KINDLING OF LIFE STRESS IN BIPOLAR DISORDER: COMPARISON OF SENSITIZATION AND AUTONOMY MODELS AND INTEGRATION WITH EMERGING BIOPSYCHOSOCIAL THEORIES

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ABSTRACT

Kindling of Life Stress in Bipolar Disorder: Comparison of Sensitization and Autonomy Models and Integration with Emerging Biopsychosocial Theories

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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. The kindling hypothesis states that over the longitudinal course of recurrent affective disorders, there is a weakening temporal relationship between major life stress and episode initiation (Post, 1992). This process could reflect either a progressive sensitization or a progressive autonomy (i.e., insensitivity) to life stress. The present study aimed to test the kindling model in BD by examining the effect of lifetime mood episodes on the relationship between proximal life events and prospectively assessed mood episodes. Polarity-specific tests of the model were conducted across the continuum of event severity, with respect to both impact and frequency of life events. Moreover, examination of the kindling hypothesis was embedded in the context of two emerging biopsychosocial theories of BD: the expanded Behavioral Approach System Dysregulation Model and the Circadian and Social Rhythm Theory. Data from 278 participants (146 bipolar spectrum participants and 132 normal control participants) were collected as part of the Temple-Wisconsin Longitudinal Investigation of Bipolar Spectrum Project. Hypotheses were polarity- and event-type specific and were in line with a stress sensitization model of bipolar spectrum disorders (BSD), rather than a stress autonomy model. Results partially supported a sensitization model: there was a decreased frequency and an

increased impact of major events, and an increased frequency and impact of minor events. However, results for specific polarities and event types were not fully consistent with a stress sensitization model. Implications of these findings are addressed, followed by a discussion of study strengths, limitations, and promising directions for future research.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

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, homelessness, incarceration, and suicide (Copeland et al., 2009; Miklowitz & Johnson, 2009). The 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 negative life events increase the likelihood of bipolar depression and that certain types of negative and positive life events increase the 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. This question is especially important given data suggesting that the 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).

Overview of the Kindling Hypothesis

Post (1992) formulated the kindling hypothesis, in which psychosocial stressors are thought to play a greater role in the initial episodes of a mood disorder than in subsequent episodes. The kindling model draws on preclinical research documenting a progressive decline in the electrophysiological input to needed to elicit seizure activity ("kindling"), and of behavioral

sensitization to psychomotor stimulant administration in rodents ("sensitization"). Based on this analog model, Post (1992) asserted that life stressors may play dual roles in relation to affective disorders: 1) an acute pathophysiological role, and 2) a stimulus that leaves long-term vulnerabilities, thereby lowering the threshold of stress exposure required for episode recurrence. Moreover, mood episodes themselves may exert lasting neurobiological damage (Post, 2007). Thus, as a function of psychosocial stressors and episodes themselves, long-term changes occur in neuronal functioning that are hypothesized to mediate future stress responses (Hlastala et al., 2000).

The kindling hypothesis therefore states that major life stressors are required to trigger initial onsets and recurrences of affective episodes, but that successive episodes become progressively less tied to stressors and may eventually occur autonomously. In examining the evidence relevant to the kindling/sensitization model, Post (1992) reviewed eight studies on unipolar depression (UD), six on BD, and two on both unipolar depression and bipolar disorder. With the exception of two, studies supported the idea that major psychosocial stress plays a more important role in initial affective episodes than in recurrences. Interestingly, of these early studies, the two that failed to support the kindling hypothesis were conducted on bipolar patients (Glassner & Haldipur, 1983; Kennedy, 1983).

Although Post (1992) initially suggested that his theory was applicable to both UD and BD, subsequent research has largely focused on UD samples. Of the twelve studies that specifically addressed the kindling hypothesis in UD since Post's (1992) original paper, eight provide support for the model, whereas four do not (for reviews, see Mazure, 1998; Monroe & Harkness, 2005; Stroud, Davila, & Moyer, 2008). Moreover, even in UD research, the model has been tested in imprecise and inconsistent ways. In reviewing studies relevant to kindling in UD,

Monroe and Harkness (2005) noted the need for clarification regarding the meaning of episode autonomy, the importance of varying degrees of stress severity, and the distinct roles of stress frequency and stress impact.

The ambiguity surrounding the meaning of episode autonomy is the most critical. Closer consideration of the kindling effect suggests that multiple processes could be capable of producing a progressive dissociation between stress and mood episodes. Monroe and Harkness (2005) identified two distinct pathways to this kindling effect, termed stress sensitization and stress autonomy models. In the sensitization model, individuals become increasingly sensitized over repeated episodes, so that psychosocial stressors that were insufficiently severe to initiate a first onset acquire the capability to initiate recurrences. Most contemporary life stress measures only assess life events that are relatively major in severity. Thus, as minor life stress begins to "dominate in the etiologic scheme (Monroe & Harkness, 2005, p. 426)," severe life stress appears to lose causal potential.

In contrast, in the stress autonomy model, episode recurrences become successively less dependent on socioenvironmental input in general. Major life stress decreases in association with successive recurrences not because it is 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 progressive stress sensitivity. Monroe and Harkness (2005) noted that the autonomy model is less conceptually intuitive and less parsimonious.

Related to the theme of sensitization versus autonomy, inadequate attention has been paid to issues of stress severity, frequency, and impact (Hlastala et al., 2000; Monroe & Harkness, 2005). As a result, it is difficult to identify precisely what accounts for the declining association between life stress and mood episode recurrences. For both sensitization and autonomy models, it is necessary to determine whether major life stress has less ability (impact; the probability of a subsequent episode, given the occurrence of a stressful event) or less opportunity (frequency; the probability of an antecedent stressor, given the occurrence of an episode) to initiate mood episodes. From a developmental psychopathology perspective, it is important to know whether both probabilities change over time as a function of episode history.

The sensitization and autonomy models entail specific testable predictions with respect to the dimensions of stress severity, impact, and frequency (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. In contrast, the stress autonomy model specifies that with each successive episode, both major and minor life stress will decrease in impact and frequency.

General Methodological Issues in Life Stress Measurement

Design and Measurement Issues

In and of itself, the conceptualization and measurement of life stress is fraught with challenges (Dohrenwend, 2006; Johnson, 2005a; Monroe, 2008). Within a developmental psychopathology framework, researchers are faced with the added challenge of quantifying changes in these dynamic stress processes over time. Studies on kindling in BD have utilized a variety of approaches, including chart reviews, questionnaires or checklists, unstructured

interviews, and semistructured interviews. The problems with questionnaire measures of life stress have been well documented (Alloy et al., 2005; Dohrenwend, 2006; Johnson, 2005a; Monroe, 2008). 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.

Also, most BD kindling studies have been cross-sectional or retrospective, with few exceptions. Cross-sectional studies are insufficient to examine a general kindling model, as an exclusively between-subjects design prohibits an examination of processes that unfold within individuals over time. Retrospective studies are of limited utility as well, in that they 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). 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, Cloitre, & Dohrenwend, 1991). Thus, results of chart review, cross-sectional, and retrospective studies must be interpreted with caution.

Conceptualization and Quantification of Life Stress

Especially in the context of implications for the course of affective disorders, "stress" is a difficult concept to define. Reflecting this challenge, stress has been used to describe "life change events" (i.e., those requiring social readjustment), as well as negative events that are especially distressing. The "severity" of stress then refers to the degree of adaptation required or the intensity of distress experienced, respectively. This distinction is important because, unlike distressing negative events, life-change events may be equally likely to be positive (e.g., marriage, desired promotion) as negative (e.g., home foreclosure, death of family member).

Early studies on the relationship between life events and mood disorders tended to adopt more of a life-change perspective, using measures such as the Social Readjustment Rating Scale (Holmes & Rahe, 1967) and Paykel's Interview for Recent Life Experiences (see Paykel, 1997). However, many of these earlier studies found that negative life events were more strongly associated with mood episodes than were 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 negative, "stressful" experiences. In the context of the present study, it is challenging to adhere to any one set of terminology (e.g., "stress," "stressors," "events"), because I examine a broader set of events from a *life stress* perspective. Thus, the terms "stress" and "events" will hereafter be used interchangeably, except when otherwise noted.

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 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, severe negative events, illness-independent events, or some combination. Given that research has yet to converge upon a preferred stress index, it is important at least 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. However, such an approach rests on the assumption that stress exerts a continuous additive burden, or "dose-response" effect. The 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 impact 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. Therefore, studies that report the likelihood of events occurring at specific severity levels, as well as the total number of events within each severity level, are optimal.

Existing Research on Kindling in Bipolar Disorder

The body of literature evaluating the kindling model in BD is relatively small, and is compromised by methodological shortcomings (see Bender & Alloy, 2011, for a detailed review). Of the five cross-sectional studies that compared rates of life events in patients experiencing a first episode versus a recurrence, four found support for the kindling model (Ambelas, 1979, 1987; Dunner et al., 1979; Perris, 1984b). The methodologically strongest study, however, found that the frequency of life events did not differ according to whether manic patients were experiencing a first or a recurrent hospitalization (Kennedy, 1983).

Three retrospective studies examined life events before patients' recent index episode, as compared to their initial episode. Glassner and colleagues (1979) found that initial episodes were significantly more likely to have been preceded by at least one stressful event, as compared to recent index episodes. However, two other studies found similar rates of life events prior to first and most recent episodes (Bidzinska, 1984; Glassner & Haldipur, 1983). An additional three studies compared the frequency of life events occurring prior to participants' earlier vs. later episodes. All three were consistent with a kindling effect (Bidzinska, 1984; Ehnvall & Ågren, 2002; Johnson, Andersson-Lundman, Aberg-Wistedt, & Mathe, 2000a). One of these studies found evidence of kindling specifically among patients who showed a pattern of decreasing well intervals over time (Johnson et al., 2000a). The authors posited that individuals with stable or increasing well intervals had an illness course that was more autonomous from onset.

Some of the BD studies described thus far measured both positive and negative events. Perris (1984b) collapsed across UD and BD patients and found greater *negative/conflict* events prior to initial onsets than recurrences but no differences in overall event rates. In another study, BD participants experienced more failure and conflict events prior to both first and most recent episodes, but not more successes or promotions as compared to normal controls (Bidzinska, 1984). The remaining studies either examined negative events exclusively or did not conduct valence-specific analyses in relation to phase of bipolar illness.

The four kindling studies conducted by Hammen and her colleagues are the methodologically strongest to date, in part due to their use of shorter recall intervals (e.g., three months, in contrast with more than ten years in some retrospective studies). These studies used Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978)-based interviews to examine negative events only. Hlastala et al. (2000) retrospectively measured stress in both a

pre-episode and within-subjects control period, and categorized participants as high stress (presence of at least one severe event), moderate stress (presence of at least one nonsevere event, and no severe events), or low stress (no events during the interval). Inconsistent with the kindling hypothesis, the number of lifetime episodes failed to predict stress levels in either the pre-episode or control observation period.

The remaining three studies conducted by these researchers (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Hammen & Gitlin, 1997; Swendsen, Hammen, Heller, & Gitlin, 1995) are the only three prospective studies that have explicitly addressed kindling in BD. In the first study, summed stress scores predicted relapse over a one-year follow-up, even among patients in the upper half of the distribution of prior episodes (Swendsen et al., 1995). A second study found that patients in the upper half of the distribution of lifetime episodes were significantly *more* likely to have experienced a life event in the six months prior to episode onset (Hammen & Gitlin, 1997). Also, a backward survival analysis indicated that patients with nine or more episodes relapsed more quickly after a major event. Results suggested that major stress is both more frequent and more impactful in the later phases of BD, following multiple mood episodes. Finally, Dienes and colleagues (2006) found that, although stress and episode history each prospectively predicted relapse status, their interaction did not.

In sum, support for Post's (1992) kindling model of BD has been inconsistent. Only seven of fifteen studies detected a kindling effect, and two of the seven found kindling within a specific subgroup of patients (those with six or more episodes, Bidzinska, 1984; those with decreasing well intervals, Ehnvall & Ågren, 2002). None of the four methodologically strongest studies found evidence consistent with kindling in BD.

However, much of the literature on kindling in BD suffers from methodological limitations (e.g., checklist measures of life events, long retrospective recall intervals). Two studies collapsed across unipolar and bipolar diagnoses in kindling analyses (Johnson et al., 2000a; 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 (Hlastala et al., 2000) examined the unique role of nonsevere or minor 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. None of the studies reviewed above carefully examined whether effects were episode polarity-specific or event valence-specific. Thus, despite underwhelming evidence in support of a kindling effect in BD, it is premature to conclude that the model does not apply.

Bipolar Disorder and Kindling: Integration of Theoretical Models

As discussed above, basic methodological inconsistencies could underlie discrepant findings on kindling in BD. 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 BD have received substantial empirical support: the Behavioral Approach System dysregulation theory (see Alloy, Bender, Wagner, Abramson, & Urošević, 2009b; Urošević, Abramson, Harmon-Jones, & Alloy, 2008) and the social rhythm

disruption theory (Grandin, Alloy, & Abramson, 2006; Malkoff-Schwartz et al., 1998; 2000). Below, I 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 (see also Bender & Alloy, 2011).

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 literature suggests that BAS sensitivity may play a uniquely important role in the onset and course of BD (Alloy et al., 2009b; 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 hyperreactive 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. Excessive BAS activation in response to these events can precipitate (hypo)manic symptoms like euphoria, increased goal-striving, increased energy and decreased need for sleep, excessive self-confidence, optimism, irritability, and distractibility. On the other hand, individuals with or vulnerable to BD 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 and psychomotor retardation, hopelessness, sadness, and decreased self-confidence. In support of this model, several studies have found that BAS-activating events predict symptoms and episodes of

(hypo)mania (Johnson, 2005b; Johnson et al., 2008; Johnson et al., 2000b; Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007), and that BAS-deactivating events predict depressive episodes (for reviews, see Nusslock, Abramson, Harmon-Jones, Alloy, & Coan, 2009; Urošević et al., 2008).

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 already high levels of BAS sensitivity over time (Alloy et al., 2009b; Urošević et al., 2008). Such increases in BAS sensitivity could render even more minor BAS-relevant events sufficient to elicit mood episodes in BD individuals (Alloy et al., 2009b). The BAS dysregulation theory necessarily predicts a sensitization rather than autonomy model, because it requires environmental input (i.e., goal or reward-relevant stimuli) to trigger dysregulation. Studies have not explicitly compared stress sensitization and autonomy models in the context of the BAS dysregulation theory of BD.

Social Rhythm Disruption Theory

Environmental cues are known to entrain certain biological rhythms. Examples of these environmental cues or "social zeitgebers" ("timegivers") 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, Frank, & Kupfer, 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). 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). From the SRD perspective, disruption to these biological rhythms plays a critical pathogenic role in bipolar mood episodes (Wehr, 1991).

Alterations in the stability of social rhythms have been found to be associated with bipolar mood episodes (Shen, Alloy, Abramson, & Grandin, 2008; Sylvia et al., 2009), although studies have been equivocal (Grandin et al., 2006). The specificity of the relationship between social rhythms and depression vs. (hypo)mania is not clear, with some studies suggesting a stronger relationship between SRD and acute mania (Malkoff-Schwartz et al., 1998; Malkoff-Schwartz et al., 2000) and others suggesting a stronger relationship between SRD and depression (Sylvia et al., 2009).

Like the majority of life events research, SRD research has not addressed changes in stress reactivity across the course of BD. However, the SRD theory is relevant to the present study for several reasons. First, the methodology utilized in most existing kindling studies is 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. 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 have been overlooked in the life stress literature as well. Thus, an SRD model of BD could explain some of the discrepant findings in the kindling model 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) and internal triggers (e.g., trait-like dysfunction in biological rhythms, such as stable abnormalities in the circadian pacemaker due to genetic

mutations). It is theoretically possible that the internal and external rhythm disruption theories could underlie models of stress autonomy and sensitization, respectively.

The Present Study

The present study aimed to conduct a more comprehensive and precise examination of the kindling effect as it applies to BD, thereby allowing for a direct comparison of sensitization and autonomy models. Data for this prospective study were drawn from the Longitudinal Investigation of Bipolar Spectrum Disorders (LIBS) project (Alloy et al., 2008). Analyses examined both frequency and impact of stress as a function of prior episodes, and addressed changes in stress sensitivity at both within- and between-subjects levels. Also, given that studies on acute mood 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), analyses were conducted separately according to episode polarity.

Overall, I predicted that results would be consistent with a stress sensitization model of BD, rather than a stress autonomy model. Polarity-specific hypotheses were formulated according to several theory-driven event schemes. Specifically, for all hypotheses, the following prediction applied: (1) the kindling relationship between events, prior depressive episodes, and new prospective depressive episodes would hold for negative, BAS-deactivating, and SRD events, but not for positive or BAS-activating events; and (2) the kindling relationship between events, prior hypomanic episodes, and new prospective (hypo)manic episodes would hold for negative, positive, BAS-activating, and SRD events, but not for BAS-deactivating events.

CHAPTER 2

METHODS

Participants and Procedure

The Temple-Wisconsin LIBS Project is a large-scale, two-site longitudinal investigation of the psychosocial, cognitive, and biological predictors of the course of bipolar spectrum disorders (BSD). Participants for the study were selected via a two-stage screening process. In Phase I, approximately 20,500 undergraduate students, ages 18-24, completed a revised General Behavior Inventory (GBI; Depue, Krauss, Spoont, & Arbisi, 1989). Participants who met high and low GBI cut-off scores (see measures section) were potentially eligible for the BSD and normal control groups, respectively, and were invited to complete a Phase II diagnostic interview. Lifetime diagnostic interviews were administered by trained interviewers blind to the participants' GBI status.

High GBI participants who met *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV; American Psychiatric Association, 1994) criteria or Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) for bipolar II disorder, cyclothymia, or bipolar disorder not otherwise specified (BD-NOS) were invited to participate in the longitudinal phase of the LIBS project as part of the BSD group. The BD-NOS category consisted of individuals who had either experienced: 1) hypomanic episode(s) but no diagnosable depressive episodes; 2) cyclothymic mood patterns with periods of affective disturbance not meeting duration criteria for hypomanic or depressive episodes; or 3) hypomanic and depressive episodes not meeting frequency criteria for a diagnosis of cyclothymia. Individuals were excluded from the study if they had experienced one or more full-blown manic episodes prior to study onset, because an aim of the overall LIBS project was to examine predictors of the progression to bipolar I

disorder.[1] Participants with low GBI scores were eligible for the normal control group if they had no lifetime history of Axis I psychopathology (with the exception of specific phobia) and no family history of affective disorders. Normal control participants were matched with BSD participants on the basis of age, sex, and ethnicity.

The final LIBS project sample included 227 bipolar spectrum and 227 normal control participants. These participants were representative of the large Phase I screening sample with respect to age, sex, and ethnicity. At an initial assessment point, participants completed a variety of measures including the Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS; Carver & White, 1994) and the Social Rhythm Metric (SRM; Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990) trait measure (see below). Following this baseline assessment, participants completed regular prospective assessments at four-month intervals for an average of 38.1 months (*SD* = 19.1, range = 73). Diagnostic interviews (Schedule for Affective Disorders and Schizophrenia - Change Version; Endicott & Spitzer, 1978) were administered at each assessment in order to collect detailed information on timing, severity, and duration of mood episodes occurring since the previous interview. An independent interviewer, who was blind to the participant's lifetime and concurrent mood diagnoses, administered a combined Life Events Scale and Life Events Interview (LES and LEI; Alloy & Clements, 1992; Francis-Raniere, Alloy, & Abramson, 2006; Needles & Abramson, 1990) to collect detailed information about timing, severity, and contextual factors of psychosocial events occurring since the last follow-up. Prior to entering the study, all participants provided written, informed consent. Participants were reimbursed for their time.

[1] Given that no BSD participants in the final sample had experienced a full-blown manic episode at baseline, previous lifetime episodes will be referred to as episodes of *hypomania.* However, some participants experienced episodes of full-blown mania during their prospective follow-up periods. For this reason, prospective episodes of this polarity will be designated by the more inclusive term *(hypo)mania,* i.e., either mania or hypomania.

Final sample demographics and clinical characteristics are presented in Table 1. The present study was based on data from all participants who had complete data for study variables of interest (i.e., lifetime history of mood episodes, prospectively assessed mood episodes, and life events; $N = 278$). Participants included and excluded based on these criteria did not significantly differ in gender ($\chi^2(1) = 1.21$, $p = .27$), age ($t(441) = -0.73$, $p = .46$), ethnicity ($\chi^2(5) = 9.26$, $p = .10$), group status ($\chi^2(1) = 0.26$, $p = .61$), or diagnosis ($\chi^2(2) = 2.75$, $p = .25$). Thus, the sample utilized in the present study can be considered representative of the larger LIBS project sample. However, power to detect effects was substantially reduced due to loss of participants with missing data. Data were most often missing for lifetime episode variables; given that testing kindling models was not a central goal of the LIBS project, this information was not initially collected systematically as part of the research study.

Measures

Phase I Screening Measure

General Behavior Inventory. The General Behavior Inventory (GBI; Depue et al., 1989) is a self-report questionnaire used during the Phase I screening process to identify potential BSD participants and normal controls. The revised GBI utilized in the present study contains 73 items, each designed to assess various experiences related to depressive, (hypo)manic, or biphasic symptoms on dimensions of intensity, duration, and frequency. For each item, the respondent provides a rating on a 4-point Likert-type scale, ranging from 1 (*not at all*) to 4 (*very often or almost constantly*). In accordance with the case scoring method recommended by Depue and colleagues (Depue et al., 1989), items rated 3 (*often*) or 4 (*very often or almost constantly*) were assigned a value of one point. Points were then summed to obtain two subscores, one for

depression items (GBI-D score) and another for (hypo)mania and biphasic items (GBI-HB score). This scoring method yields GBI scores that represent the number of symptomatic experiences satisfying the criteria of duration, intensity, and frequency. Participants whose GBI-D scores exceeded 11 and GBI-HB scores exceeded 13 were considered to be potential bipolar participants, and those scoring below these cut-offs were considered to be potential normal controls. A pilot study for the LIBS project validated this high- and low-GBI group assignment procedure against diagnoses obtained via Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L; Endicott & Spitzer, 1978) diagnostic interviews (see Alloy et al., 2008).

The GBI has been extensively validated among a range of populations, including undergraduates, psychiatric outpatients, and relatives of bipolar I probands (Depue et al., 1989; Depue et al., 1981; Klein, Depue, & Slater, 1985). Psychometric properties of the instrument are strong, with internal consistency of α's = .90 - .96, test-retest reliability of *r*'s = .71 - .74, adequate sensitivity (.78), and excellent specificity (.99) for bipolar spectrum disorders (Depue et al., 1989; Depue et al., 1981). Discriminant validity has also been good (.88 in discriminating between those with and without affective disorders; Mallon, Klein, Bornstein, & Slater, 1986).

Phase II Diagnostic Interview

Expanded Schedule for Affective Disorders and Schizophrenia – Lifetime Version. The Expanded Schedule for Affective Disorders and Schizophrenia – Lifetime Version (exp-SADS-L; Endicott & Spitzer, 1978) semi-structured diagnostic interview was administered during Phase II of the screening process. The exp-SADS-L assesses the occurrence, duration, and severity of symptoms related to mood, anxiety, eating, psychotic, and substance use disorders over the lifetime. In consultation with diagnostic experts (Drs. Endicott, Akiskal, Angst, Clayton, and

Gruenberg), the original SADS-L was expanded for use in the LIBS project in order to increase reliability and accuracy in diagnosing bipolar spectrum disorders. Specifically, the following substantive modifications were made to the SADS-L: (1) additional probes to allow for the assignment of DSM-IV diagnoses as well as RDC diagnoses; (2) improved probes in the depression, mania, hypomania, and cyclothymia sections based on Depue's (1985) Behavioral Variability Interview; (3) additional items and probes in the depression, mania, hypomania, and cyclothymia sections to capture precise details regarding frequency and duration (number of days, percentage of waking hours per day) of symptoms and episodes, and switch rapidity of cyclothymic periods; (4) additional items inquiring about the extent to which participants' symptoms/behavior changes were noticed by others; (5) an expanded 5-point severity rating scale for each symptom, with a rating of 3 or above representing clinical significance; and (6) additional or appended sections on eating disorders, attention deficit hyperactivity disorder (ADHD), acute stress disorder, medical history, family history, and organic rule-out conditions.

The exp-SADS-L interview has demonstrated good inter-rater reliability for diagnoses of major depressive episodes (*k*'s > .95) and all unipolar depression diagnoses (*k*'s > .90) based on 80 jointly rated interviews (Alloy et al., 2000), and for bipolar spectrum diagnoses (*k*'s > .96) based on 105 jointly rated interviews (Alloy et al., 2008). Interviewers completed over 200 hours of diagnostic training and were blind to participants' Phase I GBI scores. Interviews were audiotaped to obtain consensus diagnoses and to monitor inter-rater reliability. Diagnoses were determined via a three-tiered standardized diagnostic review procedure, involving senior diagnosticians and an expert psychiatric diagnostic consultant (Dr. Alan Gruenberg).

Criteria for bipolar spectrum disorders

Lifetime bipolar spectrum disorders were diagnosed according to DSM-IV criteria and Research Diagnostic Criteria (RDC). Bipolar II disorder was defined as the occurrence of at least one DSM-IV or RDC major depressive episode, as well as at least one DSM-IV or RDC hypomanic episode (see below for episode definitions). To qualify, symptoms of bipolar II disorder must have resulted in clinically significant distress or impairment in functioning. Hypomanic episodes themselves did not require functional impairment per DSM-IV but must have been associated with an unequivocal, observable change in mood and functioning. The presence of a manic or mixed episode warranted a diagnosis of bipolar I disorder at this initial assessment point, thus excluding the participant from the LIBS project.

Cyclothymic disorder was defined as recurrent periods of depression and hypomania occurring over at least a two-year period; the periods of affective disturbance could not meet criteria for major depressive or manic episodes. To receive a diagnosis of cyclothymia, participants must not have been free of symptoms for more than two months over the two-year period. The initial two-year period of cyclothymia must have been absent of major depressive episodes, although major depressive episodes could be superimposed upon a cyclothymic diagnosis after that time. Given that minimum duration of each mood disturbance is not specified by DSM-IV or RDC criteria, the LIBS project required a two-day minimum duration for both kinds of periods, as well as at least two periods each of depression and hypomania per year. During the two-day periods, criterion A symptoms (sadness or loss of interest for depression; elevated, expansive, or irritable mood for hypomania) must have been present at least 50% of each day. Significant distress or functional impairment was required for DSM-IV cyclothymia, but not for RDC cyclothymia.

Criteria for bipolar spectrum episodes

Hypomanic episodes were defined according to both DSM-IV and RDC criteria. Thus, the criteria were as follows: an abnormally and persistently elevated, expansive, or irritable mood, lasting a minimum of four days for DSM-IV and two days for RDC; hypomanic mood must persist for at least 50% of waking hours per day in episode; hypomanic mood must be concurrent with either three (DSM-IV) or two (RDC) additional criterial hypomanic symptoms. If an individual's primary mood is irritable rather than euphoric, an additional symptom is required by both diagnostic systems. As stated above, hypomanic episodes require an unequivocal, observable change in mood and functioning but are insufficiently severe to lead to impaired functioning, hospitalization, or psychotic symptoms.

Depressive episodes were also defined according to DSM-IV or RDC criteria. Depressed mood or anhedonia was present at least 50% of waking hours for 6 of every 7 days in the depressed period (minimum of 1 week). In addition, at least three (DSM-IV) or two (RDC) additional criterial depressive symptoms were required throughout the depressed period. Mood episodes could not be the direct result of substance use or a primary medical condition.

Age of onset and number of lifetime episodes

As part of the exp-SADS-L lifetime diagnostic interview, data were collected on bipolar participants' age at first onset of depression, hypomania, and/or cyclothymia. The number of previous lifetime depressive and hypomanic episodes was also recorded at Phase II. For participants meeting criteria for cyclothymia, the total number of "low" and "high" periods was recorded or was estimated using an average number of low and high periods per year, multiplied by the number of years elapsed since age at onset.

Time 1 Self-Report Measures

BIS/BAS Scores. The self-report Behavioral Inhibition System/Behavioral Activation System Scales (Carver & White, 1994) are the measures most widely used to assess BIS and BAS sensitivity. Responses to the 20 items are provided on a 4-point Likert-type scale (1 = *strongly disagree*, 4 = *strongly agree*). The instrument contains one BIS subscale (e.g., "I feel pretty worried or upset when I think or know somebody is angry at me") and three BAS subscales. The five items in the BAS Reward Responsiveness (RR) subscale were designed to assess positive responses to reward-relevant stimuli (e.g., "When I get something I want, I feel excited and energized"). The four items comprising the BAS Drive (D) subscale reflect degree of persistence in pursuing rewards ("When I want something, I usually go all-out to get it"). Finally, the four items in the BAS Fun-seeking (FS) subscale measure willingness to approach stimuli perceived as novel and rewarding (e.g., "I crave excitement and new sensations"). Confirmatory factor analyses have supported this four-factor latent structure (Campbell-Sills, Liverant, & Brown, 2004; Carver & White, 1994).

Carver and White (1994) reported internal consistencies of α's = .66 - .76, and test-retest reliabilities of *r*'s = .59 - .69, for all subscales. In the LIBS project sample, alphas were .75 for BIS, .81 for BAS Total, .81 for BAS Drive, .72 for BAS FS, and .66 for BAS RR (Alloy et al., 2009a). The measure has demonstrated construct validity through associations with prefrontal cortical activity, affect, personality traits, and performance on reaction-time and learning tasks involving reward incentives (Colder & O'Connor, 2004; Harmon-Jones & Allen, 1997; Heponiemi, Keltikangas-Jarvinen, Puttonen, & Ravaja, 2003; Kambouropoulos & Staiger, 2004; Sutton & Davidson, 1997; Zinbarg & Mohlman, 1998).

High trait levels of BAS sensitivity have predicted shorter time to (hypo)manic episodes, whereas BAS RR scores have predicted shorter time to depressive episodes (Alloy et al., 2006). Thus, in the present study, BAS scores will be entered as a covariate in all analyses examining the role of BAS-relevant events.

Social Rhythm - Trait Measure. The Social Rhythm Metric (SRM; Monk et al., 1990) assesses typical daily social rhythm patterns by targeting activities that occur with regularity. The instrument inquires about 15 specific activities and allows for two write-in activities. Activity types include sleep-related (e.g., "go to bed"), meal-related (e.g., "have lunch"), physical exercise, and first social contact events. The modified version used for the LIBS project assessed the frequency with which participants performed regular activities throughout the past month. Participants were provided with the following definition of regular activities: an activity that has happened at approximately the same time (± 45 minutes) at least three days per week. For each item, participants indicated whether or not the activity qualified as part of their daily routine. For all items endorsed, participants also indicated the number of days per week the activity happened, the usual time of day, and who if anyone was present.

The SRM produces a total (number of activities performed with regularity) and an average (average frequency of regular activities) score. In 50 healthy controls, the SRM was moderately consistent ($r = .44$, $p < .001$) between the first and second weeks of study (Monk et al., 1990; Monk, Kupfer, Frank, & Ritenour, 1991). Retest reliability in the LIBS project sample was $r = .61$ (Shen et al., 2008). SRM scores have been positively associated with other indices of social rhythm stability and circadian markers (Monk, Petrie, Hayes, & Kupfer, 1994) and negatively associated with anxiety, depression, and bereavement (Brown, Reynolds, Monk, &

Prigerson, 1996; Monk et al., 1991; Shear et al., 1994; Stetler, Dickerson, & Miller, 2004; Szuba, Yager, Guze, Allen, & Baxter, 1992).

In the LIBS project sample, SRM scores differentiated BSD from normal control participants and prospectively predicted onsets of depression and (hypo)mania (Shen et al., 2008). Thus, I will include SRM scores as a covariate in all examinations of SRD events.

Longitudinal Diagnostic Data

Diagnostic Interview. The Expanded Schedule for Affective Disorders and Schizophrenia – Change Version (exp-SADS-C; Endicott & Spitzer, 1978) is a semi-structured diagnostic interview that was used to prospectively assess occurrence, timing, duration, and severity of affective episodes throughout each four-month interval. Although not relevant to the present study, the exp-SADS-C also assesses psychotic, anxiety, eating, and substance use disorders. The version used in the current study was expanded in accordance with changes made to the SADS-L (see exp-SADS-L section above; see also Alloy et al., 2008; Francis-Raniere et al., 2006). Thus, the interview facilitated derivation of diagnoses according to both DSM-IV and RDC diagnostic systems. Exp-SADS-C interviewers participated in the same extensive training procedures required to administer the exp-SADS-L and were blind to participants' GBI status and SADS-L diagnosis. Another modification made to the original SADS-C was the incorporation of features of the Longitudinal Interval Follow-up Evaluation (LIFE II; Shapiro & Keller, 1979), such as calendars, anchoring events, and structured probes, to facilitate accurate recall of symptoms and episodes.

The exp-SADS-C has demonstrated strong inter-rater reliability (Alloy, Reilly-Harrington, Fresco, Whitehouse, & Zechmeister, 1999). Based on 60 jointly rated LIBS Project interviews, average kappas were $\geq .80$ for mood disorder diagnoses, and ranged from .62 to .98

for severity ratings of individual symptoms (Francis-Raniere et al., 2006; Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999). The exp-SADS-C produced a test-retest reliability of r = .97 for depressive episodes (Alloy & Abramson, 1999). Results of a validity study for the LIBS project indicated that participants dated their symptoms on the exp-SADS-C with at least 70% accuracy, compared to daily symptom ratings made over a four-month interval (Francis-Raniere et al., 2006).

Criteria for prospective episodes

In the present study, a "prospective episode" was defined as any mood episode occurring after the participant entered the longitudinal phase of the study (i.e., after the baseline assessment). In contrast, "lifetime episode" or "prior episode" refers to any mood episode that was reported retrospectively at baseline. Diagnostic criteria for prospective episodes as assessed by the exp-SADS-C were identical to the criteria used for lifetime episodes in the exp-SADS-L (see above). To be considered an index episode in the present study, the episode must have met criteria for a DSM-IV or RDC depressive (major or minor), hypomanic (DSM-IV or RDC), or manic episode. For testing the frequency component of the kindling model, the index episode was defined as the first prospectively assessed mood episode that was also preceded by 30 days of euthymia. For testing the impact component of the kindling model, the index episode was defined as the first prospectively assessed episode of each polarity.

Longitudinal Self-Reported Mood Symptoms

Self-reported depressive symptoms. The Beck Depression Inventory (BDI; Beck et al., 1979) is a widely validated 21-item self-report scale that assesses affective, motivational, cognitive, and somatic symptoms of depression. For each item, participants select among four statements that are graded in severity on a scale of 0 to 3. The BDI has demonstrated good

internal consistency, retest reliability, and concurrent validity with clinical depression ratings in both clinical (r = .72) and nonclinical (r = .60) samples, and has been validated in undergraduate samples (Beck, Steer & Garbin, 1988). LIBS project participants completed a BDI at each regular prospective assessment, and were asked to provide separate responses for each one-month period elapsed since the previous follow-up. In the present study, BDI scores were included as covariates to control for subsyndromal depressive symptoms that may have impacted pre-episode event rates.

Self-reported hypomanic symptoms. The Halberstadt Mania Inventory (HMI; Alloy et al., 1999) is a 28-item self-report questionnaire that was modeled after the BDI. It was designed to assess current affective, motivational, cognitive, and somatic symptoms of hypomania/mania. As with the BDI, participants select one of four statements that reflect differing degrees of hypomanic symptom severity (e.g., "I do not feel particularly happy," I feel happy," "I feel so happy and cheerful it's like a high," and "I am bursting with happiness and I'm on top of the world"). HMI scores in the LIBS project demonstrated good construct validity and were significantly correlated (r = .46) with hypomanic symptoms reported during the exp-SADS-C interview (Alloy et al., 2008). Cyclothymic participants reported HMI scores consistent with their current mood state, with significantly higher HMI scores during diagnosed hypomanic states (M = 23.9) than during depressed states (M = 15.7) or euthymic states (M = 18.8). In a sample of 1,282 undergraduates, the HMI demonstrated strong internal consistency (α = .82), adequate convergent validity with the mania scale of the MMPI (r = .32, p < .001), and adequate discriminant validity with the MMPI-Depression Scale (r = -.26, p < .001) and BDI scores (r = -.12, p < .001; Alloy et al., 1999). LIBS project participants completed an HMI at each regular prospective assessment and were asked to provide separate responses for each one-month period

elapsed since the previous follow-up. In the present study, HMI scores were included as covariates to control for subsyndromal hypomanic symptoms that may have impacted pre-episode event rates.

Longitudinal Life Events Data

Life Events Questionnaire. The present study utilized contextual threat methods based on the work of Brown and Harris (1978) and incorporated adaptations suggested by Monroe and Roberts (1990). In this two-step life events assessment, participants first completed a self-report Expanded Life Events Scale (exp-LES; Francis-Raniere et al., 2006), followed by a Life Events Interview (LEI; see below). The version of the LES employed in the LIBS project was expanded from an earlier 134-item LES (Alloy & Clements, 1992; Needles & Abramson, 1990). The exp-LES contains 193 items that comprehensively assess episodic events across multiple life domains. Each item was carefully designed to minimize ambiguity and redundancy, and items were eliminated if deemed to directly reflect symptoms of affective disturbance. Participants were asked to indicate whether and how many times the specified event occurred since the last prospective assessment (approximately 4 month intervals).

Prior to the start of the LIBS project, a team of raters determined a consensus-based objective severity rating (OSR) for each LES item. The OSR was rated on a 4-point scale ranging from 0 (*no/slight long-term implications*) to 4 (*extreme long-term implications*). The OSR was intended to reflect the degree to which each event would affect an average individual in average circumstances. During the interview portion of the life events assessment, OSRs were adjusted as necessary according to details of the individual's personal context (see below).

Each event was also *a priori* categorized by the consensus team across a series of dimensions, including valence (negative/positive) and BAS relevance (BAS-activation

relevant/BAS-deactivation relevant). BAS-activation relevant events included those involving goal striving ("Started a new project or venture [e.g., new project at school or work, new business or company, new hobby]"), rewards/gains ("Received a scholarship or fellowship or won an award for your achievements at school [e.g., was valedictorian; received Honors; won an award for the "best paper"; etc.]"), or goal frustrations/obstacles with potential for remediation (e.g., "You were held up, blocked, or otherwise interfered with by red tape, slow service, bureaucracy, slow traffic, etc. [e.g., trying to get to an important appointment and stuck in traffic, having important paperwork lost by administrative staff, writing a paper and computer crashes]"). As such, BAS-activation relevant events could be either positive or negative. BAS-deactivating events were exclusively negative, and involved definite loss or failure without potential for remediation ("Got caught doing something parents disapproved of, or parents found evidence of something they disapproved of [e.g., parents found drugs in room; parents found birth control devices; etc.]").

Both the original and expanded versions of the LES have demonstrated good reliability and validity (Alloy & Clements, 1992; Alloy et al., 1999; Francis-Raniere et al., 2006; Needles & Abramson, 1990; Safford, Alloy, Abramson, & Crossfield, 2007). For example, test-retest reliability over a period of three weeks was .82 (Saxe & Abramson, 1987). Negative LES scores were positively correlated with scores on a measure of depression ($r = .55$, $p < .01$), and interacted with cognitive vulnerability to prospectively predict depression in both unipolar depression and BSD samples (Alloy et al., 1999; Needles & Abramson, 1990; Reilly-Harrington et al., 1999). Also, LES scores for positive events interacted with a measure of optimism to predict (hypo)manic symptoms (Alloy et al., 1999).

Life Events Interview. Following completion of an LES, participants completed a Life Events Interview (LEI; Francis-Raniere et al., 2006). LEI interviewers were blind to Phase I GBI scores, Phase II diagnostic status, and concurrent symptoms and diagnoses obtained on the exp-SADS-C. The LEI served as a reliability and validity check on LES-reported events. Interviewers referred to a Life Events Manual, which contained explicit event definition criteria and an extensive list of qualifying examples. Manualized probes were used to check each reported item against these definitional criteria. Any event not meeting criteria was disqualified by the interviewer or, if applicable, recoded to the appropriate event number. The LEI also facilitated precise dating of event onsets and offsets, using individualized calendars with multiple anchors (e.g., Christmas, New Year's, major local snowstorm). Based on the detailed contextual information gathered for each event, interviewers could increase or decrease the a priori OSR by one point. In this way, contextualized objective severity ratings (hereafter called COSRs) were obtained. For the present study, events with COSRs ≥ 3 were categorized as major, whereas those with COSRs ≤ 2 were categorized as minor.

The contextual information from the LEI was also critical in establishing the extent of social rhythm disruption associated with each event. The participant was asked to recall the degree to which the event affected his/her bedtime routine. Using this information, the interviewer assigned a rating from 1 to 4 based on the following anchor points (Malkoff-Schwartz et al., 2000): 1 = "Little to no effect on bedtime routine;" 2 = "Going to bed 1-2 hours later or getting up 1-2 hours earlier"; 3 = "Going to bed > 2 hours later, waking > 2 hours earlier OR waking up in the middle of the night;" 4 = "Not going to bed $\geq$ 24 hours." For example, events such as overseas travel or staying up 4 hours later to finish a project might warrant a rating of 3, as they are highly likely to desynchronize sleep-wake patterns (Malkoff-Schwartz et

al., 2000; Sylvia et al., 2009). Events were categorized as major SRD events if they warranted an SRD score ≥ 3, and as minor SRD events if they warranted an SRD score of 2. Ratings thus derived were used as COSRs for SRD events.

This combined LES/LEI procedure is relatively robust to some of the threats to validity plaguing other life stress studies (see Johnson, 2005a). The assessment is thorough and systematic, uses recall aids, and covers only a period of approximately four months. The procedure minimizes reporting bias based on mood state by adhering to stringent, objective event definition criteria and by employing interviewers who are blind to participants' mood status. Studies have indicated that this two-phase procedure yields reliable life event information. Alloy and Abramson (1999) reported that participants correctly recalled 100% of major events using the LES/LEI, when compared to daily life event lists that were prospectively generated throughout a month-long period. Also, an inter-rater reliability study based on 40 LEIs yielded a rating of .89 for the dating of events (Alloy & Abramson, 1999; see also Safford et al., 2007). In a reliability study for the LIBS Project, 20 cyclothymic participants completed daily ratings of life events for 16 weeks. At the end of this period, they completed an LES/LEI for the entire 16-week period. Major events were dated to within one day with 92% accuracy, and minor events were dated to within one day with 80% accuracy (Francis-Raniere et al., 2006).

Taken together, these results suggest a relatively high degree of reliability in LIBS life events assessment procedures, both in terms of event occurrence and event timing. The approach yields event data that are sensitive to the participant's individual context, while also anchored in objective measurement. Also, the results suggest that the LES/LEI is capable of reliably measuring life stress across the spectrum of event severity, which is critical for furthering our understanding of the developmental relationship between stress and BD.

CHAPTER 3

HYPOTHESES

Previous research suggests important differences in psychosocial predictors of depression and (hypo)mania. However, BD kindling researchers have failed to distinguish between depressive and (hypo)manic episodes. Hypotheses for the present study were thus formulated separately according to episode polarity, and only episodes of the relevant polarity were used in each model. That is, the number of lifetime episodes of depression was used in the analyses predicting prospective depressive episodes, and the number of lifetime episodes of hypomania was used in the analyses predicting prospective (hypo)manic episodes.

All hypotheses were also formulated according to a number of life event coding schemes. Each coding scheme was theory-driven and/or facilitated comparison with previous life events studies. Events were examined according to the following three categories: valence (positive/negative), BAS relevance (BAS activating/BAS deactivating), and social rhythm disruption (social rhythm-disrupting vs. non-social rhythm disrupting). Within each category, events were further designated as major or minor in severity, according to contextualized objective severity ratings (COSRs; see LES/LEI description, above). Events with COSRs of 3 or greater were categorized as major, whereas events with COSRs of 1 or 2 were categorized as minor/moderate (hereafter simply called "minor"). Seven study hypotheses are outlined below.

Basic Group Differences in Life Events

Hypothesis 1: Life Events in Bipolar Spectrum vs. Normal Control Participants

Across groups, I predicted that BSD participants would experience higher event levels in the 30 days prior to mood episodes, compared to normal control participants during an analogous

30-day interval. I expected to find similar event levels between BSD participants' 30-day episode-free control period and an analogous interval among normal controls. In other words, I predicted similar base rates of life events between normal control participants and BSD participants during extended periods of euthymia.

Hypothesis 1a: Between-group comparisons of 30-day sums. BSD participants were expected to experience elevated rates (30-day sums) of events prior to depressive and (hypo)manic episodes, compared to normal control participants during an analogous 30-day interval. BSD participants were expected to experience similar rates (30-day sums) of events during their episode-free periods, relative to 30-day sums for normal control participants.

Hypothesis 1b: Between-group comparisons of highest severity ratings. Compared to normal controls, I expected BSD participants to experience a higher severity level (highest COSR experienced) of events prior to depressive and (hypo)manic episodes. Compared to normal controls, BSD participants were expected to experience similar severity levels (highest COSR experienced) during their episode-free control period.

Hypothesis 2: Life Events within Bipolar Spectrum Participants

Within BSD participants, I predicted that event levels would be higher in the 30-day pre-episode periods, compared to the within-subjects episode-free control periods.

Hypothesis 2a: Within-group comparisons of 30-day sums. BSD participants were expected to experience higher rates (30-day sums) of major and minor life events in pre-episode periods, compared to within-subjects episode-free control periods.

Hypothesis 2b: Within-group comparisons of highest severity ratings. I hypothesized that BSD participants would experience a higher severity level (highest COSR experienced) of events during pre-episode periods, compared to within-subjects episode-free control periods.

Test of the Kindling Hypothesis: Frequency of Life Events

Tests of the kindling hypothesis were conducted within bipolar spectrum participants only. The remaining hypotheses in the present study predicted a set of findings consistent with stress sensitization. This set of hypotheses focused on the frequency component of the kindling model (i.e., given the occurrence of an episode, what is the frequency of events in the preceding interval?). The stress sensitization hypothesis predicts that as the number of previous episodes increases, major events will decrease in frequency, and minor events will increase in frequency.

Hypothesis 3: Pre-episode Event Frequencies

I predicted that the number of prior affective episodes would be associated with pre-episode event levels in BSD participants.

Hypothesis 3a: Lifetime episodes predicting event sums in the 30 days prior to episode. I predicted that during the pre-episode period, as the number of prior episodes increased, the number of major events would decrease and the number of minor events would increase.

Hypothesis 3b: Lifetime episodes predicting highest severity ratings in the 30 days prior to episode. I predicted that as the number of prior episodes increased, there would be a decrease in the highest event severity experienced during the interval prior to new episode onset.

Hypothesis 4: Control Period Event Frequencies

Hypothesis 4 predicted that the number of previous episodes would be associated with event levels in the within-subjects episode-free control period.

Hypothesis 4a: Lifetime episodes predicting event sums in the episode-free control period. I predicted that as the number of prior episodes increased, the number of major and minor events would decrease; otherwise, significant event rates during the control period would precipitate episodes (Hlastala et al., 2000).

Hypothesis 4b: Lifetime episodes predicting highest severity ratings in the episode-free control period. I predicted that as the number of prior episodes increased, the highest event severity experienced would decrease; otherwise, severe events during the control period would precipitate episodes (Hlastala et al., 2000).

Test of the Kindling Hypothesis: Impact of Life Events

The third set of hypotheses also predicted a set of findings consistent with the stress sensitization hypothesis. This set of hypotheses focused on the impact component of the kindling model (i.e., given the occurrence of life events, what is the likelihood of subsequent episodes?) by examining the relationship between previous episodes, prospectively assessed life events, and time to onset of prospective mood episodes. The stress sensitization hypothesis predicts that as the number of previous episodes increases, both major and minor events will increase in impact. Regarding the outcome of prospective time to episode onset, hypotheses 5 and 6 predict main effects of 1) lifetime episodes, and 2) life events, respectively. Hypothesis 7 then examines putative stress sensitization processes.

Hypothesis 5: Relationship Between Lifetime Episodes and Time To Prospective Onset of Mood Episodes

Hypothesis 5 predicted that BSD participants with a greater number of lifetime episodes would demonstrate shorter time to new prospective episodes.

Hypothesis 6: Relationship Between Life Events and Time To Prospective Onset of Mood Episodes

According to hypothesis 6, higher major and minor event levels will predict shorter time to new prospective episodes.

Hypothesis 7: Test of the Kindling Hypothesis: Moderating Effects of Lifetime Episodes on the Impact of Life Events

The main hypothesis for this group of analyses predicted that the number of lifetime episodes would moderate the effect of events on episode recurrence, such that the impact of major and minor events would increase as the number of previous episodes increases. This hypothesis is consistent with a stress sensitization model.

Summary of Hypotheses

The present study examined seven main hypotheses. Specifically, it was expected that BSD participants would have higher event levels prior to episodes, compared to an analogous 30-day period for normal control participants. BSD participants would have similar event levels during episode-free periods, compared to an analogous 30-day period for normal controls. Among BSD participants, event levels would be higher prior to episodes, compared to a within-subjects episode-free control period. Consistent with a stress sensitization (rather than stress autonomy) hypothesis, as the number of previous episodes increased, major events were expected to decrease in frequency but increase in impact, whereas minor events were expected to increase in both frequency and impact. All relationships were hypothesized to be polarity- and event type-specific: depressive episodes would be associated with negative, BAS-deactivating, and SRD events, whereas (hypo)manic episodes would be associated with negative, positive, BAS-activating, and SRD events.

CHAPTER 4

RESULTS

Preliminary Analyses

Sample Description and Associations Among Study Variables

Table 1 presents demographic and clinical characteristics of the study sample. Of the 278 participants (171 TU participants, 107 UW participants), 52.5% (n = 146) were bipolar spectrum, and 47.5% (n = 132) were normal control participants. Of the 146 bipolar spectrum participants, 76.7% had bipolar II disorder, and 23.3% had cyclothymia or bipolar disorder NOS. The sample was 61.5% (n = 171) female, 64.7% (n = 180) Caucasian, 16.5% (n = 46) African-American, 4.3% (n = 12) Asian, 2.2% (n = 6) Hispanic, 2.2% (n = 6) Native American, and 9.7% (n = 27) "other." The mean age at study entry was 20.04 years (SD = 1.75), and individuals participated for an average of 1520.08 days (SD = 862.29). Bipolar and control participants did not significantly differ according to gender ($\chi^2(1) = 0.02$, $p = .90$), ethnicity ($\chi^2(5) = 4.55$, $p = .47$), age ($t(275) = -0.14$, $p = .89$), or days in study ($t(273) = -1.38$, $p = .17$). Table 2 presents daily life event rates for bipolar spectrum (BSD) participants and normal controls. To derive daily life event rates, I calculated the number of events (major or minor, depending on the specific model) reported during the participant's entire prospective follow-up period. I then divided this number by the number of days elapsed over the participant's involvement in the study. Averaged over the course of the study, bipolar participants experienced higher daily rates of all event types (magnitude of all t's ≥ 2.52, all p's $\leq .01$) except major positive events ($t(274) = -1.26$, $p = .21$).

Table 1. Demographic and Clinical Characteristics of Normal vs. Bipolar Participants

	Normal Control (*n* = 132)	Bipolar Spectrum (*n* = 146)
Demographics		
Gender		
Male	38.0%	38.6%
Female	62.1%	61.4%
Age, years (*SD*)	20.12 (1.69)	20.05 (1.69)
Ethnicity		
Caucasian	60.6%	68.5%
African American	17.4%	15.8%
Asian	6.1%	2.7%
Hispanic	2.3%	2.1%
Other	13.6%	10.4%
Lifetime Episodes		
Lifetime depressive episodes	--	3.41 (5.14)
Age at onset of depressive episodes	--	16.13 (3.71)
Lifetime manic episodes	--	0.04 (0.28)
Lifetime hypomanic episodes	--	28.57 (106.50)
Age at onset of hypomanic episodes	--	13.38 (4.74)
Prospective Episodes		
Number of major depressive episodes	0.07 (0.35)	1.54 (2.40)
Number of minor depressive episodes	0.27 (0.74)	2.12 (4.97)
Number of hypomanic episodes	0.04 (0.29)	10.28 (17.29)
Number of manic episodes	0.00 (0.00)	0.09 (0.50)

Note. SD = Standard deviation

Table 2. Bipolar Spectrum vs. Normal Control Participants' Average Events Per Day Throughout Prospective Study Participation

	Normal Mean (*SD*)	BSD Mean (*SD*)	*t*	df	*p*
Major Negative	0.01 (0.01)	0.02 (0.02)	-5.00	226	<.001
Minor Negative	0.06 (0.12)	0.14 (0.25)	-3.52	211	.001
Major Positive	0.02 (0.02)	0.02 (0.01)	-1.26	274	.21
Minor Positive	0.10 (0.10)	0.15 (0.19)	-2.52	227	.01
Major BAS-Activating	0.02 (0.02)	0.03 (0.02)	-3.59	274	<.001
Minor BAS-Activating	0.13 (0.22)	0.20 (0.26)	-2.52	272	.01
Major BAS-Deactivating	0.02 (0.02)	0.04 (0.04)	-5.20	209	<.001
Minor BAS-Deactivating	0.09 (0.16)	0.20 (0.34)	-3.45	210	.001
Major SRD*	0.00 (0.00)	0.00 (0.00)	-3.87	224	<.001
Minor SRD	0.01 (0.01)	0.02 (0.05)	-3.89	165	<.001

Note. SD = Standard Deviation; BSD = Bipolar Spectrum Disorders; BAS = Behavioral Approach System; SRD = Social Rhythm Disrupting. *Major SRD unrounded mean (*SD*): Normal = 0.0012 (0.0017), BSD = 0.0024 (0.0032)

There were no gender differences in age ($t(275) = -0.11$, $p = .91$), days in study ($t(272) = 1.12$, $p = .27$), number of lifetime episodes ($t(275) = 0.38$, $p = .71$ for lifetime depression; and $t(275) = 0.07$, $p = .94$ for hypomania), number of prospective episodes ($t(275) = 0.55$, $p = .59$), likelihood of prospective episodes ($\chi^2(1) = 0.04$, $p = .84$), average daily event rates (magnitude of all t's ≤ 1.62, all p's $\geq .11$), likelihood of a valid 30-day pre-depression period ($\chi^2(1) = 0.71$, $p = .40$), likelihood of a valid 30-day pre-(hypo)mania period ($\chi^2(1) = 0.11$, $p = .74$), or likelihood of a valid 30-day control period ($\chi^2(1) = 1.08$, $p = .30$). Males had an earlier age at onset of

depression ($t(148) = 2.19$, $p = .03$). There were gender differences in pre-episode major BAS-activating events: females experienced more events prior to (hypo)mania ($t(79.45) = -2.48$, $p = .02$), whereas males tended to experience more events prior to depression ($t(52.56) = 1.90$, $p = .06$). Age was correlated with the number of lifetime depressive episodes experienced (Pearson's $r = .14$, $p = .02$) but not with the number of lifetime hypomanic episodes experienced (Pearson's $r = .08$, $p = .02$). Age was not associated with the number of prospective episodes experienced throughout the study (Pearson's $r = .10$, $p = .11$) or with the likelihood of having a valid pre-depression ($t(275) = -0.26$, $p = .79$), pre-(hypo)mania ($t(275) = -1.10$, $p = .27$), or control period event ($t(275) = .83$, $p = .41$). Tables 3, 4, 5, and 6 present zero-order correlations among study variables.

Table 3. Bivariate Correlations Between Lifetime Episodes, Average Current Mood Symptoms, and Sum of Life Events in the 30 Days Prior to Depression Among Bipolar Spectrum Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Lifetime Dep.													
2. Lifetime Hypo.	.70**												
3. BDI	.24*	.20*											
4. HMI	-.05	-.06	.11										
5. Major Negative	.17	-.02	.12	-.03									
6. Minor Negative	.13	.10	.14	-.01	.18*								
7. Major Positive	.13	.15	-.07	.14	.15*	.10							
8. Minor Positive	-.04	-.08	-.20*	.12	.06	.23**	.21**						
9. Major BAS-A	.21*	.16	.05	.06	.70**	.12	.54**	.08					
10. Minor BAS-A	.03	.07	.10	-.05	.21**	.86**	.16*	.32**	.16*				
11. Major BAS-D	.17	-.03	.10	-.04	.97**	.18*	.11	.07	.61**	.21**			
12. Minor BAS-D	.11	.08	.14	-.01	.16*	.99**	.08	.23**	.10	.84**	.17*		
13. Major SRD	.03	.03	-.05	.18*	.34**	-.02	.26**	.04	.35**	.05	.34**	-.03	
14. Minor SRD	.06	.04	.23**	-.03	.22**	.36**	.14	.14	.19*	.47**	.21**	.34**	.11

Note. Lifetime Dep. = number of lifetime episodes of depression prior to study entry; Lifetime Hypo. = number of lifetime episodes of hypomania prior to study entry; BDI = average weekly Beck Depression Inventory score during the 30 days prior to depression; HMI = average weekly Halberstadt Mania Inventory score during the 30 days prior to depression; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting. ** $p < .01$; * $p < .05$

Table 4. Bivariate Correlations Between Lifetime Episodes, Average Current Mood Symptoms, and Sum of Life Events in the 30 Days Prior to (Hypo)mania Among Bipolar Spectrum Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Lifetime Dep.													
2. Lifetime Hypo.	.70**												
3. BDI	.12	.01											
4. HMI	-.23*	.09	.10										
5. Major Negative	-.11	-.19	.09	-.18									
6. Minor Negative	.05	.13	.03	.04	.27**								
7. Major Positive	.06	.07	-.03	.02	.11	.02							
8. Minor Positive	.00	.21	-.09	.16	.10	.35**	.18						
9. Major BAS-A	-.13	-.14	.07	-.08	.66**	.18	.54**	.19*					
10. Minor BAS-A	.02	.09	.04	.05	.27**	.96**	.01	.32**	.19*				
11. Major BAS-D	-.07	-.16	.08	-.18	.98**	.30**	.07	.11	.61**	.30**			
12. Minor BAS-D	.07	.14	.05	.02	.29**	.99**	.01	.33**	.17	.95**	.32**		
13. Major SRD	-.20	-.18	.02	-.10	.17	-.01	.47**	.02	.42**	.01	.18*	-.01	
14. Minor SRD	-.07	.12	.05	.01	.17	.49**	-.04	.33**	.06	.50**	.20*	.49**	-.07

Note. Lifetime Dep. = number of lifetime episodes of depression prior to study entry; Lifetime Hypo. = number of lifetime episodes of hypomania prior to study entry; BDI = average weekly Beck Depression Inventory score during the 30 days prior to (hypo)mania; HMI = average weekly Halberstadt Mania Inventory score during the 30 days prior to (hypo)mania; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting. ***p* < .01; **p* < .05

Table 5. Bivariate Correlations Between Lifetime Episodes, Average Current Mood Symptoms, and Sum of Life Events in the 30-day Episode-free Control Period Among Bipolar Spectrum Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Lifetime Dep.													
2. Lifetime Hypo.	.49**												
3. BDI	-.03	.04											
4. HMI	-.22*	-.10	.21*										
5. Major Negative	-.14	-.06	.10	-.08									
6. Minor Negative	-.01	.02	.05	-.09	.40**								
7. Major Positive	-.04	.01	.00	.05	.22**	.24**							
8. Minor Positive	.04	.04	-.04	-.09	.17*	.50**	.25**						
9. Major BAS-A	-.11	.05	.10	-.04	.69**	.28**	.64**	.30**					
10. Minor BAS-A	-.02	.03	-.13	-.15	.30**	.82**	.37**	.61**	.37**				
11. Major BAS-D	-.13	-.09	.09	-.08	.99**	.40**	.21*	.14	.65**	.29**			
12. Minor BAS-D	-.04	.03	.04	-.07	.40**	.98**	.26**	.51**	.32**	.85**	.40**		
13. Major SRD	-.04	-.07	.11	-.09	.43**	.07	.18*	-.07	.36**	.00	.41**	.07	
14. Minor SRD	-.10	-.12	-.02	-.09	.18*	.50**	.13	.34**	.21*	.41**	.17*	.52**	.08

Note. Lifetime Dep. = number of lifetime episodes of depression prior to study entry; Lifetime Hypo. = number of lifetime episodes of hypomania prior to study entry; BDI = average weekly Beck Depression Inventory score during the 30-day episode-free control period; HMI = average weekly Halberstadt Mania Inventory score during the 30-day episode-free control period; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting. **p < .01; *p < .05

Table 6. Bivariate Correlations Between Lifetime Episodes, Average Current Mood Symptoms, and Sum of Life Events From Baseline to First Prospective Depression and (Hypo)mania Among Bipolar Spectrum Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
1. Lifetime Dep.																											
2. Lifetime Hypo.	.49**																										
3. Pre-dep BDI	.05	-.03																									
4. Pre-hypo BDI	-.01	-.01	.97**																								
5. Pre-dep HMI	-.28**	-.14	-.13	-.12																							
6. Pre-hypo HMI	-.27**	.05	-.15	-.15	.96**																						
7. Days to Depression	-.13	-.05	-.24*	-.22*	.08	.22*																					
8. Days to (Hypo)mania	-.23**	-.25**	-.04	-.06	.01	-.14	.38**																				
Events Prior to Dep.																											
9. Major Negative	.07	.02	.05	.01	.03	.05	-.03	.03																			
10. Minor Negative	.22**	.23**	.07	.05	.02	.01	-.16	-.24**	.21*																		
11. Major Positive	.06	.09	-.02	-.03	.11	.09	-.04	-.14	.64**	.21*																	
12. Minor Positive	.21*	.14	-.03	-.08	.05	.07	.03	-.23**	.18*	.49**	.30**																
13. Major BAS-A	.08	.08	-.02	-.08	.09	.11	-.01	-.06	.78**	.35**	.60**	.24**															
14. Minor BAS-A	.18*	.19*	.02	-.07	.05	.04	-.03	-.18*	.29**	.89**	.28**	.54**	.46**														
15. Major BAS-D	.08	.00	.04	.00	.02	.06	-.04	.07	.96**	.23**	.50**	.15	.79**	.32**													
16. Minor BAS-D	.22*	.24**	.07	.05	.00	.00	-.16	-.23**	.23**	.99**	.22**	.51**	.35**	.89**	.26**												
17. Major SRD	.02	.04	.00	.00	.07	.04	-.07	-.05	.70**	.02	.85**	.20*	.40**	.05	.56**	.06											
18. Minor SRD	.18*	.09	.11	.10	.06	.07	-.10	-.10	.18*	.58**	.15	.25**	.31**	.55**	.23**	.58**	.00										
Events Prior to Hypo.																											
19. Major Negative	.10	.05	.16	.11	.00	-.08	-.12	.13	.45**	.08	.15	.16	.42**	.08	.44**	.10	.13	.06									
20. Minor Negative	.19*	.24**	.12	.13	.00	.00	-.14	-.23**	.00	.73**	.08	.35**	.08	.49**	.00	.72**	-.02	.50**	.03								
21. Major Positive	.03	.05	-.01	-.05	.10	.03	-.06	-.02	.53**	.33**	.77**	.30**	.59**	.41**	.46**	.34**	.56**	.43**	.20*	.09							
22. Minor Positive	.15	.16*	-.03	-.04	.05	.03	-.02	-.23**	.171*	.40**	.13	.58**	.24**	.34**	.17*	.43**	.03	.33**	.19*	.43**	.25**						
23. Major BAS-A	.04	.06	.06	.02	.04	-.03	-.11	.11	.39**	.18*	.24**	.20*	.58**	.22**	.40**	.19*	.06	.16	.86**	.05	.42**	.28**					
24. Minor BAS-A	.18*	.25**	.07	.03	.01	.02	-.14	-.24**	.10	.87**	.19*	.43**	.24**	.76**	.10	.86**	.00	.53**	.08	.86**	.23**	.55**	.15				
25. Major BAS-D	.10	.04	.18	.11	.01	-.05	-.14	.15	.41**	.09	.09	.16	.37**	.09	.43**	.11	.08	.07	.97**	.04	.17*	.19*	.81**	.10			
26. Minor BAS-D	.21*	.24**	.12	.13	-.02	-.02	-.15	-.23**	.00	.72**	.06	.34**	.06	.47**	.00	.71**	-.01	.48**	.03	.99**	.06	.45**	.04	.85**	.05		
27. Major SRD	.01	.06	.05	.00	.12	.01	-.06	.08	.61**	-.01	.68**	.16	.33**	.01	.49**	.03	.83**	-.01	.29**	.01	.52**	.05	.19*	.03	.29**	.02	
28. Minor SRD	.04	.19*	.07	.09	.04	.12	-.01	-.18*	.00	.48**	.06	.234**	.11	.30**	.01	.48**	-.02	.60**	.00	.75**	.10	.28**	.03	.62**	.00	.70**	-.02

Note: Lifetime Dep. = number of lifetime episodes of depression prior to study entry; Lifetime Hypo. = number of lifetime episodes of hypomania prior to study entry; Pre-dep BDI = average weekly Beck Depression Inventory score from baseline to first onset of depression; Pre-hypo BDI = average weekly Beck Depression Inventory score from baseline to first onset of (hypo)mania; Pre-dep HMI = average weekly Halberstadt Mania Inventory score from baseline to first onset of depression; Pre-hypo HMI = average weekly Halberstadt Mania Inventory score from baseline to first onset of (hypo)mania; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting. $^{**}p < .01$; $^{*}p < .05$

Distribution of Variables and Regression Diagnostics

Examination of the distribution of study variables revealed significant deviations from normality among lifetime episode and life event variables. Due to positive skew and kurtosis, lifetime depressive episodes were recoded into the following groups: 1 (n = 25), 2 (n = 21), 3 – 5 (n = 19), 6 – 9 (n = 36), 10 – 15 (n = 33), and greater than 15 (n = 12). Due to similar distributional patterns, lifetime hypomanic episodes were recoded into the following groups: 1 – 2 (n = 41), 3 – 5 (n = 24), 6 – 9 (n = 22), 10 – 20 (n = 33), and greater than 20 (n = 26).

The distribution of values among life event categories also revealed positive skew and kurtosis. Variable transformations using inverse and logarithmic values were unsuccessful in fully remediating problems with normality. Given that variable transformations did not fully remedy distributional problems and reduced interpretability of findings, raw univariate outliers were recoded to a maximum of 3 standard deviations from the mean of each specific event type. This remedial measure was considered preferable to the exclusion of univariate outliers because it 1) minimized loss of power and 2) retained participants with a large number of life events, whose data were considered to be meaningful. Given that various combinations of event types and episode polarities yielded different sets of multivariate outliers, multivariate regression assumptions were explored and addressed separately for each linear regression model. For each linear regression analysis, multivariate outliers were identified based on Mahalanobis distances (using a critical value of $\chi^2(3) = 16.27$, at $p = .001$), leverage values (using a critical value of 0.10) and Cook's statistics (using a critical value of 0.05; formulas for identifying unduly influential data drawn from Tabachnick & Fidell, 2007 and Chen, Ender, Mitchell, & Wells, 2003). Extreme multivariate outliers were removed from each regression model (maximum multivariate outliers removed = 7).

Tests of Study Hypotheses

Basic Group Differences in Life Event Rates

For each BSD participant, I identified one prospectively assessed index episode of depression and one of (hypo)mania. The index episode was defined as the first prospective episode of each polarity that was also preceded by one full month of euthymia. A within-subjects episode-free control period was identified as the middle month of the participant's prospective follow-up period, provided this interval was free of affective episodes and was both preceded and followed by at least one full month of euthymia. The midpoint of study participation was chosen to account for possible changes in reporting style across a participant's involvement in the research study. If the participant's middle month of study participation did not meet these criteria, I identified the first one-month period of euthymia after the participant's midpoint of participation that was also preceded and followed by a full month of euthymia. Control periods were required to be preceded and followed by one month of euthymia to reduce the likelihood that event rates were confounded by residual or prodromal symptoms of a mood episode. BSD participants who did not experience prospective episodes (n = 21; 14.4%) were included in the episode-free control period analyses, but not in the pre-episode period analyses.

Selection of the observation period for normal control participants was identical to the selection process used for the BSD participants' within-subjects control period (i.e., using midpoint of study participation). In this way, I was able to examine base rates of life events during the following four periods: (1) prior to depressive episodes in BSD participants; (2) prior to (hypo)manic episodes in BSD participants; (3) during an episode-free control period in BSD participants; and (4) during an analogous one-month period in normal controls.

Given that life stress researchers have yet to converge upon a theory-driven or empirically validated index of life stress, I adopted a dual approach to quantifying event levels for some analyses. In the first approach, the number of major and minor events were summed and analyzed separately, yielding categories of major negative, minor negative, major BAS-activating, minor BAS-activating, major BAS-deactivating, minor BAS-deactivating, major SRD, and minor SRD events. In the second approach, analyses predicted the single highest COSR experienced by the participant during each observation period. For example, a participant who experienced three events with COSRs of 1, one event with a COSR of 2, and two events with a COSR of 3, would receive a highest severity score of 3. Such scores were derived for the categories of negative, positive, BAS-activating, BAS-deactivating, and SRD events. Using both quantification approaches facilitated an examination of whether the event-episode relationship was driven by the *number* of events experienced, or by the *highest severity* of individual events experienced. For highest severity analyses, event categories were collapsed across major and minor categorizations to predict across the entire spectrum of COSRs.

A subset of participants did not experience intervals that would qualify for a particular observation period. Given this, analyses differed in sample size according to the particular observation period(s) examined. Among bipolar spectrum participants, 56.8% (n = 83) had at least one depressive episode that was preceded by 30 days of euthymia, and 54.8% (n = 80) had at least one (hypo)manic episode that was preceded by 30 days of euthymia. Most bipolar spectrum participants (80.8%; n = 118) were included in analyses of one or both episode polarities, and almost all (95.2%; n = 139) had a valid within-subjects episode-free control period. Only 30.8% (n = 45) of BSD participants had intervals that qualified for all three

observation periods. All normal control participants (n = 132) experienced an interval of time that qualified as a control period.

For all event categories, independent *t*-tests indicated that there were no significant differences between bipolar II and cyclothymia/bipolar NOS participants in daily rates (magnitude of all t's ≤ 0.72, all p's $\geq .47$) or in any of the three 30-day periods (pre-depression, pre-(hypo)mania, control; magnitude of all t's ≤ 1.63, all p's $\geq .11$). Therefore, BSD participants were considered to comprise a single group in all analyses.

Hypothesis 1: Life Events in Bipolar Spectrum vs. Normal Control Participants

Hypothesis 1 was that BSD participants would experience higher 30-day sums (Hypothesis 1a) and higher event severity ratings (Hypothesis 1b) prior to mood episodes, compared to normal control participants during an analogous one-month interval. I expected that event levels (30-day sums in Hypothesis 1a and highest severity ratings in Hypothesis 1b) would be similar between the BSD episode-free period and the normal control participant interval. Independent *t*-tests were used to examine group differences in life events across the various index periods.

Hypothesis 1a: Between-group comparisons of 30-day sums. Table 7 presents means, standard deviations, and statistical comparisons of 30-day event sums for BSD and normal control participants. Consistent with hypotheses, BSD participants demonstrated higher 30-day sums of multiple life event types in the interval prior to depression, compared to normal control participants. As expected, this finding held for major negative and minor negative, major BAS-deactivating and minor BAS-deactivating, and minor SRD events. Unexpectedly, BSD participants also had higher rates of major BAS-activating and minor BAS-activating events (at a

trend level) prior to depression. Rates of major positive, minor positive, and major SRD events were similar across the two groups.

Comparisons were also performed of BSD 30-day sums prior to (hypo)mania vs. 30-day sums for normal control participants. As expected, BSD participants had higher 30-day sums for minor negative, minor positive, minor BAS-activating, and minor SRD events. Contrary to hypotheses, BSD participants also had more minor BAS-deactivating events prior to (hypo)mania, as compared to normal control participants. Also unexpectedly, normal control participants experienced more major SRD events than did BSD participants in the 30 days prior to (hypo)mania. Of note, rates of SRD events in general were substantially lower than rates of other event types, with a large percentage of participants reporting no SRD events during the various observation periods. Analyses of SRD events should be interpreted cautiously.

When comparing BSD and control participants during the 30-day episode-free observation periods, BSD participants experienced higher rates of major negative, minor negative, minor BAS-activating, major BAS-deactivating, minor BAS-deactivating, and minor SRD events. These findings were inconsistent with the hypothesis that the two groups would have similar 30-day sums during episode-free periods.

Hypothesis 1b: Between-group comparisons of highest severity ratings. Table 8 presents means, standard deviations, and statistical comparisons of highest contextualized objective severity ratings (COSRs). Compared with normal controls, BSD participants experienced a higher severity of negative, BAS-deactivating, and BAS-activating events prior to depressive episodes. BSD participants experienced a higher severity of BAS-activating events, but a lower severity of SRD events, prior to (hypo)manic episodes. Finally, in comparing BSD episode-free periods to an analogous interval in normal controls, BSD participants experienced a higher

severity of negative, BAS-activating, and BAS-deactivating events. These latter findings were inconsistent with the hypothesis that the two groups would have similar COSRs during episode-free periods.

Hypothesis 2: Life Events within Bipolar Spectrum Participants

The second study hypothesis predicted that within BSD participants, event levels would be higher in the pre-episode periods, as compared to the within-subjects episode-free control period. Paired (within-subjects) *t*-tests were conducted to contrast rates of life events across pre-depression, pre-(hypo)mania, and BSD control periods. Paired *t*-tests were considered preferable to repeated-measures ANOVAs because the latter type of analysis could only accommodate participants who had valid intervals for all three observation periods ($n = 45$). Utilizing paired *t*-tests, sample sizes were as follows: $n = 81$ for comparing events in pre-depression vs. episode-free control periods; $n = 75$ for comparing events in pre-(hypo)mania vs. episode-free control periods; and $n = 45$ for comparing events in pre-depression vs. pre-(hypo)mania periods.

Hypothesis 2a: Within-group comparisons of 30-day sums. Table 7 also presents means and standard deviations for BSD participants' 30-day sums across the various observation periods. For major BAS-deactivating and major SRD events, rates were higher prior to depression than prior to (hypo)mania, at a difference approaching statistical significance ($t(44) = 1.78$, $p = .08$; and $t(44) = 1.85$, $p = .07$, respectively). For minor negative and minor BAS-deactivating events, rates were higher prior to (hypo)mania than during control periods ($t(74) = 2.19$, $p = .03$; and $t(74) = 2.23$, $p = .03$, respectively). All other within-group comparisons of 30-day sums were nonsignificant (magnitude of all t's ≤ 1.66, all p's $> .10$).

Hypothesis 2b: Within-group comparisons of highest severity ratings. Table 8 also presents means and standard deviations for BSD participants' highest COSRs across the various

observation periods. Paired *t*-tests indicated that for SRD events, COSRs were significantly higher prior to depression than during the control period ($t(80) = 2.91$, $p = .005$) and marginally higher prior to depression than prior to (hypo)mania ($t(44) = -1.73$, $p = .09$). Other within-group analyses of highest COSRs exhibited trends. Specifically, there was a higher severity of negative events and of BAS-deactivating events prior to depression than prior to (hypo)mania ($t(44) = -1.70$, $p < .10$; and $t(44) = -1.70$, $p < .10$, respectively). Participants experienced a marginally higher severity of positive events prior to (hypo)mania, relative to episode-free control periods ($t(74) = 1.73$, $p = .09$). All other paired *t*-test analyses showed no significant within-subjects differences or trends in COSRs across observation periods (magnitude of all t's ≤ 1.54, all p's $\geq .13$).

Table 7. Hypotheses 1a and 2a: Sum of Life Events in 30 Days Prior to Depression, 30 Days Prior to (Hypo)mania, and Episode-Free Control Period, in Bipolar Spectrum Participants vs. Normal Controls

	Control Participants (n = 132)	Bipolar Spectrum Participants			BSD Pre-Depression vs. Normal Control (n = 215)			BSD Pre-Hypo vs. Normal Control (n = 212)			BSD Episode-free vs. Normal Control (n = 271)		
		Pre-Depression (n = 83)	Pre-Hypomania (n = 80)	Episode-free (n = 139)									
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*t*	df	*p*	*t*	df	*p*	*t*	df	*p*
Major Negative	0.40 (0.77)	1.02 (1.45)	0.59 (0.96)	0.70 (1.12)	-3.37	117	.001	-1.37	145	.17	-2.61	245	.01
Minor Negative	2.17 (4.17)	5.60 (6.91)	6.90 (11.07)	4.31 (6.31)	-3.42	114	.001	-3.43	96	.001	-3.31	241	.001
Major Positive	0.48 (0.95)	0.46 (0.82)	0.35 (0.56)	0.43 (0.86)	0.37	213	.71	1.03	203	.30	0.51	269	.61
Minor Positive	2.96 (4.04)	3.23 (3.82)	5.11 (6.35)	3.27 (4.63)	-0.31	213	.76	-2.37	112	.02	-0.58	269	.56
Major BAS-A	0.71 (1.44)	1.17 (1.66)	0.70 (1.20)	0.95 (1.57)	-2.05	154	.04	-0.09	210	.93	-1.31	269	.19
Minor BAS-A	3.32 (6.00)	4.96 (6.15)	6.47 (10.86)	6.44 (10.71)	-1.88	213	.06	-2.32	106	.02	-2.98	219	.003
Major BAS-D	0.75 (1.47)	2.08 (2.99)	1.06 (1.70)	1.39 (2.23)	-3.51	108	.001	-1.26	154	.21	-2.82	240	.005
Minor BAS-D	3.02 (5.51)	7.51 (9.43)	9.28 (14.98)	5.76 (8.48)	-3.27	108	.001	-3.43	95	.001	-3.17	238	.005
Major SRD	0.08 (0.32)	0.16 (0.44)	0.00 (0.04)	0.09 (0.37)	-1.58	127	.12	2.27	175	.02	-0.22	269	.82
Minor SRD	0.23 (0.84)	0.75 (1.43)	0.92 (2.01)	0.68 (1.66)	-2.14	126	.03	-2.34	103	.02	-2.85	207	.005

Note: Means represent sum of events in the specified 30-day period; SD = Standard Deviation; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting.

Table 8. Hypotheses 1b and 2b: Highest Contextualized Objective Severity Ratings (COSRs) in 30 Days Prior to Depression, 30 Days Prior to (Hypo)mania, and 30-day Episode-free Control Period, in Bipolar Spectrum Participants vs. Normal Controls

	Control Participants (n = 132)	Bipolar Spectrum Participants			BSD Pre-Depression vs. Normal Control (n = 215)			BSD Pre-Hypo vs. Normal Control (n = 212)			BSD Episode-free vs. Normal Control (n = 271)		
		Pre-Depression (n = 83)	Pre-Hypomania (n = 80)	Episode-free (n = 139)									
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*t*	df	*p*	*t*	df	*p*	*t*	df	*p*
Negative	1.32 (1.13)	1.98 (1.10)	1.63 (1.07)	1.65 (1.12)	-4.24	213	<.001	-1.50	179	.14	-2.35	269	.02
Positive	1.12 (0.93)	1.20 (0.82)	1.30 (0.89)	1.10 (0.90)	-0.95	213	.34	-1.60	210	.11	-0.10	269	.92
BAS-A	1.33 (1.10)	1.89 (1.13)	1.64 (1.07)	1.59 (1.12)	-4.02	212	<.001	-2.26	178	.02	-2.74	268	.006
BAS-D	1.36 (1.12)	1.98 (1.10)	1.63 (1.07)	1.65 (1.11)	-3.90	213	<.001	-1.43	178	.16	-2.35	269	.02
SRD	0.62 (0.91)	1.34 (1.18)	0.84 (1.01)	0.84 (1.03)	-0.88	207	.38	3.13	204	.002	-1.12	269	.26

Note. Means represent the highest contextualized objective severity rating (COSR) experienced during the specified 30-day period; SD = Standard Deviation; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting.

Test of the Kindling Hypothesis: Frequency of Life Events

The remaining analyses in the present study included BSD participants only. In the second group of analyses, I examined the frequency component of the kindling model. The index episodes used for this group of analyses were the same as those used to test Hypotheses 1 and 2. The main predictor variable was the number of episodes occurring prior to the index episode, and the main criterion variable was event levels. Event levels were again operationalized using (1) separate sums for major and minor events and (2) the highest COSR experienced during the interval.

Hierarchical linear regression analyses were conducted to examine whether the number of lifetime episodes significantly predicted 1) major and minor event levels or 2) highest COSR during the pre-episode and episode-free control periods. The first step of the model consisted of control variables (see below), and the second step of the model consisted of the number of lifetime mood episodes.

To account for individual differences in baseline event levels, I included average daily event scores of the corresponding event type as a covariate in the models. By including individualized average daily event levels, I was able to conduct a more idiographically sensitive analysis of the frequency of life events prior to episode onset. For all models, the following covariates were also considered for inclusion in the model: BDI and HMI scores during the 30-day period; age at study entry; age at initial episode onset; years since diagnosis; and BAS or SRM-T scores, as relevant. In most cases, only daily event rates and/or BDI/HMI scores were significant in the models. All other potential covariates were nonsignificant and frequently produced an unacceptable level of multicollinearity (as defined by a conditioning index greater

than 30, coupled with variance proportions above .50 for at least two different variables; Tabachnick & Fidell, 2007). Thus, they were not included in the final models.

Demographic variables shown to be associated with study variables of interest (see preliminary analyses section) were also considered for inclusion in the model. These were either nonsignificant in the regression models or did not change the outcome of the analysis. Inclusion of significant BDI/HMI covariates also did not change the outcome of analyses, with few exceptions as noted below. Thus, only daily event rates were included as covariates in the final models presented.

Hypothesis 3: Pre-episode Event Frequencies

The third study hypothesis specified that the number of prior affective episodes would predict pre-episode event levels in BSD participants. Specifically, more previous episodes would be associated with fewer major events, more minor events, and a lower maximum severity rating (COSR) during the pre-episode periods.

Hypothesis 3a: Lifetime episodes predicting event sums in the 30 days prior to episode. Table 9 presents results of multiple linear regression analyses examining the relationship between lifetime history of depression and 30-day sums of life events prior to prospectively assessed depression. Controlling for average daily event levels, more lifetime depressive episodes predicted a higher frequency of minor negative events prior to depressive episodes ($p < .05$), and tended to predict a higher frequency of minor BAS-deactivating events. In all other cases, the number of lifetime depressive episodes failed to prospectively predict event frequencies prior to episodes of depression. This finding held regardless of whether or not analyses controlled for significant BDI and HMI scores.

Table 9 also presents results of multiple linear regression analyses examining the relationship between prior episodes of hypomania and 30-day sums of life events prior to prospectively assessed (hypo)mania. Of note, the frequency of major SRD events prior to (hypo)mania was not analyzed, because too few participants endorsed such events. Controlling for average daily event levels, more lifetime hypomanic episodes predicted a higher frequency of minor positive events and minor SRD events, and tended to predict a lower frequency of major negative events in the month prior to (hypo)mania. The relationship between lifetime hypomanic episodes and pre-(hypo)mania major negative events was no longer significant after controlling for HMI scores, which were themselves significant in the model. In all other cases, the number of lifetime hypomanic episodes failed to predict event frequencies prior to prospective (hypo)manic episodes.

Table 9. Hypothesis 3a: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Sum of Events in 30 Days Prior to Depression or (Hypo)mania

	Depression (n = 83)				(Hypo)mania (n = 80)			
Predictor	*B*	S. E. *B*	β	*t*	*B*	S. E. *B*	β	*t*
Major Negative								
Step 1								
Daily Major Negative	14.13	9.96	.16	1.42	27.23	6.28	.45	4.34**
Step 2								
Daily Major Negative	13.84	10.08	.16	1.37	26.45	6.21	.43	4.26**
Lifetime Episodes	0.02	0.10	.03	0.26	-0.12	0.07	-.18	-1.76^
Minor Negative								
Step 1								
Daily Minor Negative	17.38	4.99	.36	3.48**	46.82	6.09	.67	7.69**
Step 2								
Daily Minor Negative	16.48	4.90	.35	3.36**	46.25	6.06	.66	7.63**
Lifetime Episodes	0.86	0.40	.22	2.15*	0.67	0.47	.12	1.44
Major Positive								
Step 1								
Daily Major Positive	14.92	8.30	.20	1.80^	-1.78	5.02	-.04	-0.36
Step 2								
Daily Major Positive	14.22	8.50	.19	1.67^	-2.85	5.03	-.07	-0.57
Lifetime Episodes	0.02	0.06	.05	0.43	0.06	0.04	.17	1.49
Minor Positive								
Step 1								
Daily Minor Positive	12.72	3.55	.37	3.58**	6.89	3.79	.21	1.82^
Step 2								
Daily Minor Positive	12.52	3.52	.37	3.56**	6.49	3.65	.19	1.78^
Lifetime Episodes	0.38	0.25	.16	1.54	0.95	0.36	.29	2.67**
Major BAS-Activating								
Step 1								
Daily Major BAS-A	9.59	9.15	.12	1.05	14.87	6.39	.26	2.33*
Step 2								
Daily Major BAS-A	8.01	9.25	.10	0.87	15.60	6.40	.28	2.44*
Lifetime Episodes	0.13	0.12	.13	1.11	-0.11	0.09	-.14	-1.21
Minor BAS-Activating								
Step 1								
Daily Minor BAS-A	10.59	3.91	.29	2.71**	21.05	4.53	.48	4.65**
Step 2								
Daily Minor BAS-A	9.90	3.92	.27	2.52*	20.31	4.59	.47	4.42**
Lifetime Episodes	0.53	0.39	.15	1.38	0.51	0.52	.10	0.99
Major BAS-Deactivating								
Step 1								
Daily Major BAS-D	14.00	11.57	.14	1.21	23.22	5.74	.42	4.05**
Step 2								
Daily Major BAS-D	12.97	11.60	.13	1.12	22.73	5.69	.41	3.99**
Lifetime Episodes	0.22	0.21	.12	1.05	-0.19	0.12	-.16	-1.54
Minor BAS-Deactivating								
Step 1								
Daily Minor BAS-D	11.42	4.39	.28	2.60*	52.79	6.86	.67	7.70**
Step 2								
Daily Minor BAS-D	10.80	4.34	.27	2.49*	51.83	6.87	.66	7.54**
Lifetime Episodes	0.86	0.48	.19	1.77^	0.96	0.76	.11	1.27

Table 9 Continued. Hypothesis 3a: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Sum of Events in 30 Days Prior to Depression or (Hypo)mania

	Depression (n = 83)				(Hypo)mania (n = 80)			
Predictor	*B*	S. E. *B*	β	*t*	*B*	S. E. *B*	β	*t*
Major SRD								
Step 1								
Daily Major SRD	27.98	14.57	.21	1.92^	--	--	--	--
Step 2								
Daily Major SRD	27.99	14.66	.21	1.91^	--	--	--	--
Lifetime Episodes	0.00	0.03	-.01	-0.11	--	--	--	--
Minor SRD								
Step 1								
Daily Minor SRD	14.09	4.28	.34	3.29**	9.90	5.59	.20	1.77^
Step 2								
Daily Minor SRD	14.11	4.31	.34	3.28**	8.18	5.47	.17	1.49
Lifetime Episodes	0.01	0.09	.02	0.15	0.27	0.11	.26	2.36*

Note. Depression: Major negative: Step 1 $F = 2.02$, $R^2 = .03$; Step 2 $F = 1.03$, $\Delta F = 0.07$, $R^2 = .03$, $\Delta R^2 < .01$; Minor negative: Step 1 $F = 12.12$**, $R^2 = .18$; Step 2 $F = 8.64$**, $\Delta F = 4.62$*, $R^2 = .18$, $\Delta R^2 = .05$; Major positive: Step 1 $F = 3.23$^, $R^2 = .04$; Step 2 $F = 1.69$, $\Delta F = 0.18$, $R^2 = .04$, $\Delta R^2 < .01$; Minor positive: Step 1 $F = 12.84$**, $R^2 = .14$; Step 2 $F = 7.73$**, $\Delta F = 2.39$, $R^2 = .17$, $\Delta R^2 = .03$; Major BAS-Activating: Step 1 $F = 1.10$, $R^2 = .02$; Step 2 $F = 1.17$, $\Delta F = 1.24$, $R^2 = .03$, $\Delta R^2 = .02$; Minor BAS-Activating: Step 1 $F = 7.33$**, $R^2 = .09$; Step 2 $F = 4.66$*, $\Delta F = 1.90$, $R^2 = .11$, $\Delta R^2 = .02$; Major BAS-Deactivating: Step 1 $F = 1.47$, $R^2 = .02$; Step 2 $F = 1.29$, $\Delta F = 1.11$, $R^2 = .03$, $\Delta R^2 = .01$; Minor BAS-Deactivating: Step 1 $F = 6.77$*, $R^2 = .08$; Step 2 $F = 5.04$**, $\Delta F = 3.13$^, $R^2 = .12$, $\Delta R^2 = .04$; Major SRD: Step 1 $F = 3.69$^, $R^2 = .04$; Step 2 $F = 1.83$, $\Delta F = 0.01$, $R^2 = .04$, $\Delta R^2 < .01$; Minor SRD: Step 1 $F = 10.85$**, $R^2 = .12$; Step 2 $F = 5.37$**, $\Delta F = 0.02$, $R^2 = .12$, $\Delta R^2 < .01$. (Hypo)mania: Major negative: Step 1 $F = 18.81$**, $R^2 = .20$; Step 2 $F = 11.22$**, $\Delta F = 3.10$^, $R^2 = .23$, $\Delta R^2 = .03$; Minor negative: Step 1 $F = 59.10$**, $R^2 = .45$; Step 2 $F = 31.02$**, $\Delta F = 2.06$, $R^2 = .47$, $\Delta R^2 = .02$; Major positive: Step 1 $F = 0.13$, $R^2 = .03$; Step 2 $F = 1.17$, $\Delta F = 2.21$, $R^2 = .17$, $\Delta R^2 = .03$; Minor positive: Step 1 $F = 3.30$^, $R^2 = .04$; Step 2 $F = 5.34$**, $\Delta F = 7.11$**, $R^2 = .13$, $\Delta R^2 = .09$; Major BAS-Activating: Step 1 $F = 5.41$*, $R^2 = .07$; Step 2 $F = 3.45$*, $\Delta F = 1.46$, $R^2 = .09$, $\Delta R^2 = .02$; Minor BAS-Activating: Step 1 $F = 21.59$**, $R^2 = .23$; Step 2 $F = 11.28$**, $\Delta F = 0.98$, $R^2 = .24$, $\Delta R^2 = .01$; Major BAS-Deactivating: Step 1 $F = 16.39$**, $R^2 = .18$; Step 2 $F = 9.52$**, $\Delta F = 2.36$, $R^2 = .20$, $\Delta R^2 = .03$; Minor BAS-Deactivating: Step 1 $F = 59.24$**, $R^2 = .45$; Step 2 $F = 30.68$**, $\Delta F = 1.62$, $R^2 = .46$, $\Delta R^2 = .01$; Major SRD: Not computed; Minor SRD: Step 1 $F = 3.14$^, $R^2 = .04$; Step 2 $F = 4.45$*, $\Delta F = 5.57$*, $R^2 = .11$, $\Delta R^2 = .07$. *$p < .05$; **$p < .01$; ^$p < .10$

Hypothesis 3b: Lifetime episodes predicting highest severity ratings in the 30 days prior to episode. Linear regression analyses were conducted to test whether lifetime history of episodes predicted the highest "severity" (according to COSRs) event experienced during each 30-day observation period. Linear regression models were considered preferable over ordinal logistic regression models for several reasons. First, ordinal logistic models use maximum likelihood estimates, which generally requires a larger sample size compared to ordinary least squares regression. Second, small or empty cells in ordinal logistic regressions can cause the model to become unstable; thus, in some cases, the COSR scale would need to be collapsed.

Table 10 presents results of linear regression analyses in which the number of lifetime episodes was used to predict the highest COSR occurring within the 30 days prior to prospective onset of depression and (hypo)mania. After controlling for average daily event rates, more lifetime hypomanic episodes predicted a higher COSR in the positive event category, prior to prospectively assessed (hypo)mania. None of the other models examining lifetime episodes and COSRs were significant. This pattern of findings held regardless of whether or not analyses controlled for daily event levels and BDI/HMI.

Table 10. Hypothesis 3b: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Highest Contextualized Objective Severity Rating (COSR) in 30 Days Prior to Depression or (Hypo)mania

	Depression (n = 83)				(Hypo)mania (n = 80)			
Predictor	*B*	S. E. *B*	β	*t*	*B*	S. E. *B*	β	*t*
Negative								
Step 1								
Daily Negative Events	0.39	0.99	.04	0.39	3.32	0.89	.39	3.72**
Step 2								
Daily Negative Events	0.54	1.02	.06	0.53	3.26	0.90	.39	3.62**
Lifetime Episodes	-0.06	0.08	-.08	-0.73	0.06	0.08	.08	0.74
Positive								
Step 1								
Daily Positive Events	-0.35	0.80	-.05	-0.43	0.61	0.75	.09	0.81
Step 2								
Daily Positive Events	-0.43	0.80	-.06	-0.54	0.51	0.73	.08	0.71
Lifetime Episodes	0.06	0.06	.11	1.01	0.18	0.07	.27	2.40*
BAS-Activating								
Step 1								
Daily BAS-Activating Events	0.25	0.62	.05	0.41	1.78	0.53	.36	3.33**
Step 2								
Daily BAS-Activating Events	0.27	0.63	.05	0.43	1.67	0.54	.33	3.08**
Lifetime Episodes	-0.02	0.08	-.03	-0.26	0.09	0.08	.12	1.10
BAS-Deactivating								
Step 1								
Daily BAS-Deactivating Events	-0.12	0.57	-.02	-0.22	2.33	0.56	.43	4.13**
Step 2								
Daily BAS-Deactivating Events	-0.06	0.58	-.01	-0.11	2.30	0.57	.42	4.00**
Lifetime Episodes	-0.04	0.08	-.06	-0.54	0.03	0.08	.04	0.37
SRD								
Step 1								
Daily SRD Events	2.02	2.89	.08	0.70	8.02	2.24	.38	3.59**
Step 2								
Daily SRD Events	1.92	2.90	.07	0.66	7.77	2.24	.37	3.46**
Lifetime Episodes	-0.06	0.08	-.08	-0.67	0.08	0.08	.12	1.10

Note. Depression: Negative: Step 1 $F = 0.15$, $R^2 = .09$; Step 2 $F = 0.34$, $\Delta F = 0.53$, $R^2 = .09$, $\Delta R^2 < .01$; Positive: Step 1 $F = 0.19$, $R^2 < .01$; Step 2 $F = 0.60$, $\Delta F = 1.01$, $R^2 = .02$, $\Delta R^2 = .01$; BAS-Activating: Step 1 $F = 0.17$, $R^2 < .01$; Step 2 $F = 0.12$, $\Delta F = 0.07$, $R^2 < .01$, $\Delta R^2 < .01$; BAS-Deactivating: Step 1 $F = 0.05$, $R^2 < .01$; Step 2 $F = 0.17$, $\Delta F = 0.29$, $R^2 < .01$, $\Delta R^2 < .01$; SRD: Step 1 $F = 0.49$, $R^2 < .01$; Step 2 $F = 0.47$, $\Delta F = 0.45$, $R^2 = .01$, $\Delta R^2 = .01$. (Hypo)mania: Negative: Step 1 $F = 13.83$**, $R^2 = .16$; Step 2 $F = 7.15$**, $\Delta F = 0.55$, $R^2 = .16$, $\Delta R^2 = .01$; Positive: Step 1 $F = 0.66$, $R^2 = .01$; Step 2 $F = 3.23$*, $\Delta F = 5.76$*, $R^2 = .08$, $\Delta R^2 = .07$; BAS-Activating: Step 1 $F = 11.08$**, $R^2 = .13$; Step 2 $F = 6.16$**, $\Delta F = 1.22$, $R^2 = .14$, $\Delta R^2 = .01$; BAS-Deactivating: Step 1 $F = 17.09$**, $R^2 = .19$; Step 2 $F = 8.52$**, $\Delta F = 0.14$, $R^2 = .19$, $\Delta R^2 < .01$; SRD: Step 1 $F = 12.88$**, $R^2 = .15$; Step 2 $F = 7.06$**, $\Delta F = 1.21$, $R^2 = .16$, $\Delta R^2 = .01$. *$p < .05$; **$p < .01$; ^$p < .10$

Hypothesis 4: Control Period Event Frequencies

The fourth study hypothesis specified that the number of prior affective episodes would predict event levels in the within-subjects control periods. Specifically, more previous episodes would be associated with fewer major events, fewer minor events, and a lower maximum severity rating (COSR) during the within-subjects episode-free control period.

For linear regression analyses examining the relationship between lifetime episodes and frequency of events in an episode-free control period, both lifetime depression and hypomania were entered into the model. The number of episodes was recoded, and univariate and multivariate outliers were addressed as described above (maximum multivariate outliers removed = 6). Multicollinearity was a potential concern, given the correlation between lifetime depression and lifetime hypomania ($r = .48$, $p < .01$). Based on criteria specified by Tabachnick and Fidell (2007), models were examined for (1) condition indices greater than 30, and (2) two or more variables with variance proportions greater than .5. Severe multicollinearity was not apparent in any of the models.

Hypothesis 4a: Lifetime episodes predicting event sums in the episode-free control period. Results of multiple linear regression analyses examining the relationship between prior history of episodes and 30-day sums of life events during a within-subjects episode-free control period are presented in Table 11. During the episode-free control period, more previous depressive episodes predicted a lower frequency of major SRD events, at a level approaching statistical significance ($p = .08$). In all other models, there was no relationship between lifetime depressive or hypomanic episodes and the frequency of life events during control periods. Again, results examining major SRD events should be interpreted cautiously.

Table 11. Hypothesis 4a: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Sum of Events in a 30-Day Within-Subjects Control Period

	Episode-free Control Period (n = 139)			
Predictor	*B*	S. E. *B*	β	*t*
Major Negative				
Step 1				
Daily Major Negative	13.78	5.14	.23	2.68**
Step 2				
Daily Major Negative	14.07	5.11	.23	2.76**
Lifetime hypomanic episodes	-0.04	0.07	-.06	-0.57
Lifetime depressive episodes	-0.09	0.06	-.15	-1.47
Minor Negative				
Step 1				
Daily Minor Negative	25.94	2.88	.62	9.01**
Step 2				
Daily Minor Negative	26.28	2.91	.62	9.05**
Lifetime hypomanic episodes	0.09	0.28	.02	0.31
Lifetime depressive episodes	-0.31	0.27	-.09	-1.13
Major Positive				
Step 1				
Daily Major Positive	17.07	5.19	.28	3.29**
Step 2				
Daily Major Positive	16.86	5.32	.27	3.17**
Lifetime hypomanic episodes	0.00	0.04	.00	-0.04
Lifetime depressive episodes	0.01	0.04	.02	0.20
Minor Positive				
Step 1				
Daily Minor Positive	17.01	3.43	.40	4.96**
Step 2				
Daily Minor Positive	16.94	3.49	.40	4.85**
Lifetime hypomanic episodes	-0.22	0.27	-.08	-0.82
Lifetime depressive episodes	0.22	0.27	.08	0.84
Major BAS-Activating				
Step 1				
Daily Major BAS-A	9.97	6.05	.14	1.65
Step 2				
Daily Major BAS-A	10.92	6.10	.16	1.79^
Lifetime hypomanic episodes	-0.01	0.09	-.02	-0.15
Lifetime depressive episodes	-0.09	0.09	-.11	-1.03
Minor BAS-Activating				
Step 1				
Daily Minor BAS-A	26.01	3.91	.50	6.65**
Step 2				
Daily Minor BAS-A	26.41	4.01	.51	6.59**
Lifetime hypomanic episodes	-0.31	0.56	-.05	-0.54
Lifetime depressive episodes	-0.06	0.55	-.01	-0.11

Table 11 Ctd. Hypothesis 4a: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Sum of Events in 30-Day Within-Subjects Control Period

	Episode-free Control Period (n = 139)			
Predictor	*B*	S. E. *B*	β	*t*
Major BAS-Deactivating				
Step 1				
Daily Major BAS-D	16.49	5.18	.27	3.19**
Step 2				
Daily Major BAS-D	17.38	5.11	.28	3.40**
Lifetime hypomanic episodes	-0.16	0.13	-.12	-1.24
Lifetime depressive episodes	-0.15	0.13	-.12	-1.21
Minor BAS-Deactivating				
Step 1				
Daily Minor BAS-D	18.08	2.54	.53	7.12**
Step 2				
Daily Minor BAS-D	18.34	2.58	.54	7.10**
Lifetime hypomanic episodes	0.12	0.38	.03	0.32
Lifetime depressive episodes	-0.32	0.36	-.08	-0.88
Major SRD				
Step 1				
Daily Major SRD	5.99	6.45	.08	0.93
Step 2				
Daily Major SRD	5.22	6.43	.07	0.81
Lifetime hypomanic episodes	0.01	0.01	.06	0.62
Lifetime depressive episodes	-0.02	0.01	-.18	-1.77^
Minor SRD				
Step 1				
Daily Minor SRD	22.37	3.07	.54	7.29
Step 2				
Daily Minor SRD	23.27	3.08	.56	7.55
Lifetime hypomanic episodes	-0.02	0.06	-.02	-0.28
Lifetime depressive episodes	-0.10	0.06	-.13	-1.56

Note. Major negative: Step 1 $F = 7.20$**, $R^2 = .05$; Step 2 $F = 3.99$**, $\Delta F = 2.32$, $R^2 = .08$, $\Delta R^2 = .03$; Minor negative: Step 1 $F = 81.21$**, $R^2 = .38$; Step 2 $F = 27.39$**, $\Delta F = 0.67$, $R^2 = .39$, $\Delta R^2 < .01$; Major positive: Step 1 $F = 10.84$**, $R^2 = .08$; Step 2 $F = 3.57$*, $\Delta F = 0.02$, $R^2 = .08$, $\Delta R^2 < .01$; Minor positive: Step 1 $F = 24.56$**, $R^2 = .16$; Step 2 $F = 8.43$**, $\Delta F = 0.46$, $R^2 = .16$, $\Delta R^2 < .01$; Major BAS-Activating: Step 1 $F = 2.72$, $R^2 = .02$; Step 2 $F = 1.50$, $\Delta F = 0.89$, $R^2 = .03$, $\Delta R^2 = .01$; Minor BAS-Activating: Step 1 $F = 44.16$**, $R^2 = .25$; Step 2 $F = 14.72$**, $\Delta F = 0.25$, $R^2 = .25$, $\Delta R^2 < .01$; Major BAS-Deactivating: Step 1 $F = 10.15$**, $R^2 = .07$; Step 2 $F = 5.59$**, $\Delta F = 3.15$*, $R^2 = .11$, $\Delta R^2 = .04$; Minor BAS-Deactivating: Step 1 $F = 50.68$**, $R^2 = .28$; Step 2 $F = 17.00$**, $\Delta F = 0.40$, $R^2 = .28$, $\Delta R^2 < .01$; Major SRD: Step 1 $F = 0.87$, $R^2 < .01$; Step 2 $F = 1.37$, $\Delta F = 1.62$, $R^2 = .03$, $\Delta R^2 = .02$; Minor SRD: Step 1 $F = 53.16$**, $R^2 = .29$; Step 2 $F = 19.26$**, $\Delta F = 1.94$, $R^2 = .31$, $\Delta R^2 = .02$. *$p < .05$; **$p < .01$; ^$p < .10$

Hypothesis 4b: Lifetime episodes predicting highest severity ratings in the episode-free control period. Table 12 presents results of linear regression analyses in which the number of lifetime episodes is used to predict the highest COSR occurring within the control period. After controlling for average daily event rates, lifetime history of episodes failed to predict COSRs in any event category. This pattern of findings held regardless of whether or not analyses controlled for daily event levels and BDI/HMI.

Table 12. Hypothesis 4b: Linear Regression Models Among Bipolar Spectrum Participants, with Lifetime History of Episodes Predicting Highest Contextualized Objective Severity Rating (COSR) in an Episode-free Control Period

	Episode-free control period (n = 139)			
	B	S. E. *B*	β	*t*
Negative				
Step 1				
Daily Negative Events	1.53	0.61	.21	2.50*
Step 2				
Daily Negative Events	1.62	0.62	.22	2.61*
Lifetime Depression	-0.08	0.07	-.11	-1.14
Lifetime Hypomania	0.00	0.07	.00	0.00
Positive				
Step 1				
Daily Positive Events	0.62	0.62	.09	1.01
Step 2				
Daily Positive Events	0.60	0.62	.08	0.96
Lifetime Depression	-0.06	0.06	-.10	-1.05
Lifetime Hypomania	0.08	0.06	.13	1.31
BAS-Activating				
Step 1				
Daily BAS-Activating Events	0.83	0.45	.16	1.86^
Step 2				
Daily BAS-Activating Events	0.92	0.46	.17	2.02*
Lifetime Depression	-0.06	0.07	-.08	-0.81
Lifetime Hypomania	-0.02	0.07	-.03	-0.34
BAS-Deactivating				
Step 1				
Daily BAS-Deactivating Events	1.05	0.43	.21	2.45*
Step 2				
Daily BAS-Deactivating Events	1.11	0.44	.22	2.54*
Lifetime Depression	-0.08	0.07	-.11	-1.13
Lifetime Hypomania	0.01	0.07	.01	0.09
SRD				
Step 1				
Daily SRD Events	7.45	1.68	.36	4.43**
Step 2				
Daily SRD Events	7.70	1.70	.37	4.54**
Lifetime Depression	-0.06	0.06	-.08	-0.89
Lifetime Hypomania	-0.03	0.06	-.04	-0.44

Note. Negative: Step 1 $F = 6.24$*, $R^2 = .04$; Step 2 $F = 2.65$^, $\Delta F = 0.86$, $R^2 = .06$, $\Delta R^2 = .01$; Positive: Step 1 $F = 1.01$, $R^2 = .01$; Step 2 $F = 0.99$, $\Delta F = 0.98$, $R^2 = .02$, $\Delta R^2 = .01$; BAS-Activating: Step 1 $F = 3.46$^, $R^2 = .03$; Step 2 $F = 1.61$, $\Delta F = 0.69$, $R^2 = .04$, $\Delta R^2 = .01$; BAS-Deactivating: Step 1 $F = 5.98$*, $R^2 = .04$; Step 2 $F = 2.50$, $\Delta F = 0.78$, $R^2 = .05$, $\Delta R^2 = .01$; SRD: Step 1 $F = 19.59$**, $R^2 = .13$; Step 2 $F = 7.11$**, $\Delta F = 0.89$, $R^2 = .14$, $\Delta R^2 = .01$. *$p < .05$; **$p < .01$; ^$p < .10$

Test of the kindling hypothesis: Impact of life events

Analyses of the impact of life events were performed using summed event scores only. The impact of life events was examined through a series of survival analyses, using Cox proportional hazards regressions (Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008). This technique is similar to a logistic regression, but accommodates censored data and analyzes the time to events rather than the simple occurrence of events.[2] All BSD participants (n = 146) were included in this group of analyses. Models were specified separately for major and minor event types, to adequately disentangle putative sensitization and autonomy processes. Thus, I examined whether the interaction of major events and previous episodes predicted time to new prospective episodes, and then examined whether the interaction of minor events and previous episodes predicted time to new prospective episodes.

The first step of each model consisted of any covariates that represented potential confounds (see covariates specified in frequency analyses). The second step contained the number of previous episodes, as well as the number of events experienced during the interval preceding episode onset. Only events occurring prior to the onset of the first prospective episode (depression or (hypo)mania, depending on the specific model) were included when calculating the main event level variable. The life event variable was operationalized as life events per day, up until the first prospective episode of each polarity (i.e., sum of events between baseline and onset, divided by number of days between baseline and onset). The final step contained the main predictor of interest, which was the interaction between number of events and number of previous episodes. Any significant interaction terms were further examined via a stratified Cox

[2] Of note, in survival analysis, all predictor variables are termed "covariates," whether they are control variables or the main predictors of interest.

regression, in which I fit separate survival curves for participants in the upper and lower distributions of prior lifetime episodes.

This model was used to determine the hazard rates and ratios associated with each covariate predicting time to onset of depressive or (hypo)manic episodes. A hazard rate at a given point in time is the probability of an episode onset in that time period, assuming survival without an episode up to that point in time. A hazard ratio for a continuous covariate (e.g., number of previous episodes) is the ratio of the hazard rate given a one unit increase in that covariate, to the hazard rate without this increase (Garson, 2010). In other words, the hazard ratio tells the odds of an episode occurring faster or slower as a function of the covariate. A hazard ratio not significantly different from 1.0 indicates that the covariate is not strongly affecting the time to/likelihood of episode occurrence (the hazard rate). The statistical significances of the overall models were examined using the likelihood ratio test (i.e., *-2 log likelihood; -2LL).*

Although Cox regressions are robust to non-normality and are capable of accounting for censored data, the technique assumes the proportionality of hazards, i.e., that covariates do not vary systematically with time (Tabachnick & Fidell, 2007). To determine whether the proportionality of hazards assumption was met, I first ran Cox regressions with time-dependent covariates that represented the interaction of time and each variable of interest. A significant time-by-covariate interaction term would indicate a violation of the assumption of proportionality of hazards. In most cases, the models did not violate the proportional hazards assumption. Thus, it was unnecessary to conceptualize life events as segmented time-dependent covariates. Rather, life events were treated as time-independent covariates when entered into the final Cox regression models. In the following four models, however, the proportionality of hazards assumption was violated: 1) minor positive events predicting to depression; 2) major

negative events predicting to (hypo)mania; 3) major BAS-activating events predicting to (hypo)mania; and 4) major BAS-deactivating events predicting to (hypo)mania. To address this, I included a time-event interaction term in the survival analysis. Inclusion of this time-event interaction term changed neither the pattern nor the significance of results. Thus, the time-event interaction terms were not included in the final Cox regression models presented.

All analyses controlled for average depression and hypomanic symptom levels throughout the prospective time to episode onset. As would be expected, higher average BDI scores predicted a shorter time to onset of depression in all models. Higher HMI scores predicted shorter time to onset of (hypo)mania in all models examining major events, and tended to predict shorter time to onset in models examining minor negative, minor BAS-deactivating, and minor SRD events. In the remainder of the analyses, HMI scores were significant when entered into step 1 of the model, but were nonsignificant predictors in the final Cox regression models. I did not control for average daily event rates in the context of survival analyses, because these would be too closely related to the covariate representing life events prior to episode onset.

Hypothesis 5: Relationship between lifetime episodes and time to prospective onset of mood episodes. The fifth hypothesis was that BSD participants with a greater number of lifetime episodes would demonstrate a shorter time to new prospective episodes. Results of Cox regression analyses examining the relationship between lifetime episodes and time to prospective onset of episodes are presented in Tables 13 (for major events) and 14 (for minor events). For all models except that examining major positive events, a higher number of previous depressive episodes predicted a shorter time to new onset of depression. In the Cox regression model examining major positive events, lifetime depressive episodes predicted shorter time to depression onset when initially entered into the model (step 2), but this covariate became

nonsignificant in the final model (step 3). Contrary to expectation, the number of lifetime episodes of hypomania failed to predict time to onset of new prospective (hypo)manic episodes in any models.

Hypothesis 6: Relationship between life events and time to prospective onset of mood episodes. The sixth hypothesis was that higher major and minor event levels would predict shorter time to onset of new prospective episodes. Results of Cox regression analyses examining the relationship between life events and time to prospective onset of episodes are presented in Tables 13 (for major events) and 14 (for minor events). Contrary to prediction, there was no main effect of life events in any of the final depression models. Interestingly, a different pattern emerged among (hypo)mania models. In all minor event categories, more life events predicted shorter time to onset of (hypo)mania (all p's $<.05$, except in the minor positive event model, in which $p < .10$). In major event categories, all event types but positive were also significantly associated with time to onset of (hypo)mania. However, in these cases, more life events predicted a significantly longer time to (hypo)manic episode onset. This finding was inconsistent with study hypotheses.

Hypothesis 7: Test of the kindling hypothesis: Moderating effects of lifetime episodes on impact of life events. In line with a stress sensitization hypothesis, the seventh hypothesis stated that the number of lifetime episodes would moderate the effect of events on time to episode recurrence, such that the impact of major and minor events would increase as the number of previous episodes increases. In other words, as the number of previous episodes increases, both major and minor events were expected to produce higher hazard ratios. Thus, the main covariate of interest was the interaction between number of previous lifetime episodes and the number of life events prior to prospective onset of episodes.

Results of these analyses are presented in Tables 13 (for major events) and 14 (for minor events). One interaction term was statistically significant at a trend level: lifetime depression by minor SRD events (final overall model $-2LL = 938.99$, $\chi^2(5) = 30.56$, $p < .001$). Figure 1 (p. 75) presents Cox regression models of minor SRD events predicting time to depression onset, stratified by number of past depressive episodes. This stratified model indicates that individuals in the upper distribution of the number of lifetime depressive episodes relapsed more quickly following minor SRD events, as compared to those in the lower distribution of previous depressive episodes. Thus, as the number of lifetime depressive episodes increased, the impact of minor SRD events tended to increase also. Inconsistent with study hypotheses, history of depressive episodes did not interact with any other category of life events to predict time to onset of prospective depressive episodes. In other words, the impact of other life event types did not differ according to previous history of episodes. Although the depression by events interaction terms were nonsignificant, overall depression models were significant. In all omnibus tests of coefficients for final cox proportional hazards models, $-2LL \geq 705.68$, $\chi^2(5) \geq 19.56$, and $p \leq .002$.

With respect to (hypo)mania models, there was a significant interaction between lifetime history of hypomanic episodes and the number of major negative events (final overall model $-2LL = 626.08$, $\chi^2(5) = 10.42$, $p = .06$). A stratified survival curve suggested an increased hazard ratio associated with major negative events for participants with a higher number of previous hypomanic episodes. This is consistent with the idea that the impact of major negative events increases as the number of previous hypomanic episodes increases. A similar pattern emerged among major BAS-activating and major BAS-deactivating events, although these interaction terms were marginally significant (final overall model $-2LL = 627.03$, $\chi^2(5) = 9.64$, $p = .09$; and

final overall model -*2LL* = 625.87, $\chi^2(5) = 10.52$, $p = .06$, respectively). Thus, greater previous episodes were associated with a higher impact of major negative events, and tended to be associated with a higher impact of major BAS-activating and major BAS-deactivating events. Figures 2 (p. 76), 3 (p. 77), and 4 (p. 78) present Cox regression models of major negative, major BAS-activating, and major BAS-deactivating events, respectively, predicting time to (hypo)mania onset and stratified by number of past hypomanic episodes. Those participants in the upper distribution of the number of past hypomanic episodes relapsed more quickly following each of these three event types, as compared to those BSD participants in the lower distribution of past hypomanic episodes. This is somewhat consistent with stress sensitization, in that the impact of major events is hypothesized to increase as the course of the disorder progresses. Whereas study hypotheses predicted this finding among major negative and major BAS-activating events, the finding among major BAS-deactivating events was unexpected. Moreover, there was no evidence of an increased impact of minor events as well, which represents an important component of the stress sensitization model.

Although remaining event categories did not significantly interact with lifetime episodes to predict time to episode onset, omnibus tests of final model coefficients indicated that overall, the pre-(hypo)mania minor negative event model was statistically significant (-*2LL* = 597.77, $\chi^2(5) = 14.44$, $p = .01$). The pre-(hypo)mania minor BAS-activating event model was marginally significant at a trend level (-*2LL* = 600.41, $\chi^2(5) = 10.37$, $p = .07$), as was the pre-(hypo)mania minor SRD event model (-*2LL* = 600.99, $\chi^2(5) = 10.55$, $p = .06$). The remaining pre-(hypo)mania models (major positive, minor positive, and major SRD) were statistically non-significant overall (-*2LL* $\leq$ 605.48, $\chi^2(5) \leq 8.65$, $p \geq .12$).

Table 13. Hypotheses 5, 6, And 7: Cox Regression Models of Major Events Interacting with History of Episodes to Predict Time to Onset of Prospective Episodes

	Depression (n = 146)							(Hypo)mania (n = 146)						
						95% CI							95% CI	
Predictor	B	S.E. B	Wald	*P*	OR	Lower	Upper	B	S.E. B	Wald	*P*	OR	Lower	Upper
Negative Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	9.44	**.00**	1.04	1.01	1.07	0.01	0.01	0.16	.69	1.01	0.98	1.03
HMI	0.00	0.02	0.01	.90	1.00	0.97	1.03	0.04	0.02	4.96	**.03**	1.04	1.00	1.08
Episodes	0.06	0.02	12.06	**.00**	1.06	1.03	1.09	0.00	0.00	0.10	.75	1.00	1.00	1.00
Negative Events	0.72	6.36	0.01	.91	2.05	0.00	5.4E+05	-13.74	8.12	2.86	.09	0.00	0.00	8.83
Step 3														
BDI	0.04	0.01	9.59	**.00**	1.04	1.01	1.07	0.01	0.01	0.15	.70	1.01	0.98	1.03
HMI	0.00	0.02	0.00	.98	1.00	0.97	1.03	0.04	0.02	6.32	**.01**	1.05	1.01	1.08
Episodes	0.05	0.02	6.97	**.01**	1.05	1.01	1.09	0.00	0.00	0.20	.66	1.00	1.00	1.00
Negative Events	-5.45	11.45	0.23	.63	0.00	0.00	2.4E+07	-19.44	9.25	4.41	**.04**	0.00	0.00	0.27
Episodes x Neg. Events	0.75	1.09	0.48	.49	2.12	0.25	17.93	0.08	0.04	3.94	**.05**	1.09	1.00	1.18
Positive Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	10.05	**.00**	1.04	1.02	1.07	0.00	0.01	0.01	.93	1.00	0.98	1.03
HMI	0.00	0.02	0.05	.82	1.00	0.96	1.03	0.03	0.02	3.71	**.05**	1.04	1.00	1.07
Episodes	0.06	0.02	11.47	**.00**	1.06	1.02	1.09	0.00	0.00	0.20	.66	1.00	1.00	1.00
Positive Events	6.14	9.10	0.46	.50	464.19	0.00	2.6E+10	-2.38	9.71	0.06	.81	0.09	0.00	1.7E+07
Step 3														
BDI	0.04	0.01	8.97	**.00**	1.04	1.01	1.07	0.00	0.01	0.01	.92	1.00	0.98	1.03
HMI	0.00	0.02	0.01	.91	1.00	0.96	1.03	0.03	0.02	3.71	**.05**	1.04	1.00	1.07
Episodes	0.04	0.03	2.47	.12	1.05	0.99	1.11	0.00	0.00	0.00	.97	1.00	1.00	1.00
Positive Events	-2.73	19.84	0.02	.89	0.07	0.00	5.1E+15	-3.60	10.44	0.12	.73	0.03	0.00	2.1E+07
Episodes x Pos. Events	1.00	1.94	0.26	.61	2.71	0.06	121.49	0.03	0.09	0.11	.74	1.03	0.87	1.22
BAS-Activating Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	9.91	**.00**	1.04	1.02	1.07	0.00	0.01	0.02	.88	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.96	1.00	0.97	1.03	0.04	0.02	5.20	**.02**	1.04	1.01	1.08
Episodes	0.06	0.02	12.24	**.00**	1.06	1.03	1.09	0.00	0.00	0.09	.76	1.00	1.00	1.00
BAS-Activating Events	-1.27	5.23	0.06	.81	0.28	0.00	7.9E+03	-9.61	6.08	2.50	.11	0.00	0.00	10.04
Step 3														
BDI	0.04	0.01	9.72	**.00**	1.04	1.01	1.07	0.00	0.01	0.06	.81	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.98	1.00	0.97	1.03	0.05	0.02	6.62	**.01**	1.05	1.01	1.09
Episodes	0.05	0.03	4.31	**.04**	1.06	1.00	1.11	0.00	0.00	0.37	.55	1.00	1.00	1.00
BAS-Activating Events	-2.87	9.03	0.10	.75	0.06	0.00	2.7E+06	-14.19	6.86	4.29	**.04**	0.00	0.00	0.47
Episodes x BAS-A. Events	0.21	0.97	0.05	.83	1.24	0.19	8.27	0.07	0.04	3.58	.06	1.07	1.00	1.15

Table 13 Continued. Hypotheses 5, 6, And 7: Cox Regression Models of Major Events Interacting with History of Episodes to Predict Time to Onset of Prospective Episodes

	Depression (n = 146)							(Hypo)mania (n = 146)						
						95% CI							95% CI	
Predictor	B	S.E. B	Wald	*P*	OR	Lower	Upper	B	S.E. B	Wald	*p*	OR	Lower	Upper
BAS-Deactivating Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	9.28	**.00**	1.04	1.01	1.07	0.01	0.01	0.16	.68	1.01	0.98	1.03
HMI	0.00	0.02	0.02	.88	1.00	.97	1.03	0.04	0.02	5.05	**.02**	1.04	1.01	1.08
Episodes	0.06	0.02	11.99	**.00**	1.06	1.03	1.09	0.00	0.00	0.10	.75	1.00	1.00	1.00
BAS-Deactivating Events	1.01	3.37	0.09	.76	2.75	0.00	2.0E+03	-7.52	4.17	3.25	.07	0.00	0.00	1.91
Step 3														
BDI	0.04	0.01	9.39	**.00**	1.04	1.01	1.07	0.00	0.01	0.14	.71	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.97	1.00	0.97	1.03	0.05	0.02	6.36	**.01**	1.05	1.01	1.08
Episodes	0.05	0.02	6.65	**.01**	1.05	1.01	1.09	0.00	0.00	0.24	.63	1.00	1.00	1.00
BAS-Deactivating Events	-1.73	5.83	0.09	.77	0.18	0.00	1.6E+04	-10.10	4.69	4.64	**.03**	0.00	0.00	0.40
Episodes x BAS-D. Events	0.35	0.57	0.37	.54	1.42	0.46	4.35	0.05	0.02	3.50	.06	1.05	1.00	1.10
SRD Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	9.79	**.00**	1.04	1.02	1.07	0.00	0.01	0.01	.93	1.00	0.98	1.03
HMI	0.00	0.02	0.01	.92	1.00	0.97	1.03	0.04	0.02	4.23	**.04**	1.04	1.00	1.07
Episodes	0.06	0.02	12.09	**.00**	1.06	1.03	1.09	0.00	0.00	0.55	.46	1.00	1.00	1.00
SRD Events	-0.49	32.61	0.00	.99	0.61	0.00	3.5E+27	-141.87	68.91	4.24	**.04**	0.00	0.00	0.00
Step 3														
BDI	0.04	0.01	10.13	**.00**	1.04	1.02	1.07	0.00	0.01	0.02	.88	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.95	1.00	0.97	1.03	0.04	0.02	4.31	**.04**	1.04	1.00	1.07
Episodes	0.07	0.02	8.15	**.00**	1.07	1.02	1.12	0.00	0.00	0.08	.78	1.00	1.00	1.00
SRD Events	28.56	53.51	0.28	.59	2.5E+12	0.00	9.0E+57	-159.30	76.05	4.39	**.04**	0.00	0.00	0.00
Episodes x SRD Events	-3.99	5.98	0.44	.51	0.02	0.00	2.3E+03	0.19	0.29	0.43	.51	1.21	0.68	2.16

Note. BDI = average weekly Beck Depression Inventory score from baseline to first onset of episode; HMI = average weekly Halberstadt Mania Inventory score from baseline to first onset of episode; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting.

Table 14. Hypotheses 5, 6, And 7: Cox Regression Models of Minor Events Interacting With History of Episodes to Predict Time to Onset of Prospective Episodes

	Depression (n = 146)							(Hypo)mania (n = 146)						
						95% CI							95% CI	
Predictor	B	S.E. B	Wald	*P*	OR	Lower	Upper	B	S.E. B	Wald	*p*	OR	Lower	Upper
Negative Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	10.58	**.00**	1.04	1.02	1.07	0.00	0.01	0.11	.73	1.00	0.98	1.03
HMI	0.00	0.02	0.04	.84	1.00	0.96	1.03	0.03	0.02	3.22	.07	1.03	1.00	1.07
Episodes	0.06	0.02	10.60	**.00**	1.06	1.02	1.09	0.00	0.00	0.00	.97	1.00	1.00	1.00
Negative Events	0.82	0.49	2.86	.09	2.27	0.88	5.90	1.12	0.37	9.08	**.00**	3.06	1.48	6.34
Step 3														
BDI	0.04	0.01	8.42	**.00**	1.04	1.01	1.07	0.00	0.01	0.04	.84	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.96	1.00	0.97	1.04	0.03	0.02	3.00	.08	1.03	1.00	1.07
Episodes	0.04	0.02	3.83	**.05**	1.04	1.00	1.09	0.00	0.00	0.34	.56	1.00	1.00	1.00
Negative Events	-0.61	1.20	0.26	.61	0.54	0.05	5.66	1.21	0.39	9.54	**.00**	3.37	1.56	7.28
Episodes x Neg. Events	0.15	0.11	1.85	.17	1.16	0.94	1.44	0.00	0.00	0.42	.52	1.00	0.99	1.01
Positive Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	10.22	**.00**	1.04	1.02	1.07	0.01	0.01	0.19	.66	1.01	0.98	1.03
HMI	0.00	0.02	0.03	.87	1.00	0.96	1.03	0.03	0.02	2.27	.13	1.03	0.99	1.06
Episodes	0.06	0.02	11.40	**.00**	1.06	1.02	1.09	0.00	0.00	0.13	.71	1.00	1.00	1.00
Positive Events	0.67	0.80	0.70	.40	1.95	0.41	9.34	1.31	0.77	2.87	.09	3.72	0.81	16.98
Step 3														
BDI	0.04	0.01	9.29	**.00**	1.04	1.01	1.07	0.01	0.01	0.18	.67	1.01	0.98	1.03
HMI	0.00	0.02	0.01	.91	1.00	0.96	1.03	0.03	0.02	2.29	.13	1.03	0.99	1.07
Episodes	0.05	0.03	4.47	**.03**	1.05	1.00	1.11	0.00	0.00	0.07	.80	1.00	1.00	1.01
Positive Events	-0.01	3.30	0.00	1.00	0.99	0.00	634.52	1.34	0.79	2.84	.09	3.81	0.80	18.08
Episodes x Pos. Events	0.08	0.35	0.05	.83	1.08	0.54	2.16	0.00	0.01	0.02	.89	1.00	0.97	1.02
BAS-Activating Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	10.94	**.00**	1.04	1.02	1.07	0.01	0.01	0.18	.67	1.01	0.98	1.03
HMI	0.00	0.02	0.07	.79	1.00	0.96	1.03	0.03	0.02	2.99	.08	1.03	1.00	1.07
Episodes	0.06	0.02	10.69	**.00**	1.06	1.02	1.09	0.00	0.00	0.00	.99	1.00	1.00	1.00
BAS-Activating Events	1.07	0.57	3.57	.06	2.92	0.96	8.85	1.06	0.49	4.71	**.03**	2.89	1.11	7.51
Step 3														
BDI	0.04	0.01	9.48	**.00**	1.04	1.01	1.07	0.00	0.01	0.06	.81	1.00	0.98	1.03
HMI	0.00	0.02	0.01	.92	1.00	0.96	1.03	0.03	0.02	2.47	.12	1.03	0.99	1.07
Episodes	0.05	0.02	6.12	**.01**	1.05	1.01	1.09	0.00	0.00	0.75	.39	1.00	1.00	1.00
BAS-Activating Events	0.20	1.28	0.02	.88	1.22	0.10	15.03	1.30	0.53	6.02	**.01**	3.69	1.30	10.46
Episodes x BAS-A. Events	0.08	0.11	0.61	.43	1.09	0.88	1.34	0.00	0.00	0.94	.33	1.00	0.99	1.00

Table 14 Continued. Hypotheses 5, 6, And 7: Cox Regression Models of Minor Events Interacting with History of Episodes to Predict Time to Onset of Prospective Episodes

	Depression (*n* = 146)							(Hypo)mania (*n* = 146)						
						95% CI							95% CI	
Predictor	B	S.E. B	Wald	*p*	OR	Lower	Upper	B	S.E. B	Wald	*p*	OR	Lower	Upper
BAS-Deactivating Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	10.51	**.00**	1.04	1.02	1.07	0.00	0.01	0.12	.73	1.00	0.98	1.03
HMI	0.00	0.02	0.02	.88	1.00	0.97	1.03	0.03	0.02	3.56	.06	1.03	1.00	1.07
Episodes	0.06	0.02	10.88	**.00**	1.06	1.02	1.09	0.00	0.00	0.00	.97	1.00	1.00	1.00
BAS-Deactivating Events	0.52	0.36	2.09	.15	1.68	0.83	3.38	0.77	0.26	8.61	**.00**	2.17	1.29	3.63
Step 3														
BDI	0.04	0.01	8.26	**.00**	1.04	1.01	1.07	0.00	0.01	0.03	.86	1.00	0.98	1.03
HMI	0.00	0.02	0.00	.94	1.00	0.97	1.04	0.03	0.02	3.25	.07	1.03	1.00	1.07
Episodes	0.04	0.02	4.03	**.04**	1.04	1.00	1.09	0.00	0.00	0.60	.44	1.00	1.00	1.00
BAS-Deactivating Events	-0.56	0.86	0.42	.52	0.57	0.11	3.10	0.87	0.28	9.74	**.00**	2.38	1.38	4.09
Episodes x BAS-D. Events	0.11	0.08	2.03	.15	1.12	0.96	1.31	0.00	0.00	0.74	.39	1.00	0.99	1.00
SRD Events														
Step 1														
BDI	0.03	0.01	8.08	**.00**	1.04	1.01	1.06	0.00	0.01	0.02	.90	1.00	0.98	1.03
HMI	-0.01	0.02	0.13	.72	0.99	0.96	1.03	0.03	0.02	3.81	**.05**	1.03	1.00	1.07
Step 2														
BDI	0.04	0.01	9.67	**.00**	1.04	1.01	1.07	0.00	0.01	0.00	.96	1.00	0.97	1.03
HMI	0.00	0.02	0.02	.87	1.00	0.97	1.03	0.03	0.02	3.31	.07	1.03	1.00	1.07
Episodes	0.06	0.02	11.63	**.00**	1.06	1.02	1.09	0.00	0.00	0.03	.87	1.00	1.00	1.00
SRD Events	1.01	2.06	0.24	.62	2.75	0.05	154.65	2.79	1.19	5.50	**.02**	16.34	1.58	168.58
Step 3														
BDI	0.04	0.01	8.38	**.00**	1.04	1.01	1.07	0.00	0.01	0.00	.98	1.00	0.97	1.03
HMI	0.00	0.02	0.02	.88	1.00	0.97	1.04	0.03	0.02	3.00	.08	1.03	1.00	1.07
Episodes	0.05	0.02	6.33	**.01**	1.05	1.01	1.09	0.00	0.00	0.28	.60	1.00	1.00	1.00
SRD Events	-7.74	5.80	1.78	.18	0.00	0.00	37.69	2.53	1.27	3.97	**.05**	12.57	1.04	151.48
Episodes x SRD Events	0.71	0.41	3.01	.08	2.03	0.91	4.53	0.01	0.02	0.45	.50	1.01	0.98	1.05

Note. BDI = average weekly Beck Depression Inventory score from baseline to first onset of episode; HMI = average weekly Halberstadt Mania Inventory score from baseline to first onset of episode; BAS-A = BAS-activating; BAS-D = BAS-deactivating; SRD = social rhythm disrupting.

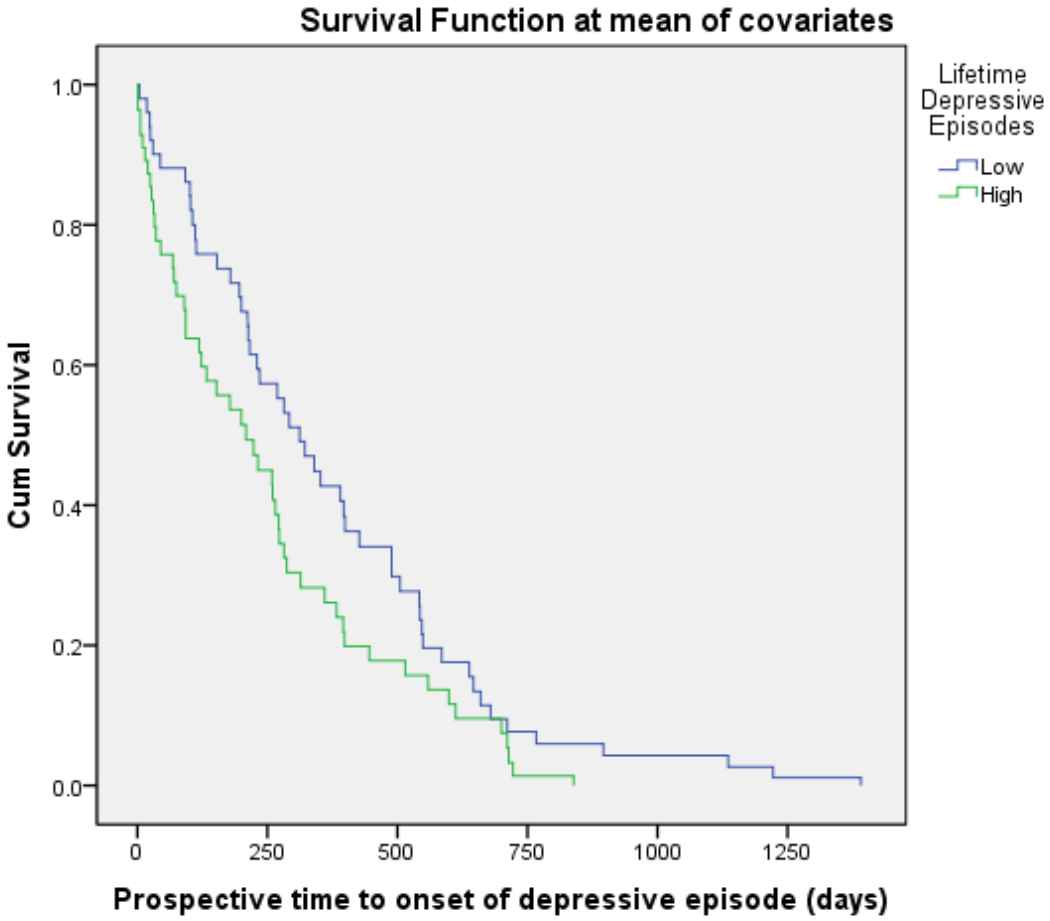

Figure 1. Time to First Prospective Depressive Episode as a Function of Minor SRD Events, Controlling for Depressive and Hypomanic Symptoms

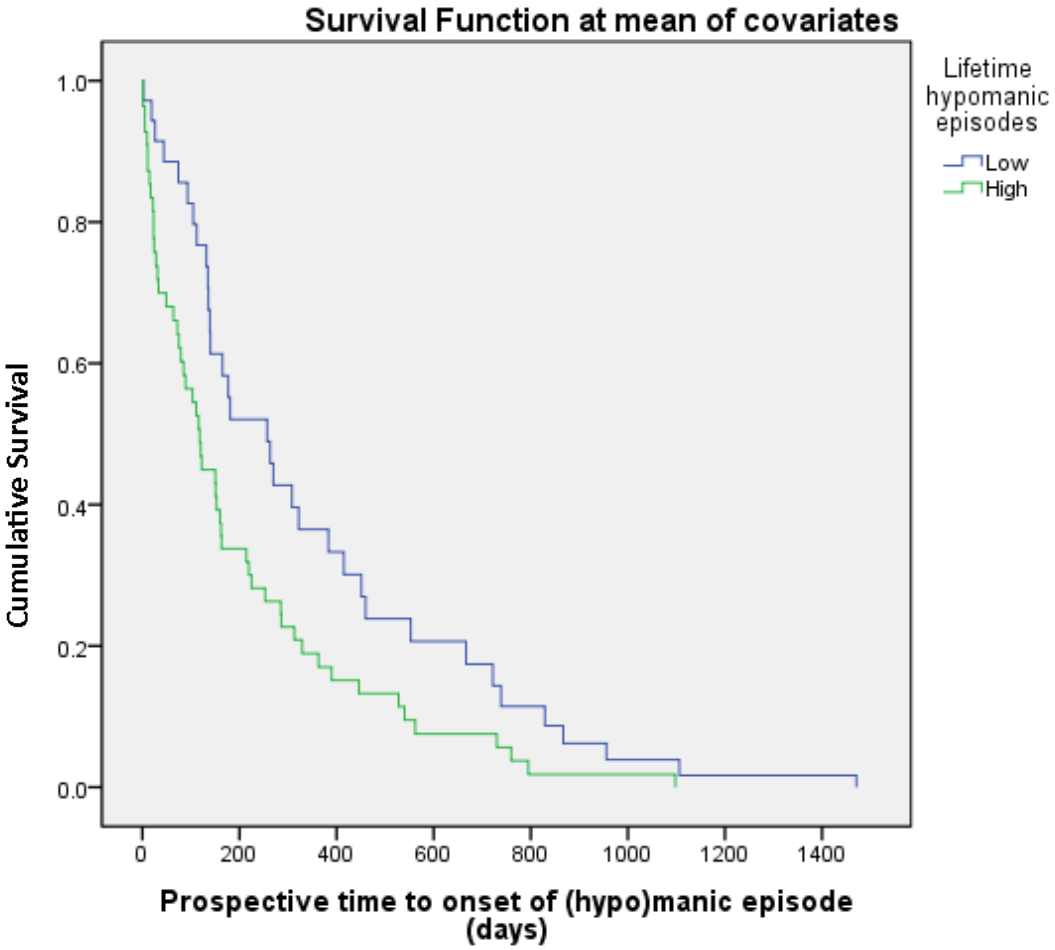

Figure 2. Time to First Prospective (Hypo)manic Episode as a Function of Major Negative Events, Controlling for Depressive and Hypomanic Symptoms

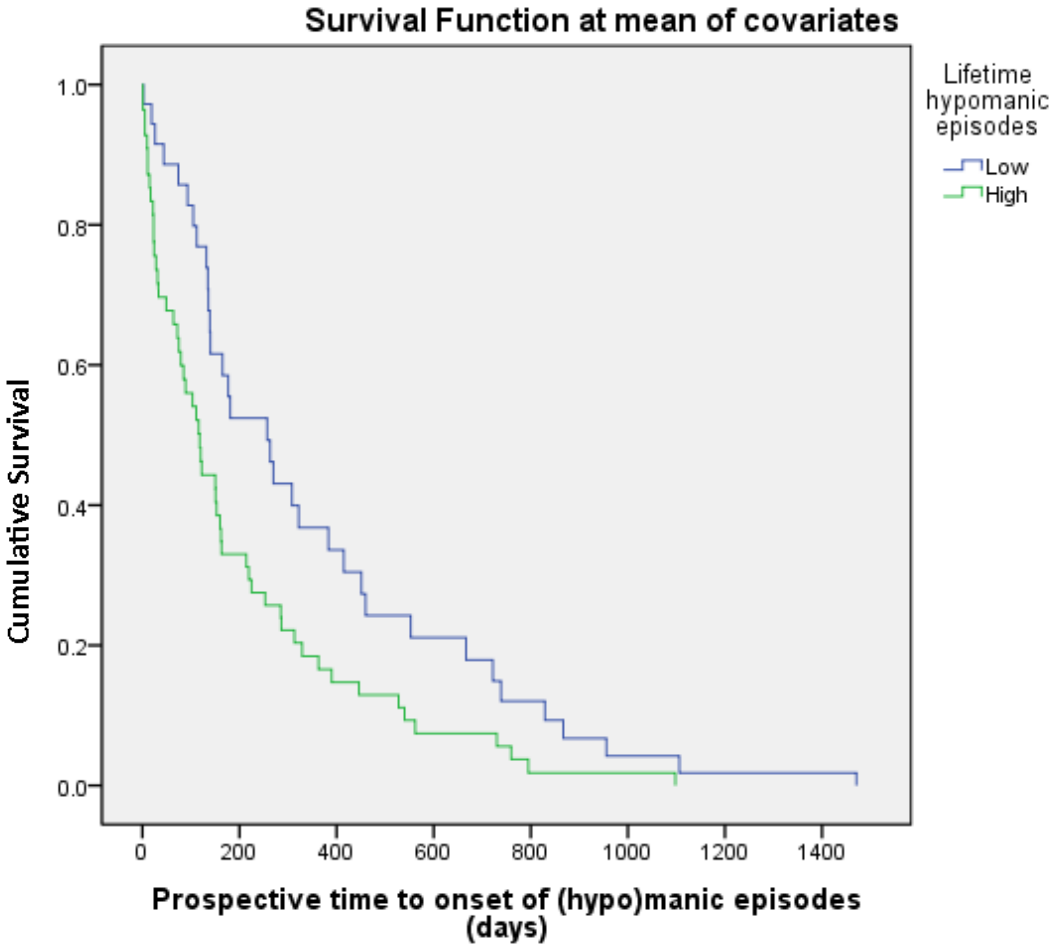

Figure 3. Time to First Prospective (Hypo)manic Episode as a Function of Major BAS-activating Events, Controlling for Depressive and Hypomanic Symptoms

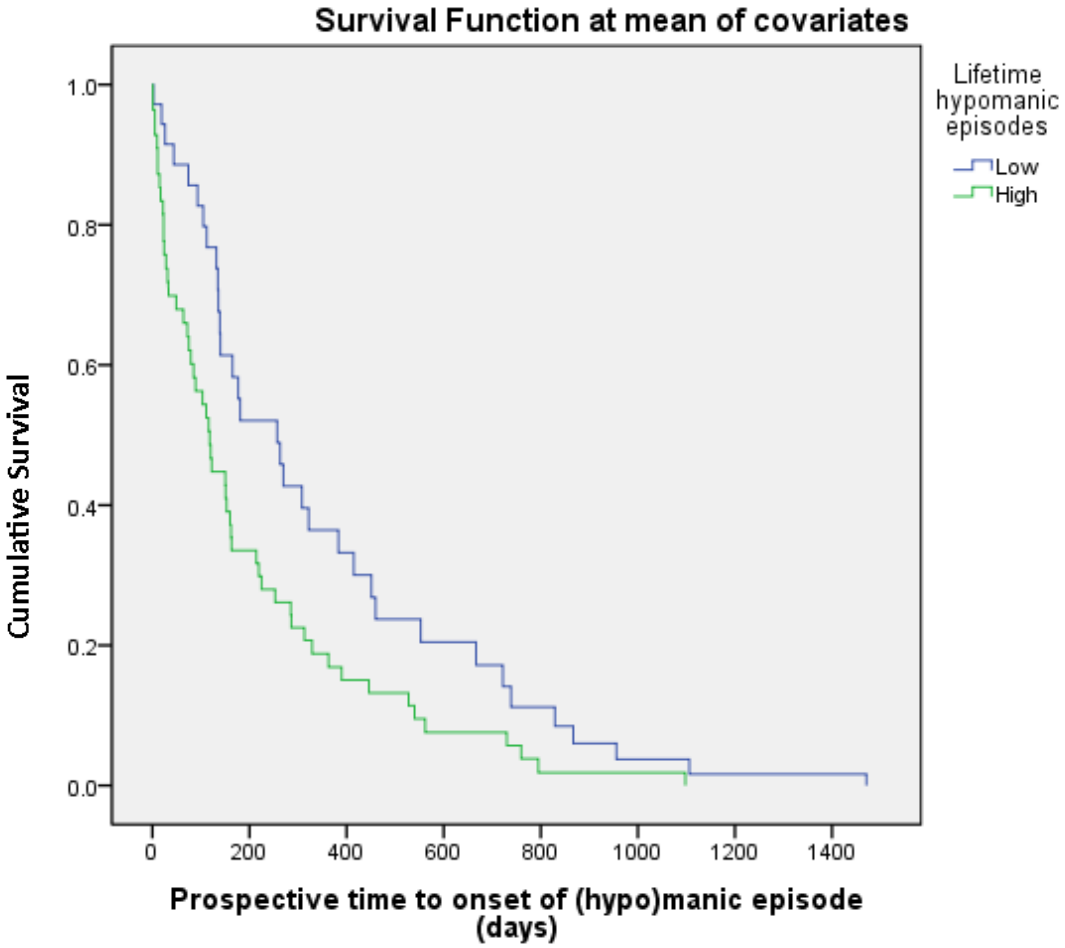

Figure 4. Time to First Prospective (Hypo)manic Episode as a Function of Major BAS-deactivating Events, Controlling for Depressive and Hypomanic Symptoms

CHAPTER 5

DISCUSSION

Summary and Conclusions

The present study aimed to conduct a more comprehensive and precise examination of the kindling effect as it applies to BSD, thereby allowing for a direct comparison of sensitization and autonomy models. With respect to diagnostic group differences, I expected that BSD participants would have higher pre-episode event levels as compared to normal control participants, but similar event levels to those exhibited during extended periods of euthymia. Within BSD participants, I hypothesized that event levels would be higher before episodes than during a within-subjects episode-free control period. Regarding tests of main hypotheses, I predicted that results would align with a stress sensitization rather than a stress autonomy model. That is, as the number of previous episodes increased, I predicted a decreased frequency of major events, an increased frequency of minor events, and an increased impact of both major and minor events. I also predicted that more previous episodes would be associated with a lower event severity rating in all BSD index periods (pre-depression, pre-hypomania, and control). Effects were predicted to be polarity- and event type-specific: depressive episodes would be associated with negative, BAS-deactivating, and SRD events, whereas (hypo)manic episodes would be associated with negative, positive, BAS-activating, and SRD events.

Findings from the present study were mixed with respect to their support for study hypotheses. Regarding diagnostic group differences in event rates, BSD participants generally experienced more events than normal control participants. Prior to depression, BSD participants experienced more negative events (major and minor), BAS-deactivating events (major and minor), BAS-activating events (significantly more major and marginally more minor), and SRD

events (minor only). These findings were expected in the categories of negative, BAS-deactivating, and SRD events, but not in the BAS-activating category. Pre-depression BSD participants also had higher COSRs for negative, BAS-deactivating, and BAS-activating events. Again, these findings were expected for negative and BAS-deactivating event categories, but not for the BAS-activating category.

Prior to (hypo)mania, BSD participants experienced more major SRD events and more events in all minor categories (minor SRD, minor negative, minor positive, minor BAS-activating, and minor BAS-deactivating). Pre-(hypo)mania BSD participants also had higher COSRs for BAS-activating events, and lower COSRs for SRD events. The finding that BSD participants experienced a lower severity of SRD events prior to (hypo)mania (compared to normal control participants) was inconsistent with study hypotheses and with the extant literature (see Grandin et al., 2006). This unexpected finding may be related to the fact that rates of SRD events among both diagnostic groups were substantially lower than rates of any other event categories. It is possible that the method of SRD measurement utilized in the present study may not be optimal for use with an undergraduate population. In particular, undergraduates are likely to have social rhythm patterns that are less regular than either younger participants (e.g., individuals in high school) or working non-students. Disruptions in social rhythm may therefore be less salient and more difficult for undergraduates to recall over a period of several months.

When comparing the BSD 30-day episode-free period to an analogous 30-day period in normal controls, BSD participants experienced significantly higher rates of negative (major and minor), BAS-activating (minor), BAS-deactivating (major and minor), and SRD events (minor). Similarly, BSD participants experienced a higher severity of events during their control periods as compared to normal participants, for negative, BAS-activating, and BAS-deactivating events.

Within the BSD group, participants were expected to experience a greater number and a higher severity of events during pre-episode periods, compared to the control period. Consistent with hypotheses, minor negative events were more frequent, and positive events tended to be more "severe," prior to (hypo)mania than during the control period. Contrary to expectation, minor BAS-deactivating events were also more frequent prior to (hypo)mania compared to during a control period; the expanded BAS dysregulation theory predicts that BAS-activating events are more likely to occur prior to (hypo)mania than are BAS-deactivating events. The severity of SRD events was higher prior to depression than during the episode-free control period, but no event category sums differed across the pre-depression vs. episode-free periods.

Several differences emerged when comparing event sums and severities between pre-depression and pre-(hypo)mania periods. Specifically, major BAS-deactivating and major SRD events tended to be more frequent prior to depression. Also, at a trend level, severities of negative, BAS-deactivating, and SRD events were higher in pre-depression relative to pre-(hypo)mania periods. Interestingly, although research has yet to determine whether SRD events are more closely tied to a particular episode polarity, results of the present study may suggest a closer association with depressive episodes among BSD individuals. Overall, few predictions were upheld in relation to within-group differences across the three observation periods.

Generally, results of examinations of basic group differences in event levels suggest that BSD participants have higher event levels in all observation periods in comparison to normal controls, but that among BSD participants, there are few within-subject differences across the three observation periods. This indicates that BSD participants experience consistently higher levels of life events regardless of temporal proximity to mood episodes. The group differences in daily life event rates (i.e., BSD participants had higher rates of daily events in all categories but

major positive) further supports the finding that BSD participants experience consistently higher levels of life events. There are three possible explanations for this finding. The first explanation is a variation of the "harsh environment" hypothesis, or the idea that individuals with bipolar disorder experience more negative events due to wholly exogenous factors (Grandin, Alloy, & Abramson, 2007; Safford et al., 2007). These events then serve as the stressors in a diathesis-stress model of the disorder. The second possible explanation is that BSD participants report more events due to reporting bias, which could be mood state-dependent or trait-like. However, in an earlier study based on the LIBS project, Bender and colleagues (2010) found no evidence of reporting bias either as a function of diagnostic status or current mood symptomatology.

The third possible explanation is "stress generation" (Hammen, 1991, 2006). The stress generation theory posits that individuals with mood disorders actively shape their own environments and, in doing so, generate stressful events. Evidence for stress generation processes occurring within the LIBS project BSD sample has been reported previously (Bender, Alloy, Sylvia, Urosevic & Abramson, 2010; Urosevic, Abramson, Alloy, Nusslock, & Harmon-Jones et al., 2010). Findings from these earlier studies, in conjunction with group comparisons in the present investigation, indicate that stress generation is likely to be occurring.

With respect to tests of the main hypotheses, significant results were globally in line with a sensitization model, but additional findings would be needed to fully support this model. Prior to depression, more lifetime episodes predicted an increased frequency of minor negative events, tended to predict an increased frequency of minor BAS-deactivating events, and predicted an increased impact of minor SRD events. Prior to (hypo)mania, more lifetime episodes predicted a decreased frequency (trend level) and an increased impact of major negative events. More lifetime hypomanic episodes also predicted an increased frequency of minor

positive events, an increased frequency of minor SRD events, and a marginally increased impact of major BAS-activating and major BAS-deactivating events. Contrary to hypotheses, more lifetime hypomanic episodes also predicted a higher severity of positive events prior to prospective (hypo)manic periods. During episode-free control periods, more previous depressive episodes predicted a decreased frequency of major SRD events. Interestingly, few findings emerged in models that examined highest event severities. In the present study, kindling processes were more apparent when stress was quantified using an additive burden model, rather than a severity threshold model.

In summary, for all significant or trend-level findings, more previous episodes predicted a decreased frequency of major events, an increased frequency of minor events, and an increased impact of major and minor events. This pattern of findings is consistent with a stress sensitization model. However, within specific event types and polarities, no complete patterns of stress sensitization emerged. For example, minor BAS-deactivating events were significantly more frequent prior to prospective depression among participants with more previous depressive episodes, but no significant results were found for major BAS-deactivating event frequency, and previous depressive episodes did not significantly affect the prospective impact of BAS-deactivating events. The finding that a greater number of past hypomanic episodes predicted a higher "severity" of positive events prior to prospective (hypo)manic episodes was also inconsistent with a stress sensitization hypothesis. The current study provided no support for a stress autonomy model, because there was an increased frequency of minor events, and an increased impact of both major and minor events, prior to episodes.

Thus, among event coding schemes based on valence, BAS-relevance, and social rhythm disruption, none fully captured any stress sensitization processes that may be occurring. This

may indicate that these theoretical approaches to conceptualizing life events are inadequate, or that measurement error (e.g., forgetting, recall bias, imprecision due to use of *a priori* event codes) confounded results. However, results underscore the importance of polarity- and event type-specific analyses, in that findings differed across these dimensions. In tests of main hypotheses, depression was associated only with negative, BAS-deactivating, and SRD events, whereas (hypo)mania was also associated with positive and BAS-activating events. Moreover, most statistically significant findings occurred among minor event categories. The present study is the first to have examined kindling in BD while making careful, theory-driven distinctions regarding episode polarities, event types, and event severities. Given the partial support for stress sensitization, further research is warranted on this understudied, but important, topic.

It should be noted that among tests of main hypotheses, effect sizes were small. For example, with the addition of lifetime depressive episodes in the model predicting to minor negative events, the change in R^2 indicated a 5% increase in variance accounted for. This magnitude of effect was similar across other significant findings in tests of the frequency component of the kindling model (range of change in R^2 for significant findings in this group of analyses = .02 - .09). Among significant models, the overall model accounted for 8% – 18% of the variance in event levels. In impact analyses, odds ratios associated with significant interaction terms were also small (range of odds ratios among models with significant interaction terms = 1.09 – 2.03). This is not surprising, given that statistical models in the present study predicted to outcomes that are likely multi-determined and highly complex.

Although not a main focus of the present study, it was interesting to see that in analyses of event impact, a differential pattern of main effects emerged according to polarity. In analytic models predicting to depression onset, there were significant main effects for prodromal

depressive symptomatology and the number of lifetime episodes, but not for current life events. In contrast, in analytic models predicting to (hypo)mania onset, there were significant main effects for prodromal (hypo)manic symptomatology and current life events, but not for lifetime history of episodes. Thus, time to onset of depression appeared to be determined by both proximal (i.e., current symptoms) and distal (i.e., longitudinal course) factors, whereas time to onset of (hypo)mania appeared to be more strongly determined by proximal factors only (i.e., current symptoms and life events). This may partially reflect the fact that diagnostic criteria were more stringent for depressive episodes than (hypo)manic ones. That is, the minimum required duration for a depressive episode was six of seven days, and some evidence of impairment was required. In contrast, the minimum required duration for a hypomanic episode was two days, and evidence of impairment was not required. Thus, depressive episodes may have been more clinically severe and likely to reflect long-term course and prognosis, whereas hypomanic episodes may have been less clinically severe and more "reactive" to immediate circumstances.

Clinical Implications

Although results from the present study warrant further replication, there are important therapeutic implications related to empirical findings on kindling processes in BSD. Results of the present study suggest that it may be important to incorporate illness progression into treatment conceptualization. That is, as the course of the disorder progresses, individuals with BSD may be increasingly vulnerable to relapse following lower levels of stress. Moreover, changing thresholds of stress sensitivity may occur in some event domains and not in others, or differentially according to episode polarity.

Many forms of psychotherapy attempt to alter the relationship between environmental

stress and affective responses. The present results underscore the notion that treatment providers should consider not just the absolute qualities of psychosocial events, but also their qualities in relation to disease history. The constructs of allostasis and allostatic load can help in conceptualizing the changing threshold of stress required to trigger affective episodes. *Allostasis* describes the process by which an organism maintains stability or homeostasis through continual adaptation (Monroe, 2008). *Allostatic load* describes the psychobiological consequences of sustained activation of the regulatory systems involved in maintaining allostasis. Perceptual processes and cognition serve a critical role in determining the allostatic load in a given situation. Moreover, allostatic load is susceptible to cumulative burden ("wear and tear"). Put simply, the allostatic load conferred by a given stressor is determined by the relative relationship between the intensity of the environmental stressor and the robustness of the organism's ability to adapt. According to the stress sensitization hypothesis and partially in line with the present findings, successive mood episodes in bipolar disorder serve to weaken allostatic processes. If allostatic processes weaken over time, a lower intensity of stress would be required to produce the same allostatic load.

Within this framework, stress-triggered episode initiation would be determined not by the absolute intensity of stressors, but by the resultant allostatic load. Thus, a job loss may confer a higher allostatic load and vulnerability to relapse for an individual with a history of more bipolar episodes, relative to an individual with fewer past episodes. An improved ability to foresee periods of high vulnerability to relapse will help patients and clinicians to more proactively address precipitants and prodromes. Post (2006) recommended coping strategies with an emphasis on active stress anticipation and management. Both problem-focused and emotion-focused coping skills (Mazure, 1998) are likely to reduce allostatic load over time. In sum, the

stress sensitization hypothesis and the current findings suggest that treatment approaches should be tailored to the individual's stage of illness.

Research that provides a more nuanced understanding of the mechanisms underlying a sensitization effect will be crucial to the development of such targeted interventions. In particular, if sensitization 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. In the present study, minor SRD events became more impactful prior to depressive episodes, and more frequent prior to (hypo)manic episodes, as the number of previous episodes increased. This suggests that IPSRT could benefit from an emphasis on the idea that as the course of the disorder progresses, even seemingly minor stressors in these domains must be monitored and addressed.

From a BAS-dysregulation perspective, 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 (Johnson & Fulford, 2009) utilizes motivational interviewing and CBT techniques to target goal dysregulation as a precipitant of manic episodes. In the present study, all BAS-relevant findings occurred at trend-level

significance. Nevertheless, results may suggest that as the disorder progresses, minor BAS-deactivating events increase in frequency prior to depression, and major BAS-activating and BAS-deactivating events increase in impact prior to (hypo)mania. Thus, careful, systematic tracking of cognitions, behaviors, emotions, and BAS-relevant events may be especially helpful in light of potential developmental changes in stress sensitivity.

With an eye towards long-term developmental changes in stress reactivity, clinicians and patients can develop a collaborative treatment plan that aims to slow or arrest progression of stress sensitization. Again, however, stronger evidence for kindling is needed before firm conclusions can be drawn about incorporating the model into treatment approaches.

Strengths and Limitations

The present study built upon existing research and had several notable strengths. First, this prospective longitudinal investigation followed participants for an average of more than four years. Assessments of mood episodes were interview-based, which produces more reliable data than self-report measures. The procedures used to prospectively assess life events were based on contextual threat methods and narrative-rating procedures, yielding event data that are both sensitive to the participant's individual context and anchored in objective measurement. Life events were thus assessed via rigorous standardized interviews with demonstrated high reliability and validity. Interviewer bias was minimized by blinding life events interviewers to diagnostic status and concurrent mood symptoms. The life events assessment procedure also afforded a more valid assessment of life stress across the spectrum of event severity, which is critical for furthering our understanding of the developmental relationship between stress and BSD. In the

present study, frequency- and impact-related findings emerged among both major and minor event categories, thus further underscoring the importance of examining less severe events.

The present study examined both the frequency and impact of stress as a function of prior episodes. Analyses examined changes in stress at both the within- and between-subjects levels. Also, the present study was the first to utilize carefully defined, theory-driven event categories and the first prospective investigation to use a polarity-specific approach to testing the kindling hypothesis. It was also the first to test the kindling model in a sample comprised entirely of bipolar spectrum disorder participants (i.e., bipolar II disorder, cyclothymia, or bipolar NOS). Individuals with milder forms of BD are less likely to be treatment-seeking, so a bipolar spectrum sample may provide a more naturalistic perspective on kindling processes.

In light of its bipolar spectrum sample, prospective design, rigorous data collection techniques, polarity-specific analyses of frequency and impact at both major and minor levels of severity (which, in turn, allows for a comparison of sensitization and autonomy models of kindling), incorporation of effects at both the within- and between-subjects levels, and use of theory-driven event categories, the present study represented a significant advancement in testing the kindling hypothesis in BD.

Several important limitations must be noted as well. Unfortunately, the final sample size included in the present study provided low power to detect hypothesized effects. *A priori* power analyses (using G*Power Version 3.1.2 software; Faul, 2009) indicated that, for linear regression analyses examining the frequency component of the kindling hypothesis, a sample size of 146 was required to detect a small-to-medium effect. *A priori* power analyses (using Power Analysis and Sample Size software version 08.0.13; Hintze, 2008) for testing the impact component of the

kindling hypothesis indicated that a sample size of 160 was needed to achieve power to detect a small-to-medium effect size.

Thus, although the full LIBS project sample would have yielded sufficient power to detect small-to-medium effects, the unexpected reduction in sample size due to missing data was problematic from this standpoint. Participants included in the final sample were demographically representative of the larger LIBS project sample, but some statistical power was lost. Bipolar spectrum participants were necessarily excluded from analyses in which they did not have a qualifying observation period, thereby further reducing power to detect effects. However, it is important to note that the final sample size for the present study was greater than all existing prospective investigations of kindling in BD (see Bender & Alloy, 2011).

It is also possible that a one-month observation period is insufficient to fully capture sensitization or autonomy processes. Thirteen of the fifteen existing kindling studies have used intervals of three months or longer. I was unable to test my hypotheses using three-month periods, because a more stringent selection criterion would have further reduced the number of participants with qualifying intervals. This, in turn, would lead to a further reduction in already-limited power. If the sample size allowed, kindling processes may have been more easily detected during the three months prior to episode onset, rather than one month.

This study included a large number of analyses that would often require an adjustment to address issues of multiplicity (e.g., a Bonferroni correction). However, a Bonferroni correction was considered overly conservative, given concerns about power to detect effects. Thus, it is critical to emphasize that results warrant replication before serving as the basis for firm theoretical or clinical conclusions. This is especially true for any marginally significant trends that have been noted among the present findings.

Sample generalizability should be considered carefully. As noted, for main study analyses, it was necessary to exclude any bipolar participants who did not experience at least one prospective episode that was preceded by 30 days of euthymia. Participants could thus be excluded for three reasons: 1) they did not experience a prospectively assessed episode; 2) they experienced an episode that spanned their entire study participation, or 3) they experienced many repeated episodes, such that there did not exist a 30-day period of euthymia. Thus, the final sample was biased towards bipolar spectrum participants who experienced episodes, but who also had longer inter-episode periods of euthymia. Results may not generalize to individuals with extremely mild or rapid-cycling forms of BSD. Interestingly, Ehnvall and Ågren (2002) found evidence of kindling processes only among patients who showed a pattern of decreasing well intervals over time.

Previous research on kindling in bipolar disorder has focused primarily on individuals with bipolar I disorder. Although use of a BSD sample represents a novel contribution to the literature, it is also possible that sensitization or autonomy is more clearly apparent at higher ends of the spectrum of episode severity. Participants did not experience enough severe hypomanic or manic episodes to examine whether sensitization or autonomy operates differently according to the severity of the mood episode. Also, the sample was comprised of bipolar spectrum participants who had already experienced a relatively high number of lifetime episodes. This may have impacted results, because some evidence suggests that kindling effects are most evident earlier in the course of the disorder. For example, in their combined UD and BD sample, Ehnvall and Ågren (2002) found that the frequency of life events decreased before each episode during the first nine episodes only, with the strongest difference detected during the first three episodes. Similar results were reported in an exclusively unipolar depressed sample (Kendler et

al., 2000). Thus, testing the kindling hypothesis among individuals with longer illness histories could obscure developmental changes that occur earlier in the course of the disorder (e.g., between first onsets and initial recurrences).

Although the careful measurement of life events in this study represents a major strength, there are several issues to be addressed. First, relatively fewer people endorsed social rhythm disruption associated with life events, and still fewer endorsed SRD ratings on the higher end of the Likert-type scale. Changes in social rhythm habits are likely more difficult for participants to recall than the actual events themselves, even after a period of only months. As noted above, this may be especially true for undergraduates. Also, BAS-activating and BAS-deactivating ratings were assigned to LES events on an *a priori* basis, based on an expert consensus panel. There was no individualized contextually-based adjustment of these ratings, in contrast to other COSRs and SRD ratings. Since the distinction between BAS-activating and BAS-deactivating events can be nuanced, contextual information is especially important for the derivation of these ratings. This issue may account for some of the unexpected findings related to BAS-relevant events. Finally, analyses also did not account for possible stress generation effects, given the unavailability of contextually-based ratings of the extent to which participants actively generated events.

Directions for Future Research

Despite some limitations, this study represents an important methodological and theoretical advancement in the body of literature on kindling in BD. Future studies may build upon the present one in several ways. First and foremost, a larger sample size would increase power to detect kindling-related effects. Longer follow-up periods would also increase the

likelihood that participants experience qualifying observation periods. Ideally, individuals would be followed starting prior to their initial onset of BD, over an extended period of years to capture the relationship between life events and subsequent episodes. An event history analysis would provide a particularly powerful test of the kindling hypothesis, as it examines within-subject changes in stress reactivity across multiple prospective episode occurrences. The ability to prospectively examine life events and multiple episode recurrences over time will be critical to furthering empirical knowledge of this complex developmental process. Genetic or behavioral high-risk samples are ideal for examining phenomena that occur at such low base rates (Dienes et al., 2006; Hammen, 2009).

Related to sample generalizability, future research should examine subgroups of BSD individuals with differing course trajectories and severities of illness. Although faster episode recurrence over time is common, some individuals show episode stability or deceleration instead (Ehnvall & Ågren, 2002; Goldberg & Harrow, 1994; Post, 1992). The ability to compare stress sensitivity between individuals with bipolar I, bipolar II, cyclothymia, and bipolar disorder NOS may be illuminating as well. There is a need to better understand how the role of life stress differs across the range of bipolar illness expression.

To enhance ability to detect subtle shifts in daily social rhythms associated with life events, future studies should supplement in-depth, in-person assessments with daily event logs and social rhythm ratings. These may be administered via internet or email surveys, which is increasingly feasible given technological advances. Actigraphy studies have shown excellent promise in previous research on social rhythm disruption (e.g., Jones, Hare, & Evershed, 2005; Millar, Espie, & Scott, 2004). Studies that incorporate measures of chronic stressors and stress

generation processes may further illuminate the role of psychosocial context in the longitudinal course of BD.

As we advance our ability to describe stress sensitization processes, it will be important to identify underlying mechanisms. The use of theory-driven event categories that are organized according to biopsychosocial conceptualizations (e.g., BAS, SRD) represents one way of approaching this task. 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). 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. Given the increased emphasis on biopsychosocial models, future research must examine relationships between multiple factors putatively contributing to a kindling effect. Multi-trait and multi-method assessments will be critical in the examination of a process that is hypothesized to occur on multiple levels of analysis.

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