BAS-activating events predict symptoms and episodes of (hypo)mania (Johnson, 2005b; 2008; Johnson et al., 2000b; Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007), and that BAS-deactivating events predict depressive episodes (for reviews, see Alloy et al., 2009; Urošević et al., 2008). In one prospective study, BD I patients who actively decreased their level of goal-directed activity in response to manic prodromes had a significantly lower rate of manic relapse (Lam, Wong, & Sham, 2001).

From a BAS dysregulation perspective, the declining temporal association between major life events and episodes should occur as a function of stress sensitization, rather than

autonomy. Specifically, stress sensitization could occur as a function of a progressive increase in levels of BAS sensitivity over time (Alloy et al., 2009; Urošević et al., 2008). Such increases in BAS sensitivity could render even more minor BAS-relevant events sufficient to elicit mood episodes in these individuals (Alloy et al., 2009). The BAS dysregulation theory predicts a sensitization rather than autonomy model, because it requires environmental input (i.e., goal or reward-relevant stimuli) to trigger dysregulation. Even when reward relevance is only perceived or anticipated, some environmental stimulus must be a focus of the BAS-relevant cognitions, emotions, and physiological effects. Notably, analogous to the "psychological foreclosure" processes discussed by Monroe and Harkness (2005), conditioned associations or cognitive biases in the later stages of BD may render individuals increasingly likely to perceive minor goal-striving situations or even objectively neutral situations as reward-relevant. This tendency could underlie episodes that appear to occur in the absence of identifiable environmental triggers. Consistent with the possibility that BAS sensitivity may progressively increase with repeated exposure to BAS activation-relevant events (goals, rewards) are findings that BD individuals respond to goal- or reward-relevant stimuli with even further goal-striving. Individuals with BD are less likely to decrease their goal-striving efforts after unexpectedly high progress toward a goal than are controls (Fulford, Johnson, Llabre & Carver, 2010). They also continue to exhibit greater brain activity indicative of continued goal-striving in response to the opportunity to gain rewards on a challenging task compared to controls (Harmon-Jones et al., 2008). In addition, individuals with BD exhibit greater behavioral, emotional, and cognitive responsiveness to rewards on behavioral tasks (Eisner, Johnson, & Carver, 2008; Hayden et al., 2008; Johnson, Ruggero, & Carver, 2005). A stress autonomy model is more difficult to explain than a stress sensitization model from a BAS dysregulation perspective. It seems more likely that an apparent stress autonomy model has been traditionally supported because in actuality, increasingly minor BAS-relevant inputs are functioning as precipitants of mood episodes.

Studies have not explicitly compared stress sensitization and autonomy models in the context of the BAS dysregulation theory of BD. Johnson and colleagues (2008; 2000b) found no significant relationships between goal attainment levels and illness characteristics (e.g., age at onset, number of episodes, number of hospitalizations), but did not directly examine illness characteristics and stress reactivity. Some indirect support for BAS sensitization can be found. Wright and colleagues (2008) tested the hypothesis that individuals with BD experience a slow recovery to baseline levels of behavioral activation, following rewarding or challenging experiences. During a 28-day follow-up interval, euthymic BD I individuals and healthy controls demonstrated similar recovery times on a measure of behavioral engagement levels. However, time to recovery from rewarding events increased as a function of previous number of manic episodes. Also, recovery time following frustrating events increased as a function of both previous manic and depressive episodes (Wright et al., 2008). These findings could reflect BAS sensitization, but prospective research is needed to delineate temporal relationships between previous episodes and BAS sensitivity.

On the other hand, there is a potential inconsistency between the BAS dysregulation model of BD and a BAS sensitivity-driven model of stress sensitization. Specifically, BAS sensitivity was originally conceptualized as a temperamental variable that is established early in life and remains relatively stable over time (Depue & Iacono, 1989; Depue et al., 1987). BAS-driven stress sensitization, however, would be reflected in increased BAS sensitivity over the course of BD. Research increasingly suggests that neural reward substrates do adapt over time, in response to life experiences, environmental factors, and exposure to psychoactive substances (Doremus-Fitzwater & Spear, 2010; Mendez et al., 2009; Pitchers, Balfour, Lehman, Richtand, Yu, et al., 2010). Much of the incentive sensitization research is based on animal models, and has been conducted in the context of

examining addictive behaviors. Indeed, as noted above, Post's (1992) original kindling model drew heavily upon research documenting sensitization to amphetamine stimulation in rodents. The hypothesized underlying neural substrates of the BAS (dopaminergic systems, particularly mesolimbic dopaminergic pathways projecting from the ventral tegmental area to the nucleus accumbens, amygdala, and prefrontal cortex) are also believed to be critically involved in the reinforcing effects of drug use (see Alloy, Bender, Wagner, Whitehouse, Abramson, et al., 2009). Thus, evidence may be converging on the idea that BAS sensitivity is to some degree experientially responsive over time. Additional prospective longitudinal studies are needed to examine whether levels of BAS sensitivity are stable or dynamic over successive mood episodes in BD.

6.2. Social Rhythm Disruption Theory

Environmental cues are known to entrain certain biological rhythms. Examples of these environmental cues or "social zeitgebers" ("time-givers") include meal times, exercise times, alarm clocks, and regular companions. The social zeitgeber theory (also referred to as the social rhythm disruption or SRD theory; Ehlers et al., 1988) proposes that in vulnerable individuals, affective episodes are triggered by life events that cause a disturbance of social zeitgebers, and consequently, of social and biological rhythms (for review, see Grandin et al., 2006; Malkoff-Schwartz et al., 2000). The theory was developed in part based on data suggesting that depressed individuals exhibit irregularities in circadian rhythms such as sleep-wake cycles, temperature, melatonin, and cortisol rhythms (e.g., Thase, Jindal, & Howland, 2002). Distinct from social rhythms, circadian rhythms are biological processes that naturally follow a 24-hour cycle, even in the absence of external time cues (Grandin et al., 2006). According to the SRD model, disruption to these biological rhythms plays a pathogenic role in bipolar mood episodes (Wehr, 1991).

As compared to normal controls, bipolar spectrum individuals have been found to have less regular social rhythms and circadian activity patterns, based on lower self-report Social Rhythm Metric (SRM; Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990) scores (Ashman et al., 1999), as well as objective actigraphic assessments (Jones, Hare, & Evershed, 2005; Millar, Espie, & Scott, 2004). This finding has been observed in both acutely ill and euthymic or mildly subsyndromal samples (Jones et al., 2005). Alterations in the stability of social rhythms have also been associated with bipolar mood episodes (Shen, Alloy, Abramson, & Grandin, 2008; Sylvia et al., 2009), although studies have been equivocal (see Grandin et al., 2006, for review). The specificity of the relationship between social rhythms and depression vs. (hypo)mania is not clear. Malkoff-Schwartz and colleagues (1998; 2000) found that individuals with BD I were significantly more likely to experience schedule-disrupting events prior to manic episodes, but not before depressive episodes, as compared to an episode-free control period. In contrast, Sylvia and colleagues (2009) found that SRD events prospectively predicted depression, but only inconsistently predicted (hypo)mania in a sample of bipolar spectrum individuals.

Although these studies are important for determining the putative role of social rhythms and SRD events in triggering affective episodes, they do not shed direct light on developmental psychopathology processes in BD. That is, like the majority of life events research, SRD research has not addressed changes in stress reactivity across the course of BD. One study controlled for the number of previous episodes (47% of the sample had at least 6 previous episodes) and found results to be largely unchanged (Malkoff-Schwartz et al., 2000). In another, manic patients were younger and had fewer previous episodes than depressed patients, leaving open the possibility that group differences in rates of SRD events could reflect a generalized kindling process rather than true polarity distinctions. In one exciting preclinical study, sleep deprivation uniquely predicted maladaptive behavioral sensitization in rats, when exposed to stressful environmental conditions (Benedetti, Fresi, Maccioni, &

Smeraldi, 2008). The behavioral effect was both dose- and time-responsive, which could be analogous to a sensitization effect.

Despite lack of existing research integrating the SRD and kindling models, the SRD theory is relevant to the present discussion for several reasons. First, the methodology utilized in most existing kindling studies would be relatively insensitive to progressive changes as a function of SRD sensitivity. The degree of regularity with which daily activities are performed can be affected by objectively more minor events (e.g., taking final exams) than are traditionally captured by life stress measures for BD. Social rhythms can also be affected by positive life events (e.g., vacations, holidays), which remain understudied. Thus, an SRD model of BD could explain some of the discrepant findings in the kindling literature to date.

Second, examining different mechanisms by which social and biological rhythms are disrupted could have implications for understanding the kindling model in BD. Grandin and colleagues (2006) distinguished between rhythm disruption due to external triggers (social zeitgebers associated with life events) vs. internal triggers (e.g., trait-like dysfunction in biological rhythms, stable abnormalities in the circadian pacemaker due to genetic mutations). The social zeitgeber or external trigger hypothesis is believed to reflect a pathway to affective episodes as follows: life events or external triggers cause changes in social zeitgebers, which first disrupt social and then biological rhythms; these disruptions cause other somatic symptoms, and eventually affective episodes (Grandin et al., 2006). According to the internal trigger hypothesis, abnormalities of the circadian pacemaker underlie both social and biological rhythm disruption, which, in turn, produce other somatic symptoms and affective episodes (Grandin et al., 2006). The “internal pacemaker” may be regulated by the suprachiasmatic nucleus (SCN), which can function either autonomously or in an entrained state (Grandin et al., 2006). Thus, the SCN receives input both from external and internal cues, and research has not definitively identified which input source is most impactful in determining affective episodes.

It is theoretically possible, then, that the internal and external rhythm disruption theories could respectively underlie models of stress autonomy and sensitization. In light of inconsistent evidence that social zeitgebers regulate biological rhythms in BD, it remains possible that an internal biological abnormality is primarily responsible for symptoms apparently precipitated by rhythm disruptions (Grandin et al., 2006). Another possibility is that internal and external triggers may operate differentially on depression and (hypo)mania (Grandin et al., 2006).

SRD event research is in its early stages, and poses methodological challenges. Accurate measurement of these events is difficult; SRD events appear to be forgotten relatively quickly, and may therefore need to be assessed daily or weekly (Johnson, 2005a). As stated earlier, many of these events can be relatively minor and thus require more intensive measurement strategies. Also, medications are known to affect circadian rhythms (Benedetti et al., 2008), and participants in several of the studies supporting the SRD theory were engaged in pharmacological and/or psychosocial treatments. Additional prospective studies are needed to better understand the role of SRD events over the longitudinal course of BD.

7. Implications for Therapeutics

Should future research demonstrate stronger evidence for a kindling model of BD, there would be important therapeutic implications. Whether BD follows a sensitization or autonomy course, early diagnosis and treatment is paramount. Among the many reasons for this include the long-lasting damage that may be inflicted by each successive episode, through progressive transformations in the mechanisms underlying illness expression (Post, 2007; Post et al., 2001). Research that provides a more nuanced understanding of the

mechanisms underlying a kindling effect will be crucial to the development of targeted interventions. In particular, if kindling is a function of either BAS sensitivity or SRD responsiveness, these frameworks can aid in pinpointing psychosocial stressors that pose the highest risk for triggering relapse. In turn, psychosocial treatments may be designed to help patients monitor and manage these specific stressors.

For example, based on the SRD theory, Frank and colleagues (2000; 2005) designed Interpersonal and Social Rhythm Therapy (IPSRT). IPSRT highlights the connection between life events and mood symptomatology, focusing especially on the management of interpersonal stressors that are likely to precipitate social rhythm disruption and affective episodes. Clients complete daily metrics cataloguing various markers of social rhythm regularity, which would be helpful for monitoring changes in affective sensitivity to SRD events. The sensitization model would suggest a necessary emphasis on the fact that as the course of the disorder progresses, even seemingly minor stressors in these domains must be monitored and addressed.

Currently, there is no widely known treatment protocol based on the BAS dysregulation theory of BD. However, some researchers have begun to incorporate the BAS perspective into cognitive-behavioral therapies (see Nusslock et al., 2009). Lam and colleagues (2003) developed a form of CBT that explicitly targets ambitious goal striving and increased goal-directed activity. It emphasizes the ability to identify prodromal symptoms, and recommends counteracting symptoms by engaging in behavioral activation or deactivation endeavors as appropriate. Similarly, the recently developed GOALS Program utilizes motivational interviewing and CBT techniques to target goal dysregulation as a precipitant of manic episodes; a small open uncontrolled trial of this program yielded promising results (Johnson & Fulford, 2009). Careful, systematic tracking of cognitions, behaviors, emotions, and BAS-relevant events is especially helpful in light of potential developmental changes in stress sensitivity (i.e., sensitization or autonomy). These exercises provide information as to the general strength of association between specific stressors and episodes, and real-time tracking can produce valid information regarding minor contextual shifts or events.

In sum, research on sensitization/autonomy in BD has clear relevance for psychosocial treatment of the disorder. Treatments that aid in ameliorating the affective consequences of stress should still be efficacious within a kindling framework, when accompanied by an added emphasis on illness progression. Though beyond the scope of this review, kindling has relevance for pharmacological treatment of the disorder as well (Post, 2007). With an eye towards long-term developmental changes in stress reactivity, clinicians and clients can develop a collaborative treatment plan that aims to slow or arrest progression of kindling processes. Again, however, stronger evidence for kindling is needed before firm conclusions can be drawn about incorporating the model into treatment approaches.

8. Directions For Future Research

The most pressing need in the kindling literature is for additional longitudinal, prospective research. Most existing studies are retrospective, which limits the ability to assess critical temporal relationships between components of the sensitization and autonomy models. Ideally, individuals would be followed starting prior to their initial onset of BD, over an extended period of years in order to capture the relationship between life events and subsequent episodes. Genetic or behavioral high-risk samples are best suited for this type of research, given the low base rates of BD in the general population.

For example, Wals and colleagues (2001) conducted an important prospective high-risk study among 140 adolescent offspring of bipolar parents. In this sample, stressful life events were more strongly associated with initial episodes of a mood disorder, as compared to

recurrences (although the finding was no longer significant after controlling for baseline symptoms; Wals et al., 2005). However, given the sample age (mean = 16), few participants ($n = 5$) were specifically diagnosed with BD by the end of the 14-month follow-up. Therefore, longer follow-up intervals are needed. The ability to prospectively examine life events and multiple bipolar episode recurrences over time will be critical to furthering empirical knowledge of this complex developmental process. Another possible approach would be to conduct prospective epidemiological or community-based studies, which would allow for an examination of longitudinal stress reactivity patterns across multiple forms of psychopathology (e.g., depression, bipolar disorder, generalized anxiety disorder, post-traumatic stress disorder).

As is the case with kindling in UD, future BD kindling research must employ increased precision in order to begin disentangling autonomy and sensitization models. Life events should be examined with respect to both frequency and impact. That is, increased attention should be paid to the impact of stress on potential onsets, rather than just the frequency of stress prior to established episode onsets. Also, an assessment of life stress across the spectrum of severity is critical to understanding the developmental relationship between stress and psychopathology. Narrative-rating procedures with shorter recall periods (e.g., within one year) represent the most valid means of assessment for both severe and nonsevere life events. Also, statistical techniques that incorporate analysis of change at both the within- and between-subjects levels are particularly advantageous for examining stress reactivity across the course of BD.

The roles of episode polarity and event valence have been overlooked in BD kindling research, and need to be examined. Dohrenwend (2010) identified a multitude of life event dimensions that may be potentially relevant to trauma-related experiences, including source, valence, unpredictability, magnitude, centrality, and physical demand. Such a multidimensional approach to measuring life events may also be informative with regard to kindling processes in BD. Also, researchers should place greater emphasis on utilizing theory-driven life event categories. Analyzing life events that are content-specific and relevant to psychobiological vulnerabilities (e.g., BAS sensitivity, SRD responsiveness) may provide a clearer picture of developmental processes in BD. Put differently, theory-driven methodology should better position the field to carve the stress sensitization or autonomy process “at its joints” (Alloy, 1997; Craighead, 1980).

The issue of sample generalizability should be explored. Kindling and sensitization studies have focused on individuals with bipolar I disorder. Future research should examine whether kindling processes unfold similarly across the bipolar disorders spectrum, for two reasons. First, individuals with milder forms of BD are less likely to be treatment-seeking, so may provide a more naturalistic perspective on the kindling process. More importantly, milder forms of bipolar disorder often progress to the more severe forms (Akiskal et al., 1979; Goodwin & Jamison, 1990; Shen et al., 2008). Thus, especially in the context of a developmental psychopathology perspective on BD, capturing affective illness early in its course may provide incrementally valuable information.

Related to sample generalizability, future research should examine subgroups of BD individuals with differing course trajectories. Although faster episode recurrence over time is common, some individuals show episode stability or deceleration instead (Ehnavall & Ågren, 2002; Goldberg & Harrow, 1994; Post, 1992). There is a need to better understand how the role of life stress differs across the range of possible illness trajectories.

As we advance our ability to describe the stress sensitization or autonomy process, it will also be important to identify the mechanisms underlying these phenomena. As we have seen,

different cognitive or biological mechanisms are likely to be implicated by the stress sensitization and stress autonomy models. Research using theory-driven event categories organized according to biopsychosocial conceptualizations (e.g., BAS, SRD) may provide additional clues as to the mechanisms. Also, a growing body of evidence suggests that early childhood adversity experiences (i.e., distal stressors) may have causal implications for stress reactivity and psychopathology across the lifespan (Dienes et al., 2006; Grandin, Alloy, & Abramson, 2007; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Leverich et al., 2002; Leverich & Post, 2006; Post et al., 2001). The effect of these distal environmental stressors may operate through neurobiological changes involving the HPA axis and cortisol regulation (Heim et al., 2008; Kendler, Kuhn, & Prescott, 2004).

Given the increased emphasis on biopsychosocial models, studies will need to examine relationships between multiple factors putatively contributing to a kindling effect. Based on the findings reviewed above, factors of potential importance include genetic predisposition, distal stressors, age of onset, and current age. Studies that incorporate measures of chronic stressors may further illuminate the role of psychosocial context in the development of BD. Neuropsychological deficits associated with BD, such as abnormalities in executive functioning, verbal learning and memory, and attentional processes (Henin et al., 2009), may be relevant to kindling as well. Multi-trait and multi-method assessments are needed to examine a process that is hypothesized to occur on multiple levels of analysis. Only when researchers investigate this broader range of risk factors can we begin identifying sources of unique and overlapping variance among them.

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Table 1

Summary of existing research on kindling in bipolar disorder

Sample ^a	Assessment	LE Measure	# Months Prior to Episode	I/ F	Event Severity ^b	Event Valence	Stress Index ^b	Episode Polarity	Findings	Kindling
<i>Cross-sectional studies of rates of life events before first vs. subsequent episodes</i>										
Ambelas, 1979	67 manic	Chart review, some follow-up interviews	1	F	Not addressed	-, +	≥ 1 event	Mania only	50% first-episode patients experienced ≥ 1 pre-episode event, vs. 28% of patients with manic recurrence.	Yes
Ambelas, 1987	90 manic	Chart review, some follow-up interviews	1	F	Scaled scores based on PLES	-, +	≥ 1 LE; weighted sum	In follow-up study, LEs more common before mania than depression.	66% first-episode patients experienced ≥ 1 pre-episode event, vs. 20% of patients with manic recurrence. Stress scores were higher at first admission (mean = 12) than readmissions (mean = 8).	Yes
Kennedy, 1983	20 manic	Interview	4	F	Subset of independent negative events classified by objective impact (mild vs. moderate to severe)	-, +	≥ 1 LE; raw sum	Mania only	No significant differences in frequency of experiencing any LE type, or in raw sum of LEs, before or after admission according to whether hospitalization was for first episode or recurrence.	No

Sample ^a	Assessment	LE Measure	# Months Prior to Episode	I/ F	Event Severity ^b	Event Valence	Stress Index ^b	Episode Polarity	Findings	Kindling	
Perris, 1984	16 BD, 58 UD, 81 reactive-neurotic, 51 unspecified mood d/o	Semi-structured interview	Specially constructed Life Events Inventory	3, 12	F	Not addressed	–, +	≥ 1 LE; raw sum	Depression only	In 3 months before index episode, 73% of first-episode patients experienced ≥ 1 negative or conflict event (mean = 2.2), compared to 57% of recurrent patients (mean = 1.5 events). Nonsignificant findings for year prior to index episode. Analyses collapsed across diagnostic groups.	Yes, for subset of events
Retrospective studies comparing rates of events before initial vs. most recent episodes											
Bidzinska, 1984	50 BD I and II, 47 UD	Interview	Unpublished questionnaire	3	F	Not addressed	–, +	≥ 1 LE	No distinction	90% experienced LE before initial episode, vs. 82% before most recent episode.	No (but see below)
Glassner et al., 1979	25 BD I	Unstructured interview	SRRS	12	F	Not addressed	–	≥ 1 LE	No distinction	75% reported LE before 1st episode vs. 56% before most recent episode	Yes
Glassner & Haldipur, 1983	46 BD I	Unstructured interviewq	SRRS	12	F	Weighted according to SRRS	N.R.	≥ 1 LE; weighted sum	No distinction	Among early-onset pts., 23% had LE before initial onset (mean stress score = 20) and 23% before recent	No

Sample ^a	Assessment	LE Measure	# Months Prior to Episode	I/ F	Event Severity ^b	Event Valence	Stress Index ^b	Episode Polarity	Findings	Kindling	
episode (mean stress score = 13). Among late-onset pts., 64% had LE before initial onset (mean stress score = 53) and 61% before recent episode (mean stress score = 42).											
Retrospective studies comparing rates of events before first/earlier vs. any or all subsequent episodes											
Bidzinska, 1984	50 BD I and II, 47 UD	Interview	Unpublished questionnaire	3	F	Not addressed	-, +	# episodes preceded by ≥ 1 LE	No distinction	Among pts. with ≥ 6 episodes, first three episodes more likely to be preceded by LE, compared to fourth through sixth episodes.	Yes, for subset of patients
Dunner et al., 1979	79 BD	Unstructured interview	Unpublished questionnaire	3	F	Not addressed	N.R.	≥ 1 LE	57% pts. w/ first-ep. mania had LE; 47% pts. w/ first-ep. depression had LE	52% patients experienced event before initial episode, vs. 15% before later episodes	Yes
Ehnavall & Agren, 2002	4 BDI, 6 BD II, 20 UD	Chart review w/semi-structured interview	Swedish life-charting program	3	F	Not addressed	N.R.	Raw sum	No distinction	Significant decrease in events prior to first nine eps. but not tenth; largest decrease in first three eps., specifically in pts. with decreasing well intervals. Kindling analyses collapsed	Yes, for subset of patients

episode (mean stress score = 1.5). Among late-onset pts., 64% had LE before initial onset (mean stress score = 53) and 61% before recent episode (mean stress score = 42).

Sample ^a	Assessment	LE Measure	# Months Prior to Episode	I/ F	Event Severity ^b	Event Valence	Stress Index ^b	Episode Polarity	Findings	Kindling
Johnson et al., 2000	Chart review	PLES (1971)	12	F	Not addressed	N.R.	≥ 1 LE	No distinction	across UD and BD. 63% experienced life event before onset, but only 30% before the fifth episode	Yes
<i>LEDS interview-based and/or prospective investigations</i>										
Dienes et al., 2006	Prospective Interview	LEDS	3	I	Weighted by objective severity	–	Weighted sum	No distinction	Number of prior episodes did not interact w/ stress levels to predict recurrence status	No
et al., 2000	Interview	LEDS	3	F	Weighted by objective severity	–	Pts. grouped by most severe event	No distinction	Number of prior episodes did not significantly predict stress level in pre-episode or control periods	No
Hammen & Gitlin, 1997	Prospective Interview	LEDS	1, 3,	F, I	Categorized events as major if ≥ 3.5 on objective severity scale	–	≥ 1 major event; days to relapse after major event	No distinction	Patients with more prior episodes relapsed more quickly following occurrence of major stressful event. 76% of patients with ≥ 9 prior episodes experienced major LE before episode, vs. 40% with ≤ 8 prior episodes.	No

Sample ^a	Assessment	LE Measure	# Months Prior to Episode	I/ F	Event Severity ^b	Event Valence	Stress Index ^b	Episode Polarity	Findings	Kindling
Swendsen et al., 1995	45 BD I, 13 BD II	Prospective Interview	3	1	Weighted sum according to objective severity; presence moderate-to-severe event	–	Weighted sum	No distinction	Patients in both upper and lower halves of the distribution of previous episodes were likely to relapse following stressful LEs	No

NOTES:

^aSome studies also included healthy or medically ill controls;

^bSome studies calculated additional stress severity indices, but did not incorporate them into analyses relevant to kindling;

BD = bipolar disorder; UD = unipolar depression; PLES = Paykel Life Events Scale (Paykel et al., 1976); RLEI = Recent Life Events Interview (Paykel et al., 1980); SRRS = Social Readjustment Rating Scale (Holmes & Rahe, 1967); LEDS = Life Events and Difficulties Schedule (Brown & Harris, 1978); I = impact, F = frequency; "–" = negative events, "+" = positive events; N.R. = not reported; LE = life event; "≥ 1 event" = dichotomous variable based on whether any LE was experienced during observation period; "Raw sum" = sum of number of LEs, irrespective of severity; "Weighted sum" = sum of LEs weighted by severity ratings; Ep = episode.